Indexing & Abstracting

Of

Drugs

YEAR 2017

Published by

LIBRARY & INFORMATION CENTRE
INDIAN PHARMACOPOEIA COMMISSION
Ministry of Health & Family Welfare
Government of India
Ghaziabad (U.P.)

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Volume 77, Issue 04, March 2017

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Volume 77, Issue 16, October 2017

Volume 77, Issue 17, November 2017

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Engaging Natural Killer T Cells as 'Universal Helpers' for Vaccination

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ABSTRACT

Conventional vaccine adjuvants enhance peptide-specific T-cell and B-cell responses by modifying peptide stability or uptake or by binding to pattern-recognition receptors on antigen-presenting cells (APCs). This article discusses the application of a distinct mechanism of adjuvant activity: the activation of type I, or invariant, natural killer T (iNKT) cells to drive cellular and humoral immune responses. Using a semi-invariant T-cell receptor (TCR), iNKT cells recognize glycolipid antigens presented on cluster of differentiation (CD)-1d molecules. When their ligands are presented in concert with peptides, iNKT cells can provide T-cell help, 'licensing' APCs to augment peptide-specific T-cell and antibody responses. We discuss the potential benefits and limitations of exploiting iNKT cells as 'universal helpers' to enhance vaccine responses for the treatment and prevention of cancer and infectious diseases.

Recent Advances in the Medical Treatment of Recurrent or Metastatic Renal Cell Cancer

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ABSTRACT

Renal cell carcinoma (RCC) historically has had limited treatment options in the metastatic setting but in the last decade, a significant arsenal of new therapies has emerged. Specifically, targeted anti-angiogenic therapies through vascular endothelial growth factor (VEGF) inhibition and immunotherapy through PD-1 inhibition have become the foundation of metastatic RCC treatment increasing not only progression-free survival but also an improved overall survival with improved toxicity profiles compared with older therapies such as IL-2 and interferon. With the development of these newer medications, the optimal sequence and pairing of treatments is not yet well understood but important studies are ongoing as this information will allow for more effective and safe treatment of patients.

Insulin Resistance and Neurodegeneration: Progress towards the Development of New Therapeutics for Alzheimer's Disease

Suzanne M. de la Monte

ABSTRACT

Alzheimer's disease (AD) should be regarded as a degenerative metabolic disease caused by brain insulin resistance and deficiency, and overlapping with the molecular, biochemical, pathophysiological, and metabolic dysfunctions in diabetes mellitus, non-alcoholic fatty liver disease, and metabolic syndrome. Although most of the diagnostic and therapeutic approaches over the past several decades have focused on amyloid-beta (Aβ42) and aberrantly phosphorylated tau, which could be caused by consequences of brain insulin resistance, the broader array of pathologies including white matter atrophy with loss of myelinated fibrils and leukoaraiosis, non-Aβ42 microvascular disease, dysregulated lipid metabolism, mitochondrial dysfunction, astrocytic gliosis, neuro-inflammation, and loss of synapses vis-à-vis growth of dystrophic neurites, is not readily accounted for by Aβ42 accumulations, but could be explained by dysregulated insulin/IGF-1 signaling with attendant impairments in signal transduction and gene expression. This review covers the diverse range of brain abnormalities in AD and discusses how insulins, incretins, and insulin sensitizers could be utilized to treat at different stages of neurodegeneration.

Current Pharmacological Approaches to Reduce Chorea in Huntington's Disease

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ABSTRACT

There are currently no effective pharmacological agents available to stop or prevent the progression of Huntington's disease (HD), a rare hereditary neurodegenerative disorder. In addition to psychiatric symptoms and cognitive impairments, HD causes progressive motor disturbances, in particular choreiform movements, which are characterized by unwanted contractions of the facial muscles, trunk and extremities. Management of choreiform movements is usually advised if chorea interferes with daily functioning, causes social isolation, gait instability, falls, or physical injury. Although drugs to reduce chorea are available, only few randomized controlled studies have assessed the efficacy of these drugs, resulting in a high variety of prescribed drugs in clinical practice. The current pharmacological treatment options to reduce chorea in HD are outlined in this review, including the latest results on deutetrabenazine, a newly developed pharmacological agent similar to tetrabenazine, but with suggested less peak dose side effects. A review of the existing literature was conducted using the PubMed, Cochrane and Medline databases. In conclusion, mainly tetrabenazine, tiapride (in European countries), olanzapine, and risperidone are the preferred first choice drugs to reduce chorea among HD experts. In the existing literature, these drugs also show a beneficial effect on motor symptom severity and improvement of psychiatric symptoms. Generally, it is recommended to start with a low dose and increase the dose with close monitoring of any adverse effects. New interesting agents, such as deutetrabenazine and pridopidine, are currently under development and more randomized controlled trials are warranted to assess the efficacy on chorea severity in HD.

Single-Dose Dalbavancin: A Review in Acute Bacterial Skin and Skin Structure Infections

Karly P. Garnock-Jones

ABSTRACT

Intravenous dalbavancin (Dalvance®, Xydalba®), first approved as a two-dose regimen for the treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI), has now been additionally approved as a single-dose regimen. This narrative review discusses the pharmacological properties of intravenous dalbavancin and its clinical efficacy and tolerability as a single-dose regimen in the treatment of adult patients with ABSSSI. Single-dose dalbavancin is an effective and generally well tolerated treatment option for adults with ABSSSI, with noninferior efficacy to the two-dose dalbavancin regimen with regard to early clinical response (at 48–72 h) and low rates of adverse events. Clinical success rates at days 14 and 28 also did not significantly differ between the single- and two-dose dalbavancin regimens; neither did clinical success rates at day 14 when analysed by baseline pathogen. It has a broad spectrum of activity against common ABSSSI-related pathogens, and a favourable pharmacokinetic profile allowing for the convenience of single-dose administration. Thus, dalbavancin presents a promising alternative to conventional antibacterials for the treatment of ABSSSI in adult patients.

Topiramate in the Treatment of Generalized Convulsive Status Epilepticus in Adults: A Systematic Review with Individual Patient Data Analysis

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ABSTRACT

Background: Generalized convulsive status epilepticus (GCSE) is a medical emergency associated with high morbidity and mortality that requires prompt medical intervention. Topiramate (TPM) is an antiepileptic drug effective against a broad spectrum of seizure types, and has been proposed as a possible therapeutic option for super-refractory status epilepticus (SRSE), the most severe form of GCSE.

Aim: This review aimed to evaluate the role of TPM in GCSE, including SRSE.

Methods: MEDLINE, CENTRAL, ClinicalTrials.gov, LILACS, Google Scholar, and Opengrey.eu were systematically searched. We compared: (1) patients who did and who did not receive TPM as their last drug; (2) patients receiving TPM as the last drug and achieving SE control and patients receiving TPM as the last drug but without termination of SE.

Results: The literature search yielded 1164 results, with individual data available for 35 patients (six with SRSE) from four studies. SE was controlled in 68.6% of patients receiving TPM either as the last drug (20) or not (15) and in 14 of the 20 patients receiving TPM as the last drug (70%). Only six patients received TPM for SRSE; in five of them, TPM was administered as the last drug with resolution of SE in four. When comparing patients who did and did not receive TPM as the last drug, no statistically significant difference was found for any of the variables considered; similarly, no difference was found comparing patients receiving TPM as the last drug and achieving SE control with those receiving TPM as the last drug but without termination of SE.

Conclusions: The lack of a statistically significant difference is likely to be due to the small sample size. In only a few patients was TPM used for SRSE. There is an unmet need for high-quality studies to evaluate the role of TPM in GCSE.

Dasatinib: A Review in Chronic Myeloid Leukaemia and Ph+ Acute Lymphoblastic Leukaemia

Gillian M. Keating

ABSTRACT

Dasatinib (Sprycel®) is an orally administered, small molecule inhibitor of multiple tyrosine kinases. In the phase 3 DASISION trial, dasatinib 100 mg once daily resulted in deeper and faster cytogenetic and molecular responses than imatinib 400 mg once daily in patients with newly diagnosed, chronic-phase chronic myeloid leukaemia (CML), although there was no significant between-group difference in progression-free survival (PFS) or overall survival (OS) in the longer term. In the phase 3 CA180-034 trial, a regimen of dasatinib 100 mg once daily provided the most favourable benefit-risk profile in patients with imatinib-resistant or -intolerant chronic-phase CML. In the phase 3 CA180-035 trial, a regimen of dasatinib 140 mg once daily demonstrated efficacy in patients with accelerated- or blast-phase CML or Ph+ acute lymphoblastic leukaemia (ALL) resistant or intolerant to imatinib. Dasatinib had an acceptable tolerability profile. In conclusion, dasatinib is an important option for the treatment of patients with newly diagnosed chronic-phase CML and for imatinib-resistant or -intolerant patients with chronic- or advanced-phase CML or Ph+ ALL.

Coagulation Factor IX (Recombinant), Albumin Fusion Protein (Albutrepenonacog Alfa; Idelvion®): A Review of Its Use in Haemophilia B

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ABSTRACT

Albutrepenonacog alfa (Idelvion®), a fusion protein that genetically fuses recombinant factor IX (rFIX) with recombinant human albumin (rAlbumin), is indicated in the treatment of haemophilia B. This narrative review discusses the pharmacological properties and clinical data related to the use of this novel fusion protein, hereafter referred to as rIX-FP. The fusion of rFIX to rAlbumin prolongs the elimination half-life of rIX-FP in the circulation, allowing routine prophylaxis to be administered once every 7–14 days. In the pivotal phase 3 clinical trials in previously treated patients with moderately severe to severe haemophilia B, routine rIX-FP prophylaxis (administered once every 7 days in children, and once every 7–14 days in adolescents and adults) was associated with low annualized spontaneous, total and joint bleeding rates, and was associated with significantly fewer bleeding episodes than on-demand treatment. rIX-FP was also effective in controlling bleeding episodes when used as on-demand treatment and in maintaining haemostasis in the perioperative setting. rIX-FP was well tolerated in the clinical trials, with no reports of inhibitor development. In conclusion, rIX-FP provides an effective, well-tolerated option for the treatment and management of haemophilia B that, by virtue of its extended half-life, is less burdensome than conventional FIX products.

Olaratumab: First Global Approval

Matt Shirley

ABSTRACT

Olaratumab (Lartruvo™) is a fully human IgG1 monoclonal antibody targeted against the human platelet-derived growth factor (PDGF) receptor α (PDGFRα). It was developed by Eli Lilly and Co. (previously ImClone Systems) after PDGFRα was identified as a potential therapeutic target in a variety of cancers. Olaratumab acts by selectively binding PDGFRα, thereby blocking PDGF ligand binding and inhibiting PDGFRα activation and downstream signalling. In October 2016, olaratumab received its first global approval, in the USA, for use in combination with doxorubicin for the treatment of adult patients with soft tissue sarcoma. The approval was granted by the US FDA under its Accelerated Approval Program based on the results of the JGDG phase II trial (NCT01185964). In addition, the EMA granted conditional approval for olaratumab in this indication in November 2016 following a review under the EMA's Accelerated Assessment Program. An international, confirmatory phase III trial in patients with soft tissue sarcoma is ongoing (ANNOUNCE; NCT02451943). Olaratumab has also been investigated in phase II trials in several other cancers. This article summarizes the milestones in the development of olaratumab leading to this first approval, for use in combination with doxorubicin for the treatment of soft tissue sarcoma in adults.

PARP Inhibitors in Reproductive System Cancers: Current Use and Developments

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ABSTRACT

The repair of DNA damage is a critical cellular process governed by multiple biochemical pathways that are often found to be defective in cancer cells. The poly(ADP-ribose) polymerase (PARP) family of proteins controls response to single-strand DNA breaks by detecting these damaged sites and recruiting the proper factors for repair. Blocking this pathway forces cells to utilize complementary mechanisms to repair DNA damage. While PARP inhibition may not, in itself, be sufficient to cause tumor cell death, inhibition of DNA repair with PARP inhibitors is an effective cytotoxic strategy when it is used in patients who carry other defective DNA-repair mechanisms, such as mutations in the genes BRCA 1 and 2. This discovery has supported the development of PARP inhibitors (PARPi), agents that have proven effective against various types of tumors that carry BRCA mutations. With the application of next-generation sequencing of tumors, there is increased interest in looking beyond BRCA mutations to identify genetic and epigenetic aberrations that might lead to similar defects in DNA repair, conferring susceptibility to PARP inhibition. Identification of these genetic lesions and the development of screening assays for their detection may allow for the selection of patients most likely to respond to this class of anticancer agents. This article provides an overview of clinical trial results obtained with PARPi and describes the companion diagnostic assays being established for patient selection. In addition, we review known mechanisms for resistance to PARPi and potential strategies for combining these agents with other types of therapy.

Genotype 3 Infection: The Last Stand of Hepatitis C Virus

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ABSTRACT

Hepatitis C virus (HCV) represents a significant global disease burden, with an estimated 130–150 million people worldwide living with chronic HCV infection. Within the six major clinical HCV genotypes, genotype 3 represents 22–30% of all infection and is described as a unique entity with higher rates of steatosis, faster progression to cirrhosis, and higher rates of hepatocellular carcinoma. Hepatic steatosis in the setting of hepatitis C genotype 3 (HCV-3) is driven by viral influence on three major pathways: microsomal triglyceride transfer protein, sterol regulatory element-binding protein-1c, and peroxisome proliferator-associated receptor-α. Historically with direct-acting antivirals, the rates of cure for HCV-3 therapies lagged behind the other genotypes. As current therapies for HCV-3 continue to close this gap, it is important to be cognizant of common drug interactions such as acid-suppressing medication and amiodarone. In this review, we discuss the rates of steatosis in HCV-3, the mechanisms behind HCV-3-specific steatosis, and current and future therapies.

Treating HIV Infection in the Central Nervous System

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ABSTRACT

Combination antiretroviral treatment is associated with clear benefits in HIV-positive subjects, and is also effective in the central nervous system (CNS), meaning HIV-associated dementia is now an uncommon event. Nevertheless, a significant number of patients show symptoms of neurocognitive impairment which may negatively affect their quality of life. Although several risk factors for HIV-associated neurocognitive disorders have been identified, there is no clear recommendation for their prevention and management. In this review, the penetration of drugs into the cerebrospinal fluid/CNS is discussed as well as the viral and clinical consequences associated with higher/lower compartmental exposure. We also review the potential interventions according to the currently identified underlying mechanisms, including persistent CNS immune activation, legacy effects, low-level viral replication and escape, co-morbidities, and antiretroviral-associated direct and indirect 'neurotoxicity'. Adjunctive therapies and interventions (including neuro-rehabilitation) are then briefly discussed. The treatment of HIV infection in the CNS is a complex area of therapeutics requiring multidisciplinary interventions and further study.

Mucosal Healing in Ulcerative Colitis: A Comprehensive Review

Pedro Boal Carvalho, José Cotter

ABSTRACT

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by periods of remission and periods of relapse. Patients often present with symptoms such as rectal bleeding, diarrhea and weight loss, and may require hospitalization and even colectomy. Long-term complications of UC include decreased quality of life and productivity and an increased risk of colorectal cancer. Mucosal healing (MH) has gained progressive importance in the management of UC patients. In this article, we review the endoscopic findings that define both mucosal injury and MH, and the strengths and limitations of the scoring systems currently available in clinical practice. The basic mechanisms behind colonic injury and MH are covered, highlighting the pathways through which different drugs exert their effect towards reducing inflammation and promoting epithelial repair. A comprehensive review of the evidence for approved drugs for UC to achieve and maintain MH is provided, including a section on the pharmacokinetics of anti-tumor necrosis factor (TNF)-α drugs. Currently approved drugs with proven efficacy in achieving MH in UC include salicylates, corticosteroids (induction only), calcineurin inhibitors (induction only), thiopurines, vedolizumab and anti-TNFα drugs (infliximab, adalimumab, and golimumab). MH is of crucial relevance in the outcomes of UC, resulting in lower incidences of clinical relapse, the need for hospitalization and surgery, as well as reduced rates of dysplasia and colorectal cancer. Finally, we present recent evidence towards the need for a more strict definition of complete MH as the preferred endpoint for UC patients, using a combination of both endoscopic and histological findings.

Lifitegrast Ophthalmic Solution 5%: A Review in Dry Eye Disease

Gillian M. Keating

ABSTRACT

Lifitegrast is a novel small molecule integrin antagonist that blocks the binding of intercellular adhesion molecule 1 (ICAM-1) to lymphocyte function-associated antigen 1 (LFA-1). Lifitegrast ophthalmic solution 5% (Xiidra™) was recently approved in the USA for the treatment of dry eye disease. The efficacy of lifitegrast ophthalmic solution 5% was compared with vehicle in a 12-week phase 2 study and three 12-week phase 3 studies (OPUS-1, OPUS-2 and OPUS-3) in patients with dry eye disease. Taken as a whole, results of these trials support the treatment effect of lifitegrast ophthalmic solution 5% in improving a symptom of dry eye disease (i.e. the change from baseline to day 84 in the eye dryness visual analogue scale score) and a sign of dry eye disease (i.e. the change from baseline to day 84 in the inferior corneal fluorescein staining score). Lifitegrast ophthalmic solution 5% was generally well tolerated. In conclusion, lifitegrast ophthalmic solution 5% provides a new option for the treatment of dry eye disease.

Sedative Effects of Levocetirizine: A Systematic Review and Meta-Analysis of Randomized Controlled Studies

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ABSTRACT

Introduction: As a substrate of P-glycoprotein, levocetirizine should not cause sedative effects. However, while cetirizine, a mixture of levocetirizine and dextrocetirizine, can slightly penetrate the blood brain barrier, the sedative effects of levocetirizine are still under study.

Objectives: The aim of this study was to investigate the sedative effects of levocetirizine.

Methods: An electronic literature search was performed using Medline and EMBASE from January 01, 2001 through August 6, 2015. Randomized controlled trials (RCTs) comparing levocetirizine with other antihistamines or placebo for patients with allergy and healthy subjects were selected. Primary outcome was risk ratio between levocetirizine and comparators. Secondary outcome was change in psychomotor speed. Data were pooled for meta-analysis using a fixed-effect model.

Results: Forty-eight studies of 18,014 patients met the inclusion criteria. When compared to placebo, levocetirizine produced modest sedative effects (RR: 1.67; 95% CI 1.17, 2.38). However, when compared to other second-generation antihistamines, sedative effects of levocetirizine did not differ (RR: 1.23; 95% CI 0.96, 1.58). In subgroup analysis, there was no difference between the sedative effects of levocetirizine and fexofenadine (RR: 1.7; 95% CI 0.59, 4.88), desloratadine (RR: 1.58; 95% CI 0.9, 2.77), loratadine (RR: 1.56; 95% CI 0.28, 8.56), bilastine (RR: 1.17; 95% CI 0.48, 2.84), olopatadine (RR: 1.09; 95% CI 0.81, 1.47), azelastine (RR: 0.19; 95% CI 0.01, 3.68) and rupatadine (RR: 1.47; 95% CI 0.14, 15.72). When compared to first-generation antihistamines, levocetirizine had less sedative effects and less change of reaction time (mean difference: −250.76 s; 95% CI −338.53, −162.98).

Conclusion: Levocetirizine has modest sedative effects with a risk ratio of 1.67 when compared with placebo. The sedative effects observed for levocetirizine are not different from other second-generation antihistamines.

Efficacy and Safety of Tacrolimus versus Cyclophosphamide for Primary Membranous Nephropathy: A Meta-Analysis

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ABSTRACT

Objective: The objective of this systematic review was to compare the efficacy and safety of tacrolimus with cyclophosphamide in primary membranous nephropathy (PMN) patients.

Data Sources and Study Eligibility Criteria: We conducted a literature search in MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CCRCT). Any study that compared the efficacy or safety between tacrolimus and cyclophosphamide in the adult PMN patients was included.

Results: We included four randomized controlled trials and two prospective cohort studies with 389 PMN patients. The pooled results using the Dersimonian and Laird method showed that renal remission rates at the longest follow-up periods were not significantly different between the tacrolimus and cyclophosphamide groups (overall remission, six trials, n = 389, relative risk [RR] 0.994 [95% confidence interval [CI] 0.768–1.286); complete remission, six trials, n = 389, RR 1.256 [95% CI 0.733–2.150]). Further analyses found that tacrolimus was comparable with cyclophosphamide for inducing renal remission within 1 year but inferior to cyclophosphamide after 1-year follow-up. It should be noted that only two studies reported the outcomes after 1-year follow-up, which might be considered as weak evidence. The rates of relapse and the drop-outs due to adverse effects were not significantly different (relapse, six trials, n = 389, RR 2.244 [95% CI 0.892–5.644]; drop-outs, six trials, n = 389, RR 1.330 [95% CI 0.412–4.291]). However, the cyclophosphamide group had a significantly higher risk of leukopenia than the tacrolimus group (four trials, n = 216, RR 0.203 [95% CI 0.045–0.916]), whereas the rates of tremor were significantly higher in the tacrolimus group than in the cyclophosphamide group (three trials, n = 202, RR 8.939 [95% CI 1.694–47.173]).

Limitations: The quality and short follow-up durations of the studies limited the reliability of our Conclusions.

Conclusions: Tacrolimus was comparable with cyclophosphamide for inducing renal remission of PMN patients within 1 year, but the long-term effects need to be investigated. The cyclophosphamide group had a significantly higher risk of leukopenia, whereas the tacrolimus group had significantly higher rates of tremor. These conclusions need to be further verified.

Sitagliptin: A Review in Type 2 Diabetes

Lesley J. Scott

ABSTRACT

The dipeptidyl peptidase-4 inhibitor sitagliptin (Januvia®; Glactiv®; Tesavel®; Xelevia™) is approved in more than 130 countries worldwide as monotherapy and in combination with other antihyperglycaemic drugs for the treatment of adult patients with type 2 diabetes (T2D). Extensive clinical experience has firmly established the glycaemic efficacy of oral sitagliptin (±other antihyperglycaemic drugs) in a broad spectrum of patients with T2D, including obese, elderly and renally impaired patients and those with established cardiovascular (CV) disease (CVD). Sitagliptin is generally well tolerated, with most adverse events being of mild to moderate intensity and relatively few patients discontinuing treatment because of these events. Sitagliptin treatment was not associated with an increased risk for the known CVD risk factors of hypoglycaemia and bodyweight gain. Of note, in the TECOS CV safety trial in patients with T2D and established CVD, sitagliptin was noninferior to placebo in terms of the risk of the 4-point major adverse cardiac event (MACE) outcome, with no increased risk in hospitalization for heart failure. Albeit discussion is equivocal regarding the potential increased risk of pancreatitis and pancreatic cancer with incretin-based therapies (including sitagliptin), no causal link between incretin-based drugs and these events has been established to date. With its convenient once-daily oral regimen, low potential for pharmacokinetic drug–drug interactions and good efficacy and safety profiles, including CV safety, sitagliptin remains an important option in the management of patients with T2D.

Ibrutinib: A Review in Chronic Lymphocytic Leukaemia

Emma D. Deeks

ABSTRACT

Ibrutinib (Imbruvica®) is an oral irreversible inhibitor of Bruton's tyrosine kinase, a B-cell receptor (BCR) signalling kinase expressed by various haematopoietic cells, B-cell lymphomas and leukaemias. The drug is indicated for the treatment of certain haematological malignancies, including chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL), which are the focus of this review. In phase III CLL/SLL trials, ibrutinib monotherapy was more effective than chlorambucil in the first-line treatment of elderly patients (RESONATE-2) and more effective than ofatumumab in previously-treated adults (RESONATE). Likewise, a combination of ibrutinib, bendamustine and rituximab was more effective in previously-treated adults than bendamustine plus rituximab in a phase III placebo-controlled study (HELIOS). These ibrutinib regimens were associated with significantly better progression-free survival, overall response rates, and overall survival than the comparators (in protocol-specified or planned analyses), with ibrutinib therapy providing benefit regardless of adverse prognostic factors, such as del(17p)/TP53 mutation and del(11q). Ibrutinib has an acceptable tolerability profile, although certain adverse events (e.g. bleeding and atrial fibrillation) require consideration. Redistribution lymphocytosis can occur, but is not indicative of disease progression. Although longer-term data would be beneficial, ibrutinib is a welcome treatment option for patients with CLL, including those who have higher-risk disease or are less physically fit. Indeed, current EU and US guidelines recommend/prefer the drug for the first- and/or subsequent-line treatment of certain patients, including those with del(17p)/TP53 mutation.

Chimeric Antigen Receptor (CAR) T Cells: Lessons Learned from Targeting of CD19 in B-Cell Malignancies

Kevin A. Hay, Cameron J. Turtle

ABSTRACT

Adoptive immunotherapy with chimeric antigen receptor-modified (CAR)-T cells is a rapidly growing therapeutic approach to treating patients with refractory cancer, with over 100 clinical trials in various malignancies in progress. The enthusiasm for CAR-T cells has been driven by the clinical success of CD19-targeted CAR-T cell therapy in B-cell acute lymphoblastic leukemia, and the promising data in B-cell non-Hodgkin's lymphoma and chronic lymphocytic leukemia. Despite the success of targeting CD19 with CAR-T cells in early clinical studies, many challenges remain to improve outcomes, reduce toxicity, and determine the appropriate settings for CAR-T cell immunotherapy. Reviewing the lessons learned thus far in CD19 CAR-T cell trials and how some of these challenges may be overcome will help guide the development of CAR-T cell therapy for malignancies of B-cell origin, as well as for other hematopoietic and non-hematopoietic cancers.

Early Combination Therapy with Oral Glucose-Lowering Agents in Type 2 Diabetes

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ABSTRACT

Despite the considerable burden of disease associated with type 2 diabetes mellitus (T2DM), most patients are not at, or are unable to achieve, recommended glycemic targets. This is partly because of the relentless progressive nature of the disease, but it may also be attributable to the current diabetes treatment paradigm. The recommended stepwise approach may lead to frequent early treatment failure with prolonged periods of elevated glucose as a consequence of clinical inertia and delays in achieving optimal glycemic control. Thus, it is most appropriate to consider the current treatment paradigm for T2DM in the context of a more aggressive initial therapy with early combination therapy. Current guidelines advise that initial combination therapy should be used for patients presenting with elevated glycated hemoglobin (HbA1c). However, several studies and recent meta-analyses suggest a potential benefit from initial combination therapy on glycemic outcomes in diabetes compared with metformin monotherapy across a wide range of baseline HbA1c levels. Indeed, combination therapy can increase the number of patients achieving glycemic goals, and the newer glucose-lowering agents may reduce the risk of hypoglycemia and body weight gain. Moreover, our improving understanding of the complex pathophysiology of T2DM and the availability of treatments tackling specific mechanisms contributing to hyperglycemia should lead to more pathophysiologically sound combination therapy. We discuss the rationale behind and evidence for early combination therapy as well as what is needed in the future to better understand its potential.

Pharmacological Management of Chronic Pelvic Pain in Women

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ABSTRACT

Chronic pelvic pain (CPP) is a multifaceted condition that often has both peripheral and central generators of pain. An understanding of neurobiology and neuropsychology of CPP should guide management. Successful treatment of CPP is typically multimodal, and pharmacologic treatment strategies include analgesics, hormonal suppression, anesthetics, antidepressants, membrane stabilizers, and anxiolytics. Evidence for these and other emerging pharmacologic therapies is presented in this article.

Drug Therapy for Stable Angina Pectoris

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ABSTRACT

Chronic stable angina pectoris refers to the predictable, reproducible occurrence of pressure or a choking sensation in the chest or adjacent areas caused by myocardial ischemia in association with physical or emotional stress, and cessation of exertion and or sublingual nitroglycerin invariably relieves the discomfort. It is a common presenting symptom of severe narrowing of one or more coronary arteries, non-obstructive coronary arteries, or even when the coronary arteries are angiographically normal. Patients often avoid activities which precipitate symptoms and have impaired quality of life. Most patients with angina pectoris can be managed with lifestyle changes, especially abstinence from smoking and regular exercise, and anti-anginal drugs. However, the choice of initial or combination antianginals as recommended in the guidelines is not evidence based. In addition, patients with stable angina due to coronary artery disease should also receive aspirin and a statin. Treatment of patients with angina and normal coronary arteries remains to be established. The aim of this article is to provide the readers not only with a guideline-based approach, which varies from one country to another, but also an individual-based approach, which takes into consideration circulatory status and the presence or absence of comorbidities in the treatment decision-making process. This manuscript primarily deals with drug therapy of stable angina pectoris and not coronary artery revascularization, which also provides angina relief but is usually reserved for patients who fail to respond to adequate drug therapy.

The Ocular Manifestations of Drugs Used to Treat Multiple Sclerosis

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ABSTRACT

Recent times have seen an increase in the number of options to treat multiple sclerosis. Ocular manifestations of multiple sclerosis are well known to treating physicians; however, the medications used to treat multiple sclerosis can also have ocular side effects. This review article focuses on the ocular manifestations of corticosteroids and disease-modifying agents such as interferon, fingolomod, natalizumab, alemtuzumab and mitoxantron used to treat the disease. The ocular manifestations of multiple sclerosis treatments can be varied depending on the drug used, and include retinopathy, chronic central serous chorioretinopathy, macular oedema, Graves' ophthalmopathy and cortical blindness. These effects may be specific to the drug or secondary to their immunosuppressive effect. The association of macular oedema with fingolomod is clear and merits ocular screening for toxicity. The immunosuppressive nature of the treatments makes patients prone to acquired infections. Hence, if a patient with multiple sclerosis presents with vision loss, infectious and drug-induced aetiology should be considered alongside relapses of multiple sclerosis itself as a cause.

Eight- or 12-Week Treatment of Hepatitis C with Ledipasvir/Sofosbuvir: Real-World Experience in a Large Integrated Health System

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ABSTRACT

Background: Second-generation direct-acting antiviral agents are integral to treatment of hepatitis C (HCV) infection. Eight-week courses of ledipasvir/sofosbuvir (LDV/SOF) have been supported in some studies, but data are limited on efficacy in real-world use. Controversy exists regarding applicability of clinical trials to real-world effectiveness. We report virologic responses of patients with HCV genotype 1 infection receiving LDV/SOF for 8 or 12 weeks in a large integrated healthcare system.

Methods: All patients receiving LDV/SOF, without ribavirin, were identified from pharmacy records, and outcomes are reported. Only treatment-naïve patients without evidence of cirrhosis and hepatitis C viral load less than 6 million IU/ml were candidates for 8-week therapy. Treatment was at clinician discretion, but delivered by a multidisciplinary team and reviewed for appropriateness and adherence to these criteria by one of the authors, all experienced in hepatitis C treatment. Sustained viral response at 12 weeks (SVR 12) was contrasted between those receiving 8 and those receiving 12 weeks of treatment.

Results: Completed prescriptions for LDV/SOF, without ribavirin, as of 30 September 2015 were identified in 1021 patients. Five patients discontinued therapy due to medical reasons and 35 had incomplete follow-up viral load data, thus there were 981 evaluable patients: 377 treated for 8 weeks and 604 treated for 12 weeks. SVR 12 was virtually identical at 93.6 and 93.5%, respectively. Baseline characteristics differed between the two groups, as only treatment-naïve, non-cirrhotic, non-HIV-infected patients were eligible for an 8-week course of therapy.

Conclusions: Eight-week courses of LDV/SOF are comparable to 12-week courses in real-world use among selected patients supported by a multidisciplinary team.

Teduglutide: A Review in Short Bowel Syndrome

Esther S. Kim, Susan J. Keam

ABSTRACT

Subcutaneous teduglutide (Revestive®), a glucagon-like peptide-2 analogue that increases intestinal absorption, is approved in the EU for the treatment of short bowel syndrome (SBS) in patients aged ≥1 year who are stable following a period of postsurgical intestinal adaptation. In a phase III trial in adults with SBS intestinal failure (IF) dependent on parenteral support (PS), a significantly greater proportion of teduglutide 0.05 mg/kg/day than placebo recipients achieved a ≥20% reduction in weekly PS volume from baseline to week 20 and maintained it to week 24. The proportion of patients who had a reduction in one or more days on PS was also significant with teduglutide compared with placebo. Improved intestinal absorption and reduced PS requirements were generally maintained in the longer term. Results from a phase III trial in paediatric patients with SBS-IF dependent on PS were consistent with those in adults. Adverse events were mostly of mild to moderate severity and generally consistent with the underlying condition or known mechanism of the drug (e.g. central line-related issues, gastrointestinal events). Teduglutide is therefore a useful treatment option in children (aged ≥1 year), adolescents and adults with SBS.

Saxagliptin/Dapagliflozin: A Review in Type 2 Diabetes Mellitus

Karly P. Garnock-Jones

ABSTRACT

Saxagliptin/dapagliflozin fixed-dose combination tablets (Qtern®) are indicated in the EU for the improvement of glycaemic control in adults with type 2 diabetes mellitus (T2DM), either when treatment with metformin and/or a sulfonylurea plus a monocomponent of saxagliptin/dapagliflozin provides inadequate glycaemic control, or when the patient is already being treated with the free combination of saxagliptin + dapagliflozin. This narrative review summarizes pharmacological, efficacy and tolerability data relevant to the use of saxagliptin/dapagliflozin in this indication. The agents have complementary mechanisms of action, and saxagliptin/dapagliflozin fixed-dose combination tablets are bioequivalent to free combination of saxagliptin + dapagliflozin. In three phase III trials, saxagliptin + dapagliflozin + metformin was more effective at providing glycaemic control than saxagliptin + metformin or dapagliflozin + metformin in previously treated patients with T2DM and inadequate glycaemic control on metformin monotherapy or metformin plus one of the monocomponents. The combination is associated with decreased bodyweight and a low risk of hypoglycaemia. As the first dipeptidyl peptidase-4 (DPP-4) inhibitor/sodium-glucose co-transporter (SGLT2) inhibitor fixed-dose combination available in the EU for glycaemic control in patients with T2DM, saxagliptin/dapagliflozin is a useful new option in this setting.

Dabigatran Etexilate: A Review in Nonvalvular Atrial Fibrillation

Hannah A. Blair, Gillian M. Keating

ABSTRACT

Dabigatran etexilate (Pradaxa®) is approved in the EU for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF) and one or more risk factors. Dabigatran etexilate is a prodrug of dabigatran, a direct inhibitor of thrombin. In patients with NVAF in the phase III RE-LY trial, dabigatran etexilate dosages of 110 and 150 mg twice daily were noninferior to warfarin with regard to the risk of stroke or systemic embolism (primary efficacy endpoint). The higher dosage was associated with a significantly lower risk of stroke or systemic embolism than warfarin, with no significant between-group difference in the risk of major bleeding (primary safety endpoint). Both dosages of dabigatran etexilate were associated with significantly lower rates of haemorrhagic stroke, intracranial bleeding and life-threatening major bleeding than warfarin. Dabigatran etexilate was also effective and generally well tolerated across various patient subgroups. The efficacy and tolerability of dabigatran etexilate was maintained for up to 6.7 years in the RELY-ABLE extension study. Routine anticoagulation monitoring is not required in patients receiving dabigatran etexilate, and it is currently the only non-vitamin K antagonist oral anticoagulant (NOAC) with a specific reversal agent available. Although direct comparisons with other NOACs would be beneficial, dabigatran etexilate is a useful option for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

New Consensus Definitions for Sepsis and Septic Shock: Implications for Treatment Strategies and Drug Development

Michael Berry, Brijesh V. PatelStephen J. Brett

ABSTRACT

Sepsis continues to escape a precise diagnostic definition. The most recent consensus definition, termed Sepsis-3, highlights the importance of the maladaptive and potentially life-threatening host response to infection. After briefly reviewing the history and epidemiology of sepsis, we go on to describe some of the challenges encountered when classifying such a heterogenous disease state. In the context of these new definitions for sepsis and septic shock, we explore current and potentially novel therapies, and conclude by mentioning some of the controversies of this most recent framework.

Incidence, Prevention and Management of Anti-Drug Antibodies against Therapeutic Antibodies in Inflammatory Bowel Disease: A Practical Overview

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ABSTRACT

The introduction of biologic therapy has revolutionized the treatment of inflammatory bowel disease (IBD). However, like all therapeutic proteins, monoclonal antibodies have immunogenic potential which is influenced by multiple drug- and patient-related factors. The reported incidence of anti-drug antibodies (ADAs) towards biologic drugs in IBD varies greatly in the literature and depends not only on differences in sensitization but also on the assay methodology and the timepoint of measurement. Sensitization with formation of ADAs is associated with an increased risk of infusion reactions, accelerated drug clearance, and a loss of response (LOR) to drug. Recently, a greater understanding of the pharmacokinetics of therapeutic antibodies has led to the development of new strategies to reduce immunogenicity and more efficient use of these drugs. These preventive strategies include regular scheduled dosing with maintenance of stable therapeutic trough drug concentrations, and co-administration of an immunosuppressive. Sub-therapeutic drug concentrations with low levels of ADAs can generally be overcome with dose escalation, whereas the presence of high concentrations of ADAs requires a switch to another therapeutic agent.

Ketamine and Beyond: Investigations into the Potential of Glutamatergic Agents to Treat Depression

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ABSTRACT

Clinical and preclinical studies suggest that dysfunction of the glutamatergic system is implicated in mood disorders such as major depressive disorder and bipolar depression. In clinical studies of individuals with major depressive disorder and bipolar depression, rapid reductions in depressive symptoms have been observed in response to subanesthetic-dose ketamine, an agent whose mechanism of action involves the modulation of glutamatergic signaling. The findings from these studies have prompted the repurposing and/or development of other glutamatergic modulators for antidepressant efficacy, both as monotherapy or as an adjunct to conventional monoaminergic antidepressants. This review highlights the evidence supporting the antidepressant effects of subanesthetic-dose ketamine as well as other glutamatergic modulators, such as d-cycloserine, riluzole, CP-101,606, CERC-301 (previously known as MK-0657), basimglurant, JNJ-40411813, dextromethorphan, nitrous oxide, GLYX-13, and esketamine.

Abuse and Misuse of Pregabalin and Gabapentin

Kirk E. Evoy, Megan D. MorrisonStephen R. Saklad

ABSTRACT

Background: Gabapentinoid (pregabalin and gabapentin) abuse is increasingly being reported.

Objective: To assess the extent of gabapentinoid abuse, characteristics of typical abusers, patterns of abuse, and potential harms in order to bring this trend to providers' attention.

Methods: A systematic review of MEDLINE, Cochrane Library, ClinicalTrials.gov, and US FDA data, indexed through 28 July 2016, utilizing the following searches: pregabalin OR gabapentin OR gabapentinoid AND one of the following: abuse, misuse, overdose, or substance-related disorders[MESH], was conducted. Additional studies were identified through review of references. English-language epidemiological studies, clinical studies, and case reports/series of gabapentinoid abuse/misuse/overdose were included. The authors reached consensus regarding study inclusion after full-text review. The body of literature was assessed for bias qualitatively.

Results: Fifty-nine studies were included in this systematic review (24 epidemiological, three clinical abuse liability, 16 abuse/misuse/dependence case reports/series, 17 acute overdose case reports/series—one included both an epidemiological study and case series and was included in both counts). Analysis of these studies indicates increasing numbers of patients are self-administering higher than recommended doses to achieve euphoric highs. In the general population, a 1.6% prevalence of gabapentinoid abuse was observed, whereas prevalence ranged from 3% to 68% among opioid abusers. An international adverse event database identified 11,940 reports of gabapentinoid abuse from 2004–2015, with >75% reported since 2012. Risk factors include a history of substance abuse, particularly opioids, and psychiatric co-morbidities. While effects of excessively high doses are generally non-lethal, gabapentinoids are increasingly being identified in post-mortem toxicology analyses.

Conclusion: Evidence suggests gabapentinoids possess potential for abuse, particularly in individuals with a history of opioid abuse, and reports of such abuse are increasingly being documented. Prescribers should be aware of high-risk populations and monitor for signs of abuse.

Outcomes Associated with Generic Drugs Approved Using Product-Specific Determinations of Therapeutic Equivalence

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ABSTRACT

Objective: We sought to examine rates of clinical outcomes among patients before and after market introduction of generic versions of five drugs approved using product-specific equivalence determinations.

Methods: We used data from a large national insurer to identify patients who initiated a study (acarbose tablets, salmon calcitonin nasal spray, enoxaparin injection, vancomycin capsules, venlafaxine extended-release tablets) or control drug (nateglinide, glimepiride, alendronate, fondaparinux, metronidazole, sertraline, paroxetine) in each calendar month between 2003 and 2012 and to determine rates of claims-based proxies for lack of effectiveness outcomes following initiation. We used segmented time-series analyses to evaluate level (short-term) and slope (longer-term) changes in outcomes upon introduction of a generic study or control drug.

Results: Among study drugs, we observed three increases (one with $p < 0.05$) and three decreases (two with $p < 0.05$) in the level of outcome rates. All changes in slope indicated decreases in outcomes from the brand-only to the generic period; four had $p < 0.05$. For control drugs, we observed positive level changes for eight of nine drug-outcome pairs; two had $p < 0.05$. We observed negative slope changes for eight out of nine pairs; six had $p < 0.05$. We observed a significant increase in level change following the introduction of generic bupropion versions that were later found to be not bioequivalent ($p < 0.01$).

Conclusions: We did not find evidence that introduction of generic drugs approved using product-specific therapeutic equivalence determinations was associated with worse clinical outcomes than those among initiators of the brand-name versions of the same products. We observed similar patterns for control drugs.

Nusinersen: First Global Approval

Sheridan M. Hoy

ABSTRACT

Spinal muscular atrophy (SMA) is a rare autosomal recessive disorder characterized by muscle atrophy and weakness resulting from motor neuron degeneration in the spinal cord and brainstem. It is most commonly caused by insufficient levels of survival motor neuron (SMN) protein (which is critical for motor neuron maintenance) secondary to deletions or mutations in the SMN1 gene. Nusinersen (SPINRAZA™) is a modified antisense oligonucleotide that binds to a specific sequence in the intron, downstream of exon 7 on the pre-messenger ribonucleic acid (pre-mRNA) of the SMN2 gene. This modulates the splicing of the SMN2 mRNA transcript to include exon 7, thereby increasing the production of full-length SMN protein. Nusinersen is approved in the USA for intrathecal use in paediatric and adult patients with SMA. Regulatory assessments for nusinersen as a treatment for SMA are underway in the EU and several other countries. This article summarizes the milestones in the development of nusinersen leading to this first approval for SMA in paediatric and adult patients.

Brentuximab Vedotin: A Review in CD30-Positive Hodgkin Lymphoma

Lesley J. Scott

ABSTRACT

Intravenous brentuximab vedotin (ADCETRIS®) is a targeted antibody-drug conjugate (ADC) active against CD30-positive cancer cells such as those associated with classical Hodgkin lymphoma (HL). In noncomparative, phase 2 trials and in the real-world setting, salvage therapy with brentuximab vedotin resulted in high objective response (complete plus partial remission) rates in patients with relapsed or refractory CD30-positive HL, including as retreatment in patients who had an objective response to previous brentuximab vedotin therapy and subsequently relapsed. These beneficial outcomes were durable during long-term follow-up. As consolidation therapy after autologous haematopoietic stem cell transplant (ASCT) in the multinational, phase 3 AETHERA trial, brentuximab vedotin prolonged progression-free-survival (PFS) compared with placebo at a median follow-up of 30 months (primary analysis), with a 43% reduction in the risk of disease progression or death. The beneficial effects of brentuximab vedotin consolidation therapy were maintained during long-term follow-up. In the clinical trial and real-world setting, brentuximab vedotin had an acceptable tolerability and safety profile, with most adverse events manageable with dose reductions and/or delays [including peripheral sensory neuropathy (PSN) and neutropenia]. With a paucity of treatments available for many patients with relapsed or refractory HL, brentuximab vedotin represents an important option for the management of patients who have failed high-dose chemotherapy/ASCT or at least two prior chemotherapy regimens and as post-ASCT consolidation therapy in patients who are at increased risk/high-risk of relapse or progression after ASCT.

Daclizumab: A Review in Relapsing Multiple Sclerosis

Matt Shirley

ABSTRACT

Daclizumab (Zinbryta®; previously known as daclizumab high-yield process) is a therapeutic monoclonal antibody that has recently been approved for the treatment of relapsing forms of multiple sclerosis (MS) in adults. Daclizumab is a humanized IgG1 monoclonal antibody directed against CD25, the alpha subunit of the high-affinity interleukin-2 receptor. As demonstrated in the phase III DECIDE trial, once-monthly subcutaneous daclizumab was superior to once-weekly intramuscular interferon (IFN) β-1a in reducing the clinical relapse rate and radiological measures of disease in patients with relapsing-remitting MS. In addition, daclizumab has demonstrated efficacy in reducing disability progression and in improving health-related quality of life in patients with relapsing MS. Ongoing open-label clinical trials indicate that daclizumab's efficacy is maintained in the longer term (3 years or more). Daclizumab appears to be generally well tolerated, with adverse events of interest (including hepatic, infectious and cutaneous events) generally manageable with regular monitoring and/or standard therapies. The place of daclizumab in MS treatment remains to be fully determined. However, based on available evidence, daclizumab provides a useful alternative option to other currently available disease-modifying therapies in the treatment of relapsing MS.

Apremilast: A Review in Psoriasis and Psoriatic Arthritis

Gillian M. Keating

ABSTRACT

Apremilast (Otezla®) is an orally administered, small molecule inhibitor of phosphodiesterase 4 (PDE4). Apremilast 30 mg twice daily reduced the severity of moderate to severe plaque psoriasis in the phase 3 ESTEEM trials, as well as improving difficult-to-treat nail, scalp and palmoplantar psoriasis. Most patient-reported outcomes, including pruritus and the total Dermatology Life Quality Index, also improved to a significantly greater extent with apremilast than with placebo, with significant improvements in pruritus and skin discomfort/pain visual analogue scale scores seen as early as week 2 with apremilast. Apremilast 30 mg twice daily improved signs and symptoms in both disease-modifying antirheumatic drug (DMARD)-naïve and DMARD-experienced patients with active psoriatic arthritis in the phase 3 PALACE trials. Enthesitis, dactylitis, physical function and fatigue were also improved with apremilast, and its efficacy was sustained for up to 208 weeks. Apremilast had an early onset of efficacy in patients with active psoriatic arthritis, with significantly more apremilast 30 mg twice daily than placebo recipients achieving a ≥20% improvement in modified American College of Rheumatology response criteria at week 2 in the phase 3b ACTIVE trial. Apremilast was generally well tolerated in patients with psoriasis and psoriatic arthritis; no laboratory monitoring is required. In conclusion, orally administered apremilast is an effective, generally well tolerated and convenient option for the treatment of psoriasis and psoriatic arthritis.

Volume 77, Issue 05, April 2017

Therapeutic Options in Refractory Diabetic Macular Oedema

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ABSTRACT

Diabetic macular oedema (DMO) results from alterations of several biochemical pathways in diabetic eyes. Centre-involving DMO is an important cause of visual loss in diabetes. Anti-vascular endothelial growth factor agents are now the mainstay of centre-involving DMO treatment. Oedema that does not achieve optimal response to these agents occurs in a sizeable proportion of eyes and is called refractory or persistent DMO. Management of refractory DMO is challenging. In this paper, the pathophysiology of DMO, and the definitions used in various studies are summarised. Therapeutic options for refractory DMO management including corticosteroids, laser, combination therapies, and surgery are explored. Novel agents on the horizon for DMO control that are being investigated at present are discussed as well. A literature review was performed and a summary of the research studies for each of the agents is provided in order to guide the reader regarding the existing evidence for their application in DMO. Importance of early recognition of disease and prompt treatment to achieve best visual outcome is discussed. Utility of optical coherence tomography to guide disease diagnosis and monitoring is highlighted. An algorithmic approach for DMO management is described. Finally, the impact that personalized medicine and genetics might have on DMO management is assessed.

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs) in the Brain–Adipocyte Axis

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ABSTRACT

The complexity of neural circuits that control food intake and energy balance in the hypothalamic nuclei explains some of the constraints involved in the prevention and treatment of obesity. Two major neuronal populations present in the arcuate nucleus control caloric intake and energy expenditure: one population co-expresses orexigenic agouti-related peptide (AgRP) and neuropeptide Y and the other expresses the anorexigenic anorectic neuropeptides proopiomelanocortin and cocaine- and amphetamine-regulated transcript (POMC/CART). In addition to integrating signals from neurotransmitters and hormones, the hypothalamic systems that regulate energy homeostasis are affected by nutrients. Fat-rich diets, for instance, elicit hypothalamic inflammation (reactive activation and proliferation of microglia, a condition named gliosis). This process generates resistance to the anorexigenic hormones leptin and insulin, contributing to the genesis of obesity. Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) have increasingly been used to treat type 2 diabetes mellitus. One compound (liraglutide) was recently approved for the treatment of obesity. Although most studies suggest that GLP-1RAs promote weight loss mainly due to their inhibitory effect on food intake, other central effects that have been described for native GLP-1 and some GLP-1RAs in rodents and humans encourage future clinical trials to explore additional mechanisms that potentially underlie the beneficial effects observed with this drug class. In this article we review the most relevant data exploring the mechanisms involved in the effects of GLP-1RAs in the brain–adipocyte axis.

Immunomodulatory Drugs in Multiple Myeloma: Mechanisms of Action and Clinical Experience

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ABSTRACT

Over the last two decades, the outcomes for patients with multiple myeloma, a plasma cell malignancy, have dramatically improved. The development of the immunomodulatory drugs (IMiDs), which include thalidomide, lenalidomide, and pomalidomide, has contributed significantly to these improved outcomes. While thalidomide is now less commonly prescribed, lenalidomide is widely used in the treatment of newly diagnosed transplant-eligible and transplant-ineligible patients, in the maintenance setting post-transplant and in the relapsed/refractory setting, while pomalidomide is currently utilized in the relapsed/refractory setting. The IMiDs have been reported to have a multitude of activities, including anti-angiogenic, cytotoxic, and immunomodulatory. However, the more recent discoveries that the IMiDs bind to cereblon and thus regulate the ubiquitination of key transcription factors including IKZF1 and IKZF3 have provided greater insight into their mechanism of action. Here, the clinical efficacy of these agents in myeloma is reviewed and the structure-function relationship, the molecular mechanisms of action, and the association of IMiDs with second primary malignancies and thrombosis are discussed.

JAK–STAT Signaling as a Target for Inflammatory and Autoimmune Diseases: Current and Future Prospects

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ABSTRACT

The Janus kinase/signal transduction and activator of transcription (JAK–STAT) signaling pathway is implicated in the pathogenesis of inflammatory and autoimmune diseases including rheumatoid arthritis, psoriasis, and inflammatory bowel disease. Many cytokines involved in the pathogenesis of autoimmune and inflammatory diseases use JAKs and STATs to transduce intracellular signals. Mutations in JAK and STAT genes cause a number of immunodeficiency syndromes, and polymorphisms in these genes are associated with autoimmune diseases. The success of small-molecule JAK inhibitors (Jakinibs) in the treatment of rheumatologic disease demonstrates that intracellular signaling pathways can be targeted therapeutically to treat autoimmunity. Tofacitinib, the first rheumatologic Jakinib, is US Food and Drug Administration (FDA) approved for rheumatoid arthritis and is currently under investigation for other autoimmune diseases. Many other Jakinibs are in preclinical development or in various phases of clinical trials. This review describes the JAK–STAT pathway, outlines its role in autoimmunity, and explains the rationale/pre-clinical evidence for targeting JAK–STAT signaling. The safety and clinical efficacy of the Jakinibs are reviewed, starting with the FDA-approved Jakinib tofacitinib, and continuing on to next-generation Jakinibs. Recent and ongoing studies are emphasized, with a focus on emerging indications for JAK inhibition and novel mechanisms of JAK–STAT signaling blockade.

The Safety of Appropriate Use of Over-the-Counter Proton Pump Inhibitors: An Evidence-Based Review and Delphi Consensus

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ABSTRACT

The availability of over-the-counter (OTC) proton pump inhibitors (PPIs) for the short-term (2 weeks) management of frequent heartburn (≥2 days/week) has increased markedly, yet evidence-based recommendations have not been developed. A panel of nine international experts in gastroesophageal reflux disease developed consensus statements regarding the risks and benefits of OTC PPIs using a modified Delphi process. Consensus (based on ≥80% approval) was reached through multiple rounds of remote voting and a final round of live voting. To identify relevant data, the available literature was searched and summarized. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system terminology was used to rate the quality of evidence and strength of recommendations; consensus was based on ≥2/3 agreement. After 4 rounds of review, consensus was achieved for 18 statements. Notably, the available data did not directly reflect OTC use, but instead, prescription use; therefore, extrapolations to the OTC setting were often necessary. This limitation is regrettable, but it justifies performing this exercise to provide evidence-based expert opinion on a widely used class of drugs. The panel determined that using OTC PPIs according to label instructions is unlikely to mask the symptoms of esophageal or gastric cancer or adversely impact the natural history of related precursor conditions. OTC PPIs are not expected to substantially affect micronutrient absorption or bone mineral density or cause community-acquired pneumonia, Clostridium difficile infection, or cardiovascular adverse events. However, OTC PPI use may be associated with slightly increased risks for infectious diarrhea, certain idiosyncratic reactions, and cirrhosis-related spontaneous bacterial peritonitis. The available evidence does not suggest that OTC PPI use consistent with label instructions is associated with substantial health risks. To minimize potential risks, healthcare professionals and consumers must actively participate in decision making when managing reflux-related symptoms in the self-care setting.

Delta-9-Tetrahydrocannabinol/Cannabidiol Oromucosal Spray (Sativex®): A Review in Multiple Sclerosis-Related Spasticity

Gillian M. Keating

ABSTRACT

Delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray (THC/CBD, Sativex®, nabiximols) is available in numerous countries worldwide for the treatment of multiple sclerosis (MS)-related moderate to severe spasticity in patients who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy. Twelve weeks' therapy with THC/CBD improved MS-related spasticity in patients with an inadequate response to other anti-spasticity agents who had undergone a successful initial trial of THC/CBD therapy, according to the results of a pivotal phase 3 trial. Improvements in spasticity were maintained in the longer term with THC/CBD with no evidence of dose tolerance, and results of real-world studies confirm the effectiveness of THC/CBD in everyday clinical practice. Improvements in health-related quality of life and activities of daily living were also seen with THC/CBD. THC/CBD is generally well tolerated; adverse effects such as dizziness may occur whilst the THC/CBD dosage is being optimized. THC/CBD has low abuse potential and a low risk of psychoactive effects. In conclusion, THC/CBD oromucosal spray is a useful option for the treatment of MS-related spasticity not completely relieved with current anti-spasticity medication.

Fluocinolone Acetonide Intravitreal Implant 0.19 mg (ILUVIEN®): A Review in Diabetic Macular Edema

Yahiya Y. Syed

ABSTRACT

Fluocinolone acetonide intravitreal implant 0.19 mg (ILUVIEN®) is a nonbiodegradable, injectable, corticosteroid implant that is approved in several countries, including the USA, for the treatment of diabetic macular edema (DME). ILUVIEN® releases fluocinolone acetonide at an initial rate of 0.25 µg/day (average rate 0.2 µg/day) and lasts 36 months. In the two pooled pivotal FAME trials in patients with DME previously treated with macular laser photocoagulation, fluocinolone acetonide intravitreal implant 0.2 µg/day was significantly more effective than sham injection with respect to the proportion of patients with an improvement from baseline in best-corrected visual acuity of ≥15 letters at 24 months (primary endpoint). This therapeutic effect was maintained at 36 months. The implant also significantly decreased foveal thickness at 24 months. FAME study results are broadly supported by real-world studies in patients with chronic DME considered insufficiently responsive to available therapies. Consistent with corticosteroid class-specific adverse events, cataract and elevated intraocular pressure (IOP) were the most common adverse events with the fluocinolone acetonide intravitreal implant. Raised IOP was treated with medications in most patients, with <5% requiring incisional IOP-lowering surgery. In the USA, fluocinolone acetonide intravitreal implant should be used only in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant increase in IOP. Available data indicate that fluocinolone acetonide intravitreal implant 0.19 mg is a useful option for the treatment of DME in these patients.

Rucaparib: First Global Approval

Yahiya Y. Syed

ABSTRACT

Rucaparib (Rubraca™) is an oral, small molecule, poly (ADP-ribose) polymerase inhibitor being developed by Clovis Oncology, Inc. (Boulder, CO, USA) for the treatment of solid tumours. It has been approved in the USA as monotherapy for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. A marketing authorization application for rucaparib for the same indication has been submitted to the European Medicines Agency. Rucaparib is also under phase II or III investigation in ovarian, breast and prostate cancer. This article summarizes the milestones in the development of rucaparib leading to this first approval for ovarian cancer.

Plecanatide: First Global Approval

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ABSTRACT

Plecanatide (TrulanceTM) is an oral guanylate cyclase-C agonist that is being developed by Synergy Pharmaceuticals for the treatment of gastrointestinal disorders, such as chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C). It is a synthetic analogue of human uroguanylin, a 16 amino acid peptide that regulates ion and fluid transport in the gastrointestinal tract. In January 2017, plecanatide received its first global approval in the USA for the treatment of adult patients with CIC. Plecanatide is undergoing phase III investigation in IBS-C. This article summarizes the milestones in the development of plecanatide leading to this first approval in CIC.

Volume 77, Issue 06, April 2017

Triazole Resistance in Aspergillus Species: An Emerging Problem

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ABSTRACT

Aspergillus species are ubiquitous fungal saprophytes found in diverse ecological niches worldwide. Among them, Aspergillus fumigatus is the most prevalent and is largely responsible for the increased incidence of invasive aspergillosis with high mortality rates in some immunocompromised hosts. Azoles are the first-line drugs in treating diseases caused by Aspergillus spp. However, increasing reports in A. fumigatus azole resistance, both in the clinical setting and in the environment, are threatening the effectiveness of clinical and agricultural azole drugs. The azole target is the 14-α sterol demethylase encoded by cyp51A gene and the main mechanisms of resistance involve the integration of tandem repeats in its promoter and/or single point mutations in this gene. In A. fumigatus, azole resistance can emerge in two different scenarios: a medical route in which azole resistance is generated during long periods of azole treatment in the clinical setting and a route of resistance derived from environmental origin due to extended use of demethylation inhibitors in agriculture. The understanding of A. fumigatus azole resistance development and its evolution is needed in order to prevent or minimize its impact. In this article, we review the current situation of azole resistance epidemiology and the predominant molecular mechanisms described based on the resistance acquisition routes. In addition, the clinical implications of A. fumigatus azole resistance and future research are discussed.

Novel Beta-Lactamase Inhibitors: Unlocking Their Potential in Therapy

Darren WongDavid van Duin

ABSTRACT

Carbapenem-resistant Enterobacteriaceae are amongst the most feared pathogens due to severely limited treatment options. In response to this threat, three novel β-lactamase inhibitors have been developed in an attempt to reinvigorate and sustain our current antimicrobial therapies. Avibactam, vaborbactam, and relebactam are inhibitor agents with high affinity to Ambler class A and C β-lactamases and favorable outcomes in current clinical trials. However, although they do possess key similarities, these agents have unique differences which may have important clinical implications. The microbiologic spectrum, pharmacokinetics, and key clinical trials for each of these novel agents are reviewed. A proposed role in therapy and potential novel combinations are examined.

Options for Treating Pain in Cancer Patients with Dysphagia

Sebastiano Mercadante

ABSTRACT

Patients with chronic pain often develop dysphagia during the course of an advanced disease such as cancer. Opioids are the cornerstone of the management of cancer pain and are commonly administered orally. However, the oral route does not suit patients with dysphagia, who require alternative methods to administer analgesic drugs. Opioids given by parenteral or transdermal routes provide adequate pain control, being at least as efficacious as the oral route, but knowledge and experience in conversion ratios are mandatory when using these routes of administration. For breakthrough pain, transmucosal fentanyl preparations should be the preferred option and these can be given as needed due to the route of absorption. In addition, a new class of opioid formulations has been developed for use in dysphagic patients that are administered via nasogastric or enteral tubes while maintaining their sustained-release properties.

Diagnosis and Treatment of Non-24-h Sleep–Wake Disorder in the Blind

Jonathan S. Emens, Charmane I. Eastman

ABSTRACT

Non-24-h sleep–wake disorder (non-24) is a circadian rhythm disorder occurring in 55–70% of totally blind individuals (those lacking conscious light perception) in which the 24-h biological clock (central, hypothalamic, circadian pacemaker) is no longer synchronized, or entrained, to the 24-h day. Instead, the overt rhythms controlled by the biological clock gradually shift progressively earlier or later (free run) in accordance with the clock's near-24-h period, resulting in a recurrent pattern of daytime hypersomnolence and night-time insomnia. Orally administered melatonin and the melatonin agonist tasimelteon have been shown to entrain (synchronize) the circadian clock, resulting in improvements in night-time sleep and daytime alertness. We review the basic principles of circadian rhythms necessary to understand and treat non-24. The time of melatonin or tasimelteon administration must be considered carefully. For most individuals, those with circadian periods longer than 24 h, low-dose melatonin should be administered about 6 h before the desired bedtime, while in a minority, those with circadian periods shorter than 24 h (more commonly female individuals and African–Americans), melatonin should be administered at the desired wake time. Small doses (e.g., 0.5 mg of melatonin) that are not soporific would thus be preferable. Administration of melatonin or tasimelteon at bedtime will entrain individuals with non-24 but at an abnormally late time, resulting in continued problems with sleep and alertness. To date, tasimelteon has only been administered 1 h before the target bedtime in patients with non-24. Issues of cost, dose accuracy, and purity may figure into the decision of whether tasimelteon or melatonin is chosen to treat non-24. However, there are no head-to-head studies comparing efficacy, and studies to date show comparable rates of treatment success (entrainment).

Bringing Stability to the Chronic Obstructive Pulmonary Disease Patient: Clinical and Pharmacological Considerations for Frequent Exacerbators

Swati GulatiJ. Michael Wells

ABSTRACT

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are critical events associated with an accelerated loss of lung function, increased morbidity, and excess mortality. AECOPD are heterogeneous in nature and this may directly impact clinical decision making, specifically in patients with frequent exacerbations. A 'frequent exacerbator' is a sub-phenotype of chronic obstructive pulmonary disease (COPD) and is defined as an individual who experiences two or more moderate-to-severe exacerbations per year. This distinct subgroup has higher mortality and accounts for more than half of COPD-related hospitalizations annually. Thus, it is imperative to identify individuals at risk for frequent exacerbations and choose optimal strategies to minimize risk for these events. New paradigms for using combination inhalers and the introduction of novel oral compounds provide expanded treatment options to reduce the risk and frequency of exacerbations. The goals of managing frequent exacerbators or patients at risk for AECOPD are: (1) maximizing bronchodilation; (2) reducing inflammation; and (3) targeting specific molecular pathways implicated in COPD and AECOPD pathogenesis. Novel inhaler therapies including combination long-acting muscarinic agents plus long-acting beta agonists show promising results compared with monotherapy or a long-acting beta agonist inhaled corticosteroid combination in reducing exacerbation risk among individuals at risk for exacerbations and among frequent exacerbators. Likewise, oral medications including macrolides and phosphodiesterase-4 inhibitors reduce the risk for AECOPD in select groups of individuals at high risk for exacerbation. Future direction in COPD management is based on the identification of various subtypes or 'endotypes' and targeting therapies based on their pathophysiology. This review describes the impact of AECOPD and the challenges posed by frequent exacerbators, and explores the rationale for different pharmacologic approaches to preventing AECOPD in these individuals.

The Language of Biosimilars: Clarification, Definitions, and Regulatory Aspects

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ABSTRACT

Biologic therapies have revolutionized treatment of a number of diseases. Patents and exclusivity for a number of biologics are expiring. This has created the opportunity for the development and approval of biosimilars. Biosimilars are biologic products developed using a step-wise approach to result in a biologic that demonstrates no clinically meaningful differences in terms of quality attributes, efficacy, safety, and immunogenicity compared with an existing licensed, originator biologic. As more biosimilars receive regulatory approval and reach the market, it is increasingly important for healthcare providers to understand the terminology about biosimilars. To help support healthcare providers, the aim of this manuscript is to (i) support understanding of the language of biosimilars, (ii) review the regulatory and manufacturing processes employed in developing a biosimilar, and (iii) provide information for clinical decisions about the use of biosimilars. Because biologics are large, structurally complex proteins, biosimilars cannot be considered generic equivalents to the originator. Biosimilars are developed and evaluated using rigorous processes involving detailed analytical and functional studies, nonclinical assessments, and clinical trials. Clinical studies evaluating the potential biosimilar are designed differently than those for approval of a novel biologic since the aim is merely to confirm similar efficacy and safety and not to demonstrate clinical benefit per se. Extrapolation of data may be used to grant approval of biosimilars in indications not directly evaluated in clinical studies using the biosimilar.

Pediatric Osteoporosis: Diagnosis and Treatment Considerations

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ABSTRACT

Osteoporosis is now increasingly recognized in children due to the increased prevalence of disorders associated with bone loss. Fragility fractures represent the cardinal clinical features of pediatric osteoporosis and children presenting with fragility fractures deserve an accurate assessment to rule out a secondary cause. Indeed, in the pediatric population, a low bone mass is often a consequence of a chronic disease or its treatment; genetic bone disorders represent the cause of only a small fraction of cases. The position statement of the International Society for Clinical Densitometry guides physicians in interpreting densitometric data and making diagnoses of osteoporosis in children. Once a diagnosis of osteoporosis has been made, the aim is to identify children in whom bone status may deteriorate if left untreated. To date, bisphosphonates have represented the mainstay of treatment for pediatric osteoporosis. However, due to the peculiar pathophysiology of osteoporosis in this age group, a pharmacological agent with an anabolic effect on bone may provide clinicians with other therapeutic options in children. Multicenter studies are needed to optimize treatments and define optimal clinical response in treated children.

Baricitinib: First Global Approval

Anthony Markham

ABSTRACT

Baricitinib (Olumiant™) is an orally-administered, small-molecule, janus-associated kinase (JAK) inhibitor developed by Eli Lilly and Incyte Corporation for the treatment of rheumatoid arthritis (RA), atopic dermatitis and systemic lupus erythematosus. JAKs transduce intracellular signals from cell surface receptors for various cytokines and growth factors involved in inflammation and immune function, suggesting JAK inhibitors may be of therapeutic benefit in inflammatory conditions. In February 2017, baricitinib was approved in the EU, as monotherapy or in combination with methotrexate, for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Regulatory approval to market baricitinib as a treatment for RA has also been sought in the USA and Japan. This article summarizes the milestones in the development of baricitinib leading to this first global approval for the treatment for moderate to severe active RA in adult patients who have responded inadequately to, or are intolerant to one or more DMARDs.

Sarilumab: First Global Approval

Lesley J. Scott

ABSTRACT

Sarilumab (Kevzara™) is a fully human IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound interleukin (IL)-6 receptors (sIL-6Rα and mIL-6Rα) and thereby inhibits IL-6-mediated signalling through these receptors. Subcutaneous sarilumab is approved in Canada for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more biological or non-biological disease-modifying anti-rheumatic drugs. It is under regulatory review for use in rheumatoid arthritis in other countries, including in the EU, USA and Japan. Sarilumab is also under phase II investigation for the treatment of juvenile idiopathic arthritis. This article summarizes the milestones in the development of sarilumab leading to its first global approval for the treatment of rheumatoid arthritis.

Progression-Free Survival as a Surrogate for Overall Survival in Clinical Trials of Targeted Therapy in Advanced Solid Tumors

Stefan Michiels, Everardo D. SaadMarc Buyse

ABSTRACT

Over the past 15 years, targeted therapy has revolutionized the systemic treatment of cancer. In parallel, there has been a growing debate on the choice of end points in clinical trials in oncology. This debate basically hinges on the choice between overall survival (OS) and progression-free survival (PFS). PFS is advantageous because it is measured earlier than OS, requires a smaller sample size than OS to achieve the desired power, and is not influenced by cross-over. On the other hand, PFS is prone to measurement error and bias, and may not capture the entire treatment effect on the outcomes of most interest to patients with an incurable disease: a prolonged survival and improved quality of life. Therefore, how can we choose between two imperfect end points? The answer to this question would certainly be made easier if PFS could be demonstrated to be a valid surrogate for OS. The validation of a surrogate end point is best made using individual-patient data (IPD) from randomized trials, which allows for standardized assessments of the patient-level and the trial-level correlations between surrogate and final end points. Proper IPD meta-analytical evaluations for targeted agents have still been rare, and to our knowledge only three studies on this topic are currently available in the metastatic setting: one in breast cancer, one in colorectal cancer and one in lung cancer. Although these three studies suffer from limitations inherent to the availability of IPD and the design of the original clinical trials, they have not been able to validate PFS as surrogate for OS, because only modest correlations were found between these two end points, both at the patient and at the trial level. Even if properly conducted surrogate-endpoint evaluations have thus far been unsuccessful, these evaluations are a step in the right direction and can be expected to be applied on a much larger scale in the era of data sharing of clinical trials.

Management of Chronic Obstructive Pulmonary Disease in Patients with Cardiovascular Diseases

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) and cardiovascular diseases often coexist. The mechanistic links between these two diseases are complex, multifactorial and not entirely understood, but they can influence the therapeutic approach. Therapy can be primarily directed towards treating the respiratory symptoms and reducing lung inflammation. Smoking cessation, bronchodilators and inhaled corticosteroids are central to this therapeutic approach. The underlying pathophysiological mechanisms that are responsible for the increased cardiovascular risk in COPD remain unclear, but might include arterial stiffness, inflammation and endothelial dysfunction as a consequence of systemic exposure to chemicals in cigarette smoke or airborne pollution. Therefore, it is plausible that treatment of cardiovascular co-morbidities might reduce morbidity and mortality in patients with COPD and, consequently, therapy of COPD should be shifted to the treatment of cardiovascular diseases and systemic inflammation. In support of this approach, early data suggest that patients with COPD treated with angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor blockers, statins, anti-platelet drugs or β-adrenoceptor blockers may have improved survival and reduced hospitalisation from acute exacerbations of COPD. In this review, the potential impact of traditional therapies for COPD that are centred on treating the lungs and newer strategies potentially able to affect and mitigate cardiovascular risks in patients with COPD are discussed.

The Treatment of Advanced Thyroid Cancer in the Age of Novel Targeted Therapies

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ABSTRACT

Until recently, patients with advanced thyroid cancers had limited options for systemic treatment. With the introduction of tyrosine kinase inhibitors (TKIs) as a promising new class of targeted therapies for thyroid cancer, suddenly patients with advanced disease were given new options to extend survival. Guidelines worldwide have been updated to include general indications for these newer agents, but questions remain regarding which agent(s) to select, when to begin treatment, and how long therapy should continue. Additionally, the true impact of TKIs on overall survival and quality-of-life in thyroid cancer patients needs further clarification. As familiarity with approved agents and longer-term data become available, better strategies for implementation of these targeted drugs will evolve to optimize benefit for patients living with metastatic disease.

Fentanyl Formulations in the Management of Pain: An Update

Stephan A. Schug, Sonya Ting

ABSTRACT

Fentanyl is a synthetic, highly selective opioid with many desirable physicochemical properties, including a high lipophilicity and predictable pharmacokinetics. These properties have an established record in the management of pain in a variety of settings, particularly acute pain and breakthrough cancer pain. Fentanyl was initially developed for parenteral use; however, this is invasive and impractical in the outpatient setting. Unfortunately, the high first-pass metabolism of fentanyl makes oral formulations unfeasible. However, its high lipophilicity allows fentanyl to be absorbed via a number of other routes. Thus new formulations were designed to allow non-invasive methods of administration. Transmucosal and transdermal fentanyl formulations are well established, and have proven useful in the settings of breakthrough cancer pain, emergencies and in the paediatric population. The iontophoretic transdermal system was developed to provide a needle-free system of delivering bolus doses of fentanyl on demand, a novel way of delivering patient-controlled opioid analgesia. Transpulmonary administration of fentanyl remains experimental. The aim of this review is to provide an update on current non-parenteral fentanyl formulations, with attention to their particular pharmacokinetics and features relevant to clinical use in pain management.

Reslizumab in Eosinophilic Asthma: A Review

Emma D. Deeks, Guy Brusselle

ABSTRACT

Reslizumab (Cinqaero®; Cinqair®) is a humanized monoclonal antibody against interleukin-5 (IL-5), a cytokine mediator of eosinophilic airway inflammation. Reslizumab is indicated as an add-on treatment for severe eosinophilic asthma in adults, on the basis of data from the BREATH phase III clinical trial programme. In three double-blind BREATH studies of up to 52 weeks' duration, adding intravenous reslizumab (3 mg/kg, once every 4 weeks) to the current asthma therapy of patients (aged 12–75 years) with eosinophilic asthma inadequately controlled with inhaled corticosteroids resulted in significant reductions in clinical asthma exacerbation frequency and significant improvements in lung function, asthma control and health-related quality of life relative to adding placebo. Pooled data from the two trials of 52 weeks' duration indicated similar benefits with reslizumab across various patient subgroups, including patients with severe eosinophilic asthma. Reslizumab was generally well tolerated, with very few recipients experiencing severe or serious treatment-related adverse events. Moreover, in an open-label extension study, continued use of reslizumab for up to 2 years was associated with durable lung function benefit, without any new tolerability concerns. Thus, intravenous reslizumab extends the valuable add-on treatment options for adults with severe eosinophilic asthma inadequately controlled with standard therapies.

Efficacy and Safety of Quinolone-Containing Rescue Therapies after the Failure of Non-Bismuth Quadruple Treatments for Helicobacter pylori Eradication: Systematic Review and Meta-Analysis

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ABSTRACT

Background: Anti-Helicobacter pylori eradication treatment fails in a significant percentage of cases. Although this percentage has been reduced to 5–15% with the use of non-bismuth quadruple therapies, limited data exist regarding rescue after failure of these treatments.

Aim: The aim of this study was to systematically review the efficacy and safety of quinolone-containing therapies after the failure of non-bismuth quadruple regimens.

Methods: Studies evaluating the efficacy of second-line quinolone-containing therapies after the failure of non-bismuth sequential or concomitant regimens were selected. Efficacy (by intention to treat) was analyzed using the inverse variance method; safety data were recorded as the occurrence of any adverse event. The risk of bias of each primary study was evaluated using the Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I) tool. The quality of the evidence was summarized using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.

Results: Sixteen studies were included. The 10-day levofloxacin/amoxicillin/proton pump inhibitor (PPI) triple therapy (LT) achieved eradication rates of 80% (95% CI 71–88). Regarding the moxifloxacin/amoxicillin/PPI triple therapy (MT), its efficacy was higher when administered for 14 days instead of 7 days (80 vs 63%). Two studies investigated the levofloxacin/bismuth-containing quadruple therapies (LBQ) obtaining eradication rates over 90%. Safety was similar in all treatments. The sensitivity analyses showed that results for LT were robust, but MT had weak evidence.

Conclusions: Quinolone-containing triple therapies reported eradication rates ≤80%, but LBQ therapies showed encouraging rates. However, the strength of the evidence was very low. The efficacy of LBQ should be corroborated in more studies, and the usefulness of quinolones needs to be evaluated in areas with moderate to high bacterial resistances.

Liposomal Irinotecan: A Review in Metastatic Pancreatic Adenocarcinoma

Yvette N. Lamb, Lesley J. Scott

ABSTRACT

Intravenous liposomal irinotecan injection (Onivyde®) is approved for use in combination with 5-fluorouracil and leucovorin (5-FU/LV) in patients with metastatic pancreatic adenocarcinoma that has progressed following gemcitabine-based therapy. Liposomal irinotecan is a liposome-encapsulated formulation of the topoisomerase-1 inhibitor irinotecan, developed to overcome the pharmacological and clinical limitations of non-liposomal irinotecan. In the pivotal multinational, phase III NAPOLI-1 trial in patients with metastatic pancreatic adenocarcinoma that had progressed following gemcitabine-based therapy, liposomal irinotecan in combination with 5-FU/LV significantly prolonged median overall survival (OS; primary endpoint) and median progression-free survival (PFS) at the time of the primary analysis (after 313 events) and final analysis (after 382 events) compared with 5-FU/LV control therapy. The objective response rate was also significantly higher in the liposomal irinotecan plus 5-FU/LV group than in the control group. Liposomal irinotecan-based combination therapy had a manageable safety profile; the most common treatment-emergent adverse events (TEAEs) of grade ≥3 severity were haematological or gastrointestinal in nature. The incidence of neutropenic sepsis was low. In a setting where there is a paucity of second-line treatment options, liposomal irinotecan in combination with 5-FU/LV is an important emerging treatment option for metastatic adenocarcinoma of the pancreas that has progressed following gemcitabine-based therapy.

Telotristat Ethyl: First Global Approval

Anthony Markham

ABSTRACT

Telotristat ethyl (Xermelo™) is a peripheral tryptophan hydroxylase (TPH) inhibitor that was developed by Lexicon Pharmaceuticals, Inc. for the treatment of carcinoid syndrome. Many neuroendocrine tumours secrete serotonin (5-HT) into the blood stream, resulting in a number of symptoms, notably diarrhoea. Telotristat ethyl inhibits TPH, thereby reducing the production of 5-HT. In February 2017, telotristat ethyl was approved in the USA for the treatment of carcinoid syndrome diarrhoea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy. This article summarizes the milestones in the development of telotristat ethyl leading to this first global approval.

Ribociclib: First Global Approval

Yahiya Y. Syed

ABSTRACT

Ribociclib is an oral, small-molecule inhibitor of cyclin-dependent kinase (CDK) 4 and 6 that is under development by Novartis for the treatment of cancer. CDKs play an important role in cell cycle progression and cellular proliferation, and inhibition of these kinases with ribociclib results in G1 phase cell-cycle arrest. Ribociclib, in combination with an aromatase inhibitor, was recently approved in the USA for the first-line treatment of advanced breast cancer and has been submitted for approval in the EU for this indication. Ribociclib is undergoing further phase III investigations in breast cancer and is being evaluated in phase I or II trials for various solid tumour types and haematological malignancies. This article summarizes the milestones in the development of ribociclib leading to this first global approval for use as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer.

Volume 77, Issue 08, May 2017

Medical Expulsive Therapy: Is It Time to SUSPEND Judgement

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ABSTRACT

Medical expulsive therapy (MET) has been a matter of debate for many years. A number of randomised controlled trials (RCTs) and meta-analyses have been conducted, but outcomes have been varied. This makes it challenging to determine the benefit of using MET as an adjunct in patients with expectantly managed ureteric stones. This article aimed to summarize both the historic and the more contemporary literature in this area by focusing on published meta-analyses and recent RCTs. Studies of interest were those comparing either an α-blocker or a calcium channel blocker with a control. Outcome measures of interest were expulsion rates, expulsion times, and medication-related side effects. All systematic reviews included are in favour of MET versus controls. However, many of the component RCTs had limitations such as a high risk of bias, incomplete blinding and heterogeneous inclusion criteria. A recent well-powered RCT found no benefit of MET for the purpose of conservatively managed ureteric stones. This study had some limitations that stimulated further research in the area, adding to the uncertainty. The most recent RCT and meta-analysis indicates MET is more beneficial in both larger (>5 mm) and distal stones. Uncertainty remains in this arena, and there is a need for a robust multi-institution study to assess MET in a cohort of patients who are expectantly managed with ureteric stones. This should serve to counter the marked heterogeneity and limitations of existing trials and meta-analyses.

Advances in the Development of Molecularly Targeted Agents in Non-Small-Cell Lung Cancer

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ABSTRACT

Non-small-cell lung cancer (NSCLC) remains a significant global health challenge and the leading cause of cancer-related mortality. The traditional 'one-size-fits-all' treatment approach has now evolved into one that involves personalized strategies based on histological and molecular subtypes. The molecular era has revolutionized the treatment of patients harboring epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and ROS1 gene aberrations. In the appropriately selected population, anti-tumor agents against these molecular targets can significantly improve progression-free survival. However, the emergence of acquired resistance is inevitable. Novel potent compounds with much improved and rational selectivity profiles, such as third-generation EGFR T790M resistance mutation-specific inhibitors, have been developed and added to the NSCLC armamentarium. To date, attempts to overcome resistance bypass pathways through downstream signaling blockade has had limited success. Furthermore, the majority of patients still do not harbor known driver genetic or epigenetic alterations and/or have no new available treatment options, with chemotherapy remaining their standard of care. Several potentially actionable driver aberrations have recently been identified, with the early clinical development of multiple inhibitors against these promising targets currently in progress. The advent of immune checkpoint inhibitors has led to significant benefit for advanced NSCLC patients with durable responses observed. Further interrogation of the underlying biology of NSCLC, coupled with modern clinical trial designs, is now required to develop novel targeted therapeutics rationally matched with predictive biomarkers of response, so as to further advance NSCLC therapeutics through the next decade.

Psychiatric Symptoms in Patients with Cushing's Syndrome: Prevalence, Diagnosis and Management

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ABSTRACT

Cushing's syndrome (CS) results from chronic exposure to cortisol excess, produced by the adrenal cortex. Hypercortisolism predisposes to psychiatric and neurocognitive disorders, mainly to depression and anxiety disorders. Screening tools to identify psychiatric symptoms are available for clinicians in their daily practice, although a specific diagnosis should be performed by specialists. Even if psychiatric symptoms improve after remission of hypercortisolism, complete recovery may not be achieved. Given the burden of these symptoms, psychiatric or psychological monitoring and treatment should be offered through all phases of CS, with a multidisciplinary approach. The aim of this article is to review data on the prevalence, diagnosis and management of psychiatric symptoms seen in patients with CS and to propose therapeutic approaches that may be followed in clinical practice. The prevalence of different psychiatric disorders has been described in both the active phase and after CS remission. Patients may not talk spontaneously about psychiatric symptoms they present, thus clinicians should ask directly about them. We recommend the use of screening tools in clinical practice to detect and treat these symptoms promptly. Even if reference endocrinologists cannot perform a definite psychiatric diagnosis, it will be important to ask patients directly about the presence of symptoms and refer if necessary to a psychiatrist. Additionally, patient information and educational programmes could be useful to manage psychiatric symptoms and to improve quality of life in patients with CS.

Targeted Therapy in Head and Neck Cancer: An Update on Current Clinical Developments in Epidermal Growth Factor Receptor-Targeted Therapy and Immunotherapies

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ABSTRACT

Most patients diagnosed with head and neck squamous cell carcinoma (HNSCC) will present with locally advanced disease, requiring multimodality therapy. Despite this curative approach, a significant subset of these patients will develop locoregional failure and/or distant metastases. Despite significant progress in the treatment and subsequent prognosis of locally advanced HNSCC, the prognosis of those patients with recurrent and/or metastatic (R/M) HNSCC is poor, with short-lived responses to palliative chemotherapy and few therapeutic agents available. The discovery of the integral role of epidermal growth factor receptor overexpression in the pathogenesis of HNSCC, coupled with emerging data on the role of tumor evasion of the immune system, has opened new pathways in the development of novel therapeutic agents for the treatment of R/M HNSCC. As a result, cetuximab, a monoclonal antibody targeting epidermal growth factor receptor, as well as pembrolizumab and nivolumab, monoclonal antibodies targeting programmed cell death 1 (PD-1), are now US Food and Drug Administration approved for the treatment of R/M HNSCC. This review will detail the data supporting the use of these agents, as well as clinical trials evaluating the efficacy of other novel and promising drugs.

Clinical Implications of P-Glycoprotein Modulation in Drug–Drug Interactions

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ABSTRACT

Drug–drug interactions (DDIs) occur commonly and may lead to severe adverse drug reactions if not handled appropriately. Considerable information to support clinical decision making regarding potential DDIs is available in the literature and through various systems providing electronic decision support for healthcare providers. The challenge for the prescribing physician lies in sorting out the evidence and identifying those drugs for which potential interactions are likely to become clinically manifest. P-glycoprotein (P-gp) is a drug transporting protein that is found in the plasma membranes in cells of barrier and elimination organs, and plays a role in drug absorption and excretion. Increasingly, P-gp has been acknowledged as an important player in potential DDIs and a growing body of information on the role of this transporter in DDIs has become available from research and from the drug approval process. This has led to a clear need for a comprehensive review of P-gp-mediated DDIs with a focus on highlighting the drugs that are likely to lead to clinically relevant DDIs. The objective of this review is to provide information for identifying and interpreting evidence of P-gp-mediated DDIs and to suggest a classification for individual drugs based on both in vitro and in vivo evidence (substrates, inhibitors and inducers). Further, various ways of handling potential DDIs in clinical practice are described and exemplified in relation to drugs interfering with P-gp.

Pharmacological Approaches to the Management of Secondary Progressive Multiple Sclerosis

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ABSTRACT

It is well recognised that the majority of the impact of multiple sclerosis (MS), both personal and societal, arises in the progressive phase where disability accumulates inexorably. As such, progressive MS (PMS) has been the target of pharmacological therapies for many years. However, there are no current licensed treatments for PMS. This stands in marked contrast to relapsing remitting MS (RRMS) where trials have resulted in numerous licensed therapies. PMS has proven to be a more difficult challenge compared to RRMS and this review focuses on secondary progressive MS (SPMS), where relapses occur before the onset of gradual, irreversible disability, and not primary progressive MS where disability accumulation occurs without prior relapses. Although there are similarities between the two forms, in both cases pinpointing when PMS starts is difficult in a condition in which disability can vary from day to day. There is also an overlap between the pathology of relapsing and progressive MS and this has contributed to the lack of well-defined outcomes, both surrogates and clinically relevant outcomes in PMS. In this review, we used the search term 'randomised controlled clinical drug trials in secondary progressive MS' in publications since 1988 together with recently completed trials where results were available. We found 34 trials involving 21 different molecules, of which 38% were successful in reaching their primary outcome. In general, the trials were well designed (e.g. double blind) with sample sizes ranging from 35 to 1949 subjects. The majority were parallel group, but there were also multi-arm and multidose trials as well as the more recent use of adaptive designs. The disability outcome most commonly used was the Expanded Disability Status Scale (EDSS) in all phases, but also magnetic resonance imaging (MRI)-measured brain atrophy has been utilised as a surrogate endpoint in phase II studies. The majority of the treatments tested in SPMS over the years were initially successful in RRMS. This has a number of implications in terms of targeting SPMS, but principally implies that the optimal strategy to target SPMS is to utilise the prodrome of relapses to initiate a therapy that will aim to both prevent progression and slow its accumulation. This approach is in agreement with the early targeting of MS but requires treatments that are both effective and safe if it is to be used before disability is a major problem. Recent successes will hopefully result in the first licensed therapy for PMS and enable us to test this approach.

Elbasvir/Grazoprevir: A Review in Chronic HCV Genotypes 1 and 4

Zaina T. Al-Salama, Emma D. Deeks

ABSTRACT

A fixed-dose combination tablet comprising the hepatitis C virus (HCV) NS5A inhibitor elbasvir and the HCV NS3/4A protease inhibitor grazoprevir (elbasvir/grazoprevir; Zepatier™) was recently approved for the treatment of chronic HCV genotype 1 and 4 infection in the EU and the USA. In phase III trials, 12 or 16 weeks of treatment with once-daily elbasvir/grazoprevir (fixed-dose tablet or as individual agents), taken with or without ribavirin, generally provided high rates of sustained virological response at 12 weeks (SVR12) in treatment-naive and -experienced adult patients with chronic HCV genotype 1a, 1b or 4 infection, including those with or without compensated cirrhosis, HIV co-infection, inherited blood disorders or chronic kidney disease or patients receiving opioid agonist therapy or of Japanese origin. Elbasvir/grazoprevir was generally well tolerated. Thus, elbasvir/grazoprevir, with or without ribavirin, represents an effective new option for the treatment of adults with chronic HCV genotype 1 and 4 infection, including a number of difficult-to-treat populations.

Avelumab: First Global Approval

Esther S. Kim

ABSTRACT

Avelumab (Bavencio®) is an intravenously administered programmed cell death ligand-1-blocking human antibody initially developed by EMD Serono Inc. (the biopharmaceutical division of Merck KGaA, Darmstadt, Germany) [now jointly developed and commercialized by EMD Serono Inc. and Pfizer] for the treatment of various tumours. It has received accelerated approval in the USA for the treatment of metastatic Merkel cell carcinoma (mMCC) in adults and paediatric patients aged ≥12 years. The marketing authorization application for avelumab in the treatment of mMCC is undergoing regulatory review in the EU, the biologics license application for avelumab in the treatment of urothelial carcinoma is undergoing priority review by the FDA, and avelumab is in various stages of development internationally for a variety of cancers. This article summarizes the milestones in the development of avelumab leading to this first approval for mMCC.

Volume 77, Issue 09, June 2017

The Potential Role of Fosfomycin in Neonatal Sepsis Caused by Multidrug-Resistant Bacteria

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ABSTRACT

The broad-spectrum activity of fosfomycin, including against multidrug-resistant (MDR) strains, has led to renewed interest in its use in recent years. Neonatal sepsis remains a substantial cause of morbidity and mortality at a global level, with evidence that MDR bacteria play an increasing role. The evidence for use of fosfomycin in neonatal subjects is limited. We summarise current knowledge of the pharmacokinetics and clinical outcomes for the use of fosfomycin in neonatal sepsis and issues specific to neonatal physiology. While fosfomycin has a broad range of coverage, we evaluate the extent to which it may be effective against MDR bacteria in a neonatal setting, in light of recent evidence suggesting it to be most effective when administered in combination with other antibiotics. Given the urgency of clinical demand for treatment of MDR bacterial sepsis, we outline directions for further work, including the need for future clinical trials in this at-risk population.

Pharmacotherapeutic Targeting of G Protein-Coupled Receptors in Oncology: Examples of Approved Therapies and Emerging Concepts

Rosamaria Lappano, Marcello Maggiolini

ABSTRACT

G protein-coupled receptors (GPCRs) are involved in numerous physio-pathological processes, including the stimulation of cancer progression. In this regard, it should be mentioned that although GPCRs may represent major pharmaceutical targets, only a few drugs acting as GPCR inhibitors are currently used in anti-tumor therapies. For instance, certain pro-malignancy effects mediated by GPCRs are actually counteracted by the use of small molecules and peptides that function as receptor antagonists or inverse agonists. Recently, humanized monoclonal antibodies targeting GPCRs have also been developed. Here, we review the current GPCR-targeted therapies for cancer treatment, summarizing the clinical studies that led to their official approval. We provide a broad overview of the mechanisms of action of the available anti-cancer drugs targeting gonadotropin-releasing hormone, somatostatin, chemokine, and Smoothened receptors. In addition, we discuss the anti-tumor potential of novel non-approved molecules and antibodies able to target some of the aforementioned GPCRs in different experimental models and clinical trials. Likewise, we focus on the repurposing in cancer patients of non-oncological GPCR-based drugs, elucidating the rationale behind this approach and providing clinical evidence on their safety and efficacy.

Neuropathic Pain and Spinal Cord Injury: Phenotypes and Pharmacological Management

Eva Widerström-Noga

ABSTRACT

Chronic neuropathic pain is a complicated condition after a spinal cord injury (SCI) that often has a lifelong and significant negative impact on life after the injury; therefore, improved pain management is considered a significant and unmet need. Neuropathic pain mechanisms are heterogeneous and the difficulty in determining their individual contribution to specific pain types may contribute to poor treatment outcomes in this population. Thus, identifying human neuropathic pain phenotypes based on pain symptoms, somatosensory changes, or cognitive and psychosocial factors that reflect specific spinal cord or brain mechanisms of neuropathic pain is an important goal. Once a pain phenotype can be reliably replicated, its relationship with biomarkers and clinical treatment outcomes can be analyzed, and thereby facilitate translational research and further the mechanistic understanding of individual differences in the pain experience and in clinical trial outcomes. The present article will discuss clinical aspects of SCI-related neuropathic pain, neuropathic pain phenotypes, pain mechanisms, potential biomarkers and pharmacological interventions, and progress regarding how defining neuropathic pain phenotypes may lead to more targeted treatments for these difficult pain conditions.

Current Status of Biosimilars in Oncology

Luis H. Camacho

ABSTRACT

Four medicinal cancer biological blockbusters will end their patent lifespan by 2020. It is estimated that the total market for cancer biologicals will reach approximately US$68 billion at that time. Approximately 20 biosimilars have entered the European market since the launch of the original approval guidelines in 2005, and four biosimilars have been approved in the USA since 2015. Data from European countries with the highest market entrance of biosimilars suggest that the incorporation of biosimilars into healthcare systems worldwide may result in a 30–45% cost savings. Initial levels of apprehension expressed by healthcare providers regarding the safety and efficacy of integrating biosimilars into the treatment of cancer patients have gradually decreased through active educational programs. The trust generated by regulatory agencies and drug manufacturers will ultimately make the adoption of biosimilars by healthcare providers and patients a smooth process. Future efforts to improve on the global acceptance and safety of biosimilars must include standardization of naming, regulatory requirements, and pharmacovigilance programs worldwide. High expectations are being placed on the cost savings, safety, and efficacy of these products. The entry costs for biosimilars and the pricing reaction of their originator products will determine the true savings by troubled health systems in dire need of cost cuts. This article discusses basic principles of biosimilars in hematology and oncology, the current status of their clinical development, and trends of acceptance by healthcare providers, and provides insight into potential future challenges.

Chronic Pruritus: Current and Emerging Treatment Options

Manuel P. Pereira Sonja Ständer

ABSTRACT

Chronic pruritus remains a central societal issue because of its high occurrence and the substantial decrease in quality of life it may cause to affected individuals. Not only dermatological conditions, but also systemic, neurological, or psychiatric diseases may lead to chronic pruritus. Additionally, various underlying conditions may coexist or the cause may be unknown. Due to its heterogeneity, the therapeutic approach is complex and remains a challenge for the clinician. Basic measures such as emollients to avoid xerosis and treatment of the underlying disease should be initiated regardless of the duration of the symptom. Depending on the indication, other topical (e.g., calcineurin inhibitors, topical corticosteroids, capsaicin) and systemic agents (immunosuppressive drugs, gabapentinoids, antidepressants, mu-opioid receptor antagonists) may provide further relief. Additionally, accompanying disorders such as sleep impairment, depression, or anxiety should also be treated. New insights into pathways involved in the development and maintenance of chronic pruritus have led in the past years to the development of a considerable number of novel antipruritic drugs. Several randomized controlled trials have been recently completed or are currently underway testing biological compounds with promising approaches. These include antagonists for nerve growth factor, neuropeptides, histamine 4 receptors, certain interleukin receptors, and opioid receptors.

Eluxadoline: A Review in Diarrhoea-Predominant Irritable Bowel Syndrome

Gillian M. Keating

ABSTRACT

Eluxadoline (Truberzi®) is an orally administered, minimally absorbed agent that acts locally in the gastrointestinal tract as a mixed μ-opioid receptor agonist and δ-opioid receptor antagonist. The randomized, double-blind, placebo-controlled, multinational, phase 3 IBS-3001 and IBS-3002 trials examined the efficacy of eluxadoline in patients with diarrhoea-predominant irritable bowel syndrome (IBS-D). The composite response rate (i.e. the proportion of patients with improvement in both worst abdominal pain and stool consistency on ≥50% of days; primary endpoint), was significantly higher in patients receiving eluxadoline 100 mg twice daily than in those receiving placebo after 12 and 26 weeks' therapy. Other abdominal and bowel symptoms (e.g. bloating, urgency, frequency of bowel movement) and health-related quality of life scores were also improved with eluxadoline. Eluxadoline was generally well tolerated in patients with IBS-D. Constipation was the most commonly occurring adverse event, although no serious constipation events were reported. Pancreatitis and adverse events consistent with sphincter of Oddi spasm were uncommon. In conclusion, eluxadoline is a new option to consider in the treatment of adult patients with IBS-D.

Ocrelizumab: First Global Approval

James E. Frampton

ABSTRACT

Ocrelizumab (Ocrevus™) is a humanised anti-CD20 monoclonal antibody that has been developed by Genentech, Inc. (a subsidiary of Roche) for the treatment of multiple sclerosis (MS). The drug is designed to deplete B cells, which play an important role in the pathogenesis of MS. In March 2017, ocrelizumab was approved in the USA for the treatment of patients with relapsing or primary progressive forms of MS; currently, it is awaiting approval in the EU for the same indications. This article summarizes the milestones in the development of ocrelizumab leading to its first global approval for the treatment of MS.

Tenofovir Alafenamide: A Review in Chronic Hepatitis B

Lesley J. Scott, Henry L. Y. Chan

ABSTRACT

Tenofovir alafenamide (AF) [Vemlidy®], an oral prodrug of tenofovir, was developed to optimize the antiviral potency and clinical safety of the active moiety tenofovir diphosphate (selective reverse transcriptase nucleotide inhibitor). In two identically designed, ongoing, multinational trials in treatment-naive and -experienced adult patients with hepatitis B e antigen (HBeAg)-positive or -negative chronic hepatitis B virus (HBV) infection, once-daily tenofovir AF 25 mg provided effective and sustained viral suppression (120-week analysis), and was generally well tolerated. In the primary 48-week analysis, tenofovir AF was noninferior to once-daily tenofovir disoproxil fumarate (DF) 300 mg in terms of the proportion of patients achieving viral suppression (HBV DNA <29 IU/mL) and was associated with significantly higher alanine aminotransferase (ALT) normalization rates than tenofovir DF based on AASLD criteria (but not central laboratory criteria). In pooled analyses and/or individual trials, ALT normalization rates by AASLD and central laboratory criteria were significantly higher in tenofovir AF than tenofovir DF recipients at most assessed timepoints up to 96 weeks. Given the bone and renal safety concerns associated with long-term tenofovir DF treatment, the more favourable pharmacological profile of tenofovir AF permits a marked reduction in the dosage of this tenofovir prodrug and thereby reduces systemic exposure to tenofovir, potentially improving the bone and renal safety of tenofovir AF versus tenofovir DF. Long-term clinical experience will more definitively establish the relative bone and renal safety of these tenofovir prodrugs. With its potential for an improved safety profile, tenofovir AF is an important emerging first-line option for the treatment of chronic HBV infection in adults and adolescents (aged ≥12 years and with a bodyweight of ≥35 kg).

Niraparib: First Global Approval

Lesley J. Scott

ABSTRACT

Oral niraparib, a highly-selective, potent poly(ADP-ribose) polymerase (PARP)-1 and PARP-2 inhibitor, is approved in the USA for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. It is also under regulatory review in the EU for use in maintenance treatment in patients with platinum-sensitive, recurrent epithelial ovarian cancer who are in response to platinum-based chemotherapy. In the multinational, phase 3 NOVA trial in adult patients with platinum-sensitive, recurrent ovarian cancer, niraparib significantly prolonged median progression-free survival, irrespective of the presence or absence of a germline BRCA (gBRCA) mutation and irrespective of the presence or absence of homologous recombinant deficiency. Niraparib is also in development for use in other solid tumours, including breast and prostate cancer. This article summarizes the milestones in the development of niraparib leading to its first global approval for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer.

Resistance Mechanisms in Hepatitis C Virus: implications for Direct-Acting Antiviral Use

Sabrina Bagaglio, Caterina Uberti-FoppaGiulia Morsica

ABSTRACT

Multiple direct-acting antiviral (DAA)-based regimens are currently approved that provide one or more interferon-free treatment options for hepatitis C virus (HCV) genotypes (G) 1–6. The choice of a DAA regimen, duration of therapy, and use of ribavirin depends on multiple viral and host factors, including HCV genotype, the detection of resistance-associated amino acid (aa) substitutions (RASs), prior treatment experience, and presence of cirrhosis. In regard to viral factors that may guide the treatment choice, the most important is the infecting genotype because a number of DAAs are genotype-designed. The potency and the genetic barrier may also impact the choice of treatment. One important and debated possible virologic factor that may negatively influence the response to DAAs is the presence of baseline RASs. Baseline resistance testing is currently not routinely considered or recommended for initiating HCV treatment, due to the overall high response rates (sustained virological response >90%) obtained. Exceptions are patients infected by HCV G1a when initiating treatment with simeprevir and elbasvir/grazoprevir or in those with cirrhosis prior to daclatasvir/sofosbuvir treatment because of natural polymorphisms demonstrated in sites of resistance. On the basis of these observations, first-line strategies should be optimized to overcome treatment failure due to HCV resistance.

Advances in the Development of Janus Kinase Inhibitors in Inflammatory Bowel Disease: Future Prospects

Mathurin Flamant, Josselin RigaillStephane PaulXavier Roblin

ABSTRACT

Inflammatory bowel disease (IBD) is caused by a dysregulation of the immune system, inducing the production of proinflammatory cytokines and adhesion molecules. A better understanding of the mucosal immune response in IBD has led to the development of new drugs directed at inflammatory cytokines and leukocyte-trafficking molecules. Beyond tumor necrosis factor antagonists and anti-integrin molecules, which act by blocking the interaction between gut-specific lymphocytes and their receptor on vascular endothelium, the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway represents a new target in IBD. JAK inhibitors are small molecules able to selectively target the activity of specific JAKs that play a role in signal transmission via interleukins. This review presents an overview of the role of the JAK/STAT signaling pathway and updated information for JAK molecules, which are promising drugs in IBD. Currently developed to treat ulcerative colitis and Crohn's disease, tofacitinib (in a phase III study) and filgotinib (in a phase II study), respectively, are the JAK inhibitors in the most advanced stage of development for IBD. However, the utility of, and adverse events associated with, these new drugs remain to be determined and clarified (in particular, the risk of herpes zoster infections), depending on the efficacy and tolerance determined from definitive studies. The availability of these drugs could enhance the therapeutic approach to IBD in the coming years, and reinforce the concept of personalized medicine for IBD patients.

Advanced Analgesic Drug Delivery and Nanobiotechnology

Nicoleta Stoicea, Juan Fiorda-DiazNicholas JosephMuhammad ShabsighCarlos Arias-MoralesAlicia A. Gonzalez-ZacariasAna Mavarez-MartinezStephen MarjoribanksSergio D. Bergese

ABSTRACT

Transdermal administration of analgesic medications offers several benefits over alternative routes of administration, including a decreased systemic drug load with fewer side effects, and avoidance of drug degradation by the gastrointestinal tract. Transdermal administration also offers a convenient mode of drug administration over an extended period of time, particularly desirable in pain medicine. A transdermal administration route may also offer increased safety for drugs with a narrow therapeutic window. The primary barrier to transdermal drug absorption is the skin itself. Transdermal nanotechnology offers a novel method of achieving enhanced dermal penetration with an extended delivery profile for analgesic drugs, due to their small size and relatively large surface area. Several materials have been used to enhance drug duration and transdermal penetration. The application of nanotechnology in transdermal delivery of analgesics has raised new questions regarding safety and ethical issues. The small molecular size of nanoparticles enables drug delivery to previously inaccessible body sites. To ensure safety, the interaction of nanoparticles with the human body requires further investigation on an individual drug basis, since different formulations have unique properties and side effects.

Immunotherapy in Urothelial Cancer: Recent Results and Future Perspectives

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ABSTRACT

Cytotoxic chemotherapy has been the only systemic treatment of locally advanced and metastatic urothelial carcinoma for decades. Long-term survival remains stagnant around 12–14 months for patients with advanced disease who have progressed on or recurred after receiving first-line platinum-based chemotherapy. Improving clinical outcomes for patients with urothelial carcinoma in all disease settings requires the development of novel treatments, especially for patients who failed on first-line chemotherapy. Since the discovery of intravesical Bacillus-Calmette Guerin (BCG) in the 1970s for non-muscle invasive disease, there have not been any major breakthrough drugs that exploit the immune-sensitivity of bladder cancer until recently. Immune-checkpoint inhibitors targeting the programmed death 1/programmed death-ligand 1 (PD-1/PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathways have shown significant anti-tumor activity, tolerable safety profiles and durable, long-term responses in clinical trials. Atezolizumab, avelumab, durvalumab, nivolumab and pembrolizumab are promising PD-1/PD-L1 blockade drugs under investigation that will redefine the standard of care for bladder cancer. CTLA-4 inhibitors are also under investigation in this setting. Atezolizumab, approved in May 2016, and nivolumab, approved in February 2017, are the first Food and Drug Administration (FDA)-approved immune-checkpoint inhibitors in bladder cancer for platinum-pretreated patients based on phase II data. On March 16, 2017, results from the phase III trial KEYNOTE-045 demonstrated that survival was significantly longer in patients treated with pembrolizumab when compared with the standard second-line chemotherapy. Research into biomarkers such as PD-L1 expression, messenger RNA subtype, mutational and neoantigen load and gene signature expression will be crucial to determining why some patients respond to immunotherapy and others do not. This review article describes the advances in immunotherapy since the development of BCG, presents results from clinical trials investigating immune-checkpoint inhibitors and discusses biomarkers and prognostic factors associated with response to these new drugs.

Napabucasin: An Update on the First-in-Class Cancer Stemness Inhibitor

Joleen M. HubbardAxel Grothey

ABSTRACT

Napabucasin (BBI608) is an orally administered small molecule that blocks stem cell activity in cancer cells by targeting the signal transducer and activator of transcription 3 pathway. The signal transducer and activator of transcription 3 pathway is over-activated in many types of cancer and has been shown to be an important pathway in cancer stem cell-mediated propagation of cancer. Cancer stem cells are a subpopulation of cancer cells considered to be the primary source of tumor growth, metastasis, and resistance to conventional therapies, and thus, responsible for cancer relapse. This review describes the clinical development program of this first-in-class cancer stemness inhibitor, including preclinical discovery, early clinical trials, current phase III clinical trial evaluation, and future therapeutic combinations. The therapeutic potential of napabucasin was first reported in a preclinical study that demonstrated the potent anti-tumor and anti-metastatic activity of napabucasin in several different cancer types, both in vitro and in vivo. In mouse models, napabucasin was effective both as a monotherapy and in combination with other agents; in particular, synergy was observed with paclitaxel in vivo. Napabucasin clinical trials have demonstrated encouraging anti-tumor activity as monotherapy and in combination with conventional therapeutics, with no significant pharmacokinetic interactions when used in combination therapies. Adverse events attributed to napabucasin have been predominantly mild, although some patients have experienced grade 3 gastrointestinal adverse events. More severe adverse events required reduced or discontinued dosing of napabucasin or medication to reverse or manage symptoms. In conclusion, napabucasin may prove useful in targeting cancer stem cells, with the potential to suppress metastasis and prevent relapse in patients with varying cancer types.

Ustekinumab: A Review in Moderate to Severe Crohn's Disease

Yvette N. Lamb, Sean T. Duggan

ABSTRACT

Ustekinumab (Stelara®) has been recently approved in the EU and the USA as intravenous induction and subcutaneous maintenance therapy for adult patients with moderately to severely active Crohn's disease who have failed or were intolerant to treatment with immunomodulators, corticosteroids or at least one tumour necrosis factor (TNF) antagonist. Ustekinumab, a monoclonal antibody to the shared p40 subunit of the proinflammatory interleukin (IL)-12 and IL-23 cytokines, has a unique mechanism of action distinct from that of TNF antagonists. In pivotal phase III trials, compared with placebo, ustekinumab induction therapy improved clinical response and remission rates in patients who had previously failed or were intolerant to conventional therapies or at least one TNF antagonist. When administered as subcutaneous maintenance therapy, ustekinumab continued to offer benefits over placebo for clinical response and remission in patients who had clinically responded to the induction therapy. Ustekinumab was generally well tolerated as both induction and maintenance therapy; serious infections and malignancies were rare. Thus, ustekinumab presents a promising alternative treatment option in patients with moderately to severely active Crohn's disease who have failed or are intolerant to treatment with conventional therapies or TNF antagonists.

Dupilumab: First Global Approval

Matt Shirley

ABSTRACT

Dupilumab (Dupixent®) is a fully human monoclonal antibody directed against the interleukin (IL)-4 receptor α (IL-4Rα) subunit. Dupilumab inhibits the signalling of the type 2 cytokines IL-4 and IL-13 and was co-developed by Regeneron Pharmaceuticals and Sanofi as a potential therapeutic agent for the treatment of atopic or allergic diseases. In March 2017 dupilumab received its first global approval, in the USA, for use in the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab is in preregistration for this indication in the EU. In addition, dupilumab is currently under phase III development across the world for the treatment of asthma and nasal polyposis as well as for atopic dermatitis in paediatric patients. The agent has also entered phase II development in the USA for the treatment of eosinophilic oesophagitis. This article summarizes the milestones in the development of dupilumab leading to this first approval for the treatment of moderate-to-severe atopic dermatitis in adults.

Valbenazine: First Global Approval

Esther S. Kim

ABSTRACT

Valbenazine (Ingrezza™) is an orally bioavailable, selective, vesicular monoamine transporter 2 (VMAT2) inhibitor being developed by Neurocrine Biosciences for the treatment of various central nervous system disorders. Valbenazine has been approved in the USA for the treatment of adults with tardive dyskinesia (TD), is at various stages of development in other countries for TD and is in phase 2 development in the USA for Tourette syndrome. This article summarizes the milestones in the development of valbenazine leading to its first global approval in the USA for the treatment of adults with TD.

Brigatinib: First Global Approval

Anthony Markham

ABSTRACT

Brigatinib (ALUNBRIG™) is a small molecule antineoplastic anaplastic lymphoma kinase (ALK) inhibitor being developed by ARIAD Pharmaceuticals (a wholly-owned subsidiary of Takeda Pharmaceutical Company). In April 2017 brigatinib received accelerated approval in the USA for the treatment of patients with ALK-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. The development of resistance to crizotinib is a therapeutic challenge that has led to the development of second-generation ALK-inhibitors such as brigatinib, which have activity against treatment-resistant ALK mutants. This article summarizes the milestones in the development of brigatinib leading to this first global approval for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib.

The Whole Price of Vancomycin: Toxicities, Troughs, and Time

Meghan N. Jeffres

ABSTRACT

Vancomycin is a glycopeptide antibiotic that is active against Gram-positive bacteria, including methicillin-resistant Staphylococcus aureus. Nephrotoxicity, which is usually reversible, is the most serious common adverse effect of vancomycin. Vancomycin-associated nephrotoxicity prolongs hospital stays, imposes a need for additional antibiotics and, in rare circumstances, dialysis treatment, and increases medical costs and mortality. Risk factors for nephrotoxicity include the dose and duration of vancomycin treatment, serum trough concentration, patient characteristics, and concomitant receipt of nephrotoxins. Contemporary guidelines recommend targeting vancomycin trough concentrations of ≥10 mg/L to prevent resistance and trough concentrations of 15–20 mg/L to optimize outcomes. There is significant correlation between vancomycin trough serum concentrations and the incidence of vancomycin-associated nephrotoxicity; however, evidence of an association between trough concentrations and efficacy is less convincing. Routine monitoring of serum vancomycin concentrations consumes time and limited healthcare resources and may not be cost effective. The use of alternative antibacterial agents that do not require monitoring would free up pharmacy resources. This time could then be devoted to initiatives such as pharmacist-led antibiotic stewardship programs that are known to reduce antibiotic use and promote improved patient outcomes.

A Review of Phosphate Binders in Chronic Kidney Disease: Incremental Progress or Just Higher Costs

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ABSTRACT

As kidney disease progresses, phosphorus retention also increases and phosphate binders are used to treat hyperphosphatemia. Clinicians prescribe phosphate binders thinking that reducing total body burden of phosphorus may decrease risks of mineral and bone disorder, fractures, cardiovascular disease, progression of kidney disease, and mortality. Recent meta-analyses suggest that sevelamer use results in lower mortality than use of calcium-containing phosphate binders. However, studies included in meta-analyses show significant heterogeneity, and exclusion or inclusion of specific studies alters results. Since no long-term studies have been conducted to determine whether treatment with any phosphate binder is better than placebo on any hard clinical endpoint (including mortality), it is unclear whether possible benefit with sevelamer represents net benefit of sevelamer, net harm with calcium-containing phosphate binders, or both. Although one meta-analysis suggested that calcium acetate may be more efficacious gram for gram than calcium carbonate as a binder, calcium acetate did not reduce hypercalcemia, and gastrointestinal intolerance was higher. Data are insufficient to determine whether calcium acetate provides lower risk of vascular calcification than calcium carbonate. Fears of lanthanum accumulation in the central nervous system or bone with long-term treatment do not appear to be warranted. Newer iron-containing phosphate binders have potential benefits, such as lower pill burden (sucroferric oxyhydroxide) and improved iron parameters (ferric citrate). The biggest challenge to phosphate binder efficacy is non-adherence. This article reviews the current knowledge regarding safety, effectiveness, and adherence with currently marketed phosphate binders and those in development.

The Effects of Tamoxifen on Plasma Lipoprotein (a) Concentrations: Systematic Review and Meta-Analysis

Amirhossein SahebkarMaria-Corina SerbanPeter PensonCamelia GurbanSorin UrsoniuPeter P. TothSteven R. JonesGiuseppe LippiKazuhiko KotaniKaram KostnerManfredi RizzoJacek RyszMaciej Banach, Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group

ABSTRACT

Introduction: Tamoxifen is a selective estrogen receptor modulator widely used in the treatment of breast cancer. Tamoxifen therapy is associated with lower circulating low-density lipoprotein cholesterol and increased triglycerides, but its effects on other lipids are less well studied.

Aims: We aimed to investigate the effect of tamoxifen on circulating concentrations of lipoprotein(a) [Lp(a)] through a meta-analysis of available randomized controlled trials (RCTs) and observational studies.

Methods: This study was registered in the PROSPERO database (CRD42016036890). Scopus, MEDLINE and EMBASE were searched from inception until 22 March 2016 to identify studies investigating the effect of tamoxifen on Lp(a) values in humans. Meta-analysis was performed using an inverse variance-weighted, random-effects model with standardized mean difference (SMD) as the effect size estimate.

Results: Meta-analysis of five studies with 215 participants suggested a statistically significant reduction of Lp(a) levels following tamoxifen treatment (SMD −0.41, 95% confidence interval −0.68 to −0.14, p = 0.003). This effect was robust in the sensitivity analysis.

Conclusions: Meta-analysis suggested a statistically significant reduction of Lp(a) levels following tamoxifen treatment. Further well-designed trials are required to validate these results.

A Retrospective Cohort Study of Obstetric Outcomes in Opioid-Dependent Women Treated with Implant Naltrexone, Oral Methadone or Sublingual Buprenorphine, and Non-Dependent Controls

Erin Kelty, Gary Hulse

ABSTRACT

Background: Opioid pharmacotherapies play an important role in the treatment of opioid-dependent women; however, very little is known about the safety of naltrexone in pregnant patients.

Objective: This study examined the obstetric health of opioid-dependent women who were treated with implant naltrexone during pregnancy, and compared them with women treated with methadone and/or buprenorphine and a cohort of non-opioid-dependent controls.

Methods: Women treated with implant naltrexone, oral methadone or sublingual buprenorphine between 2001 and 2010, along with a cohort of age-matched controls, were linked with records from midwives, hospital and emergency departments (EDs) and the death registry to identify pregnancy and health events that occurred during pregnancy and in the post-partum period.

Results: Overall rates of pregnancy loss (requiring hospital or ED attendance) were significantly elevated in naltrexone-treated women compared with buprenorphine-treated women ($p = 0.018$) and controls ($p < 0.001$); however, they were not statistically different to methadone-treated women ($p = 0.210$). Birth rates in women on naltrexone implant treatment were significantly higher than in all three comparison groups ($p < 0.001$). Rates of hospital and ED attendance during pregnancy in the naltrexone-treated women were not statistically different to those of either the methadone or buprenorphine groups, and neither were overall complications during pregnancy and labour. Overall rates of complications during pregnancy were significantly higher in the naltrexone-treated women than in the controls.

Conclusion: Opioid-dependent women treated with naltrexone implant had higher rates of birth than the other three groups (methadone- or buprenorphine-treated women, or age-matched controls). Overall rates of complications during pregnancy were elevated in naltrexone-treated women when compared with the control group, but were generally not significantly different to rates in methadone- or buprenorphine-treated women.

A Retrospective Cohort Study of Birth Outcomes in Neonates Exposed to Naltrexone in Utero: A Comparison with Methadone-, Buprenorphine- and Non-opioid-Exposed Neonates

Erin Kelty, Gary Hulse

ABSTRACT

Background: Naltrexone may provide a suitable alternative to methadone and buprenorphine in the treatment of pregnant opioid-dependent women; however, little is known about its effects on neonatal morbidity and mortality.

Objective: The aim was to evaluate the health of neonates exposed to naltrexone in utero, and compare it with outcomes in neonates exposed to methadone or buprenorphine and a non-exposed control group.

Methods: Sequential cohorts of Western Australian (WA) opioid-dependent women treated with implant naltrexone, oral methadone or sublingual buprenorphine were identified via records from a drug and alcohol clinic (Subiaco, WA) for naltrexone and state prescribing records for methadone and buprenorphine. A control cohort of non-opioid-dependent women was obtained from the WA electoral roll. Identifying information and treatment records for these women were linked against the Midwife Notification System records to identify exposed offspring born between 2001 and 2011. Birth characteristics, congenital anomalies and perinatal mortality for all neonates were extracted from state records.

Results: The birth characteristics of naltrexone-exposed neonates (n = 68) were superior to methadone-exposed neonates (n = 199) in terms of birth size (birth weight, head circumference and length), hospital length of stay (5.5 vs. 11.3 days), and rates of neonatal abstinence syndrome (NAS) (7.5 vs. 51.5%). Naltrexone-exposed neonates were generally not significantly different to buprenorphine-exposed neonates (n = 124), with the exception of significantly lower rates of NAS (7.5 vs. 41.8%) and shorter hospital length of stay (5.5 vs. 8.0 days) in naltrexone-exposed neonates. Compared with the control group of neonates (n = 569), naltrexone-exposed neonates were not significantly different in terms of overall rates of congenital anomalies, stillbirths and neonatal mortality; however, they were significantly smaller (3137.1 vs. 3378.0 g), spent more time in hospital following birth (5.5 vs. 4.3 days) and had higher rates of NAS (7.5 vs. 0.2%). Exposure of neonates to prenatal methadone was associated with a high incidence of neonatal mortality (2.0 vs. 0.2 per 100 live births) and congenital anomalies (10.6 vs. 4.4 per 100 births) compared with the control group. Rates of neonatal mortality and congenital abnormalities in buprenorphine-exposed neonates were not significantly different to the control group.

Conclusions: The use of implant naltrexone during pregnancy was not associated with higher rates of negative birth outcomes compared with methadone- and buprenorphine-exposed neonates. Significantly, naltrexone and buprenorphine were not associated with the high rates of neonatal mortality or congenital anomalies seen in methadone-exposed neonates.

Abatacept: A Review in Rheumatoid Arthritis

Hannah A. Blair, Emma D. Deeks

ABSTRACT

The biological DMARD (bDMARD) abatacept (Orencia®), a recombinant fusion protein, selectively modulates a co-stimulatory signal necessary for T-cell activation. In the EU, abatacept is approved for use in patients with highly active and progressive rheumatoid arthritis (RA) not previously treated with methotrexate. Abatacept is also approved for the treatment of moderate to severe active RA in patients with an inadequate response to previous therapy with at least one conventional DMARD (cDMARD), including methotrexate or a TNF inhibitor. In phase III trials, beneficial effects on RA signs and symptoms, disease activity, structural damage progression and physical function were seen with intravenous (IV) or subcutaneous (SC) abatacept regimens, including abatacept plus methotrexate in methotrexate-naive patients with early RA and poor prognostic factors, and abatacept plus methotrexate or other cDMARDs in patients with inadequate response to methotrexate or TNF inhibitors. Benefits were generally maintained during longer-term follow-up. Absolute drug-free remission rates following withdrawal of all RA treatments were significantly higher with abatacept plus methotrexate than with methotrexate alone. Both IV and SC abatacept were generally well tolerated, with low rates of immunogenicity. Current evidence therefore suggests that abatacept is a useful treatment option for patients with RA.

Eftrenonacog Alfa: A Review in Haemophilia B

Sheridan M. Hoy

ABSTRACT

Eftrenonacog alfa (Alprolix™) is a recombinant fusion protein comprising human factor IX (FIX) covalently linked to the constant region (Fc) domain of human IgG1 (i.e. rFIXFc). The presence of the Fc domain extends the terminal half-life (t½) of rFIXFc, permitting prolonged treatment intervals. rFIXFc is available for intravenous use for the prophylaxis and treatment of bleeding in patients with haemophilia B. In two multinational, phase III studies in previously treated children, adolescents and adults with severe haemophilia B, rFIXFc prophylaxis resulted in low median annualized bleeding rates (ABRs), and was associated with reductions in median weekly factor consumption and dosing frequency compared with pre-study FIX regimens. Preliminary data from an extension of both studies indicated sustained efficacy, as demonstrated by low median ABRs, with longer-term rFIXFc prophylaxis. rFIXFc was also effective in the treatment of bleeding episodes and when used in the perioperative setting in all age groups. rFIXFc was well tolerated in clinical studies in previously treated patients, with the majority of treatment-emergent adverse events considered to be unrelated to rFIXFc; there were no reports of inhibitor development. In conclusion, rFIXFc provides an effective alternative to plasma-derived and recombinant FIX products for the management of patients with haemophilia B, with its extended t½ permitting a less frequent administration schedule and potentially providing a prolonged protective haemostatic effect, which eases the treatment burden on the patient.

Cerliponase Alfa: First Global Approval

Anthony Markham

ABSTRACT

Cerliponase alfa (Brineura™) is a recombinant human tripeptidyl peptidase-1 (TPP1) being developed by BioMarin Pharmaceutical Inc. for use in patients with neuronal ceroid lipofuscinosis type 2 (CLN2), a paediatric neurodegenerative disease caused by a deficiency in TPP1. CLN2 is characterised by progressive impairment of motor function, language deficiencies, seizures, ataxia, blindness and early death, and intracerebroventricular infusion of cerliponase alfa has been shown to reduce the progression of functional decline. This article summarizes the milestones in the development of cerliponase alfa leading to its first global approval in the USA for the treatment of motor function loss in paediatric patients ≥3 years of age with CLN2, and subsequent approval in the EU for CLN2 in all ages.

Midostaurin: First Global Approval

Esther S. Kim

ABSTRACT

Midostaurin (Rydapt®) is a multikinase inhibitor being developed by Novartis Pharmaceuticals. In April 2017, midostaurin was approved in the USA for the treatment of adult patients with newly diagnosed, FMS-like tyrosine kinase 3 (FLT3) mutation-positive acute myeloid leukaemia (AML) [in combination with standard cytarabine and daunorubicin induction, and cytarabine consolidation], or aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL) [collectively known as advanced SM]. The article summarizes the milestones in the development of midostaurin leading to this first global approval.

Volume 77, Issue 12, August 2017

Drugs in Development for Hepatitis B

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ABSTRACT

With high morbidity and mortality worldwide, there is great interest in effective therapies for chronic hepatitis B (CHB) virus. There are currently several dozen investigational agents being developed for treatment of CHB. They can be broadly divided into two categories: (1) direct-acting antivirals (DAAs) that interfere with a specific step in viral replication; and (2) host-targeting agents that inhibit viral replication by modifying host cell function, with the latter group further divided into the subcategories of immune modulators and agents that target other host functions. Included among the DAAs being developed are RNA interference therapies, covalently closed circular DNA (cccDNA) formation and transcription inhibitors, core/capsid inhibitors, reverse transcriptase inhibitors, hepatitis B surface antigen (HBsAg) release inhibitors, antisense oligonucleotides, and helioxanthin analogues. Included among the host-targeting agents are entry inhibitors, cyclophilin inhibitors, and multiple immunomodulatory agents, including Toll-like receptor agonists, immune checkpoint inhibitors, therapeutic vaccines, engineered T cells, and several cytokine agents, including recombinant human interleukin-7 (CYT107) and SB 9200, a novel therapy that is believed to both have direct antiviral properties and to induce endogenous interferon. In this review we discuss agents that are currently in the clinical stage of development for CHB treatment as well as strategies and agents currently at the evaluation and discovery phase and potential future targets. Effective approaches to CHB may require suppression of viral replication combined with one or more host-targeting agents. Some of the recent research advances have led to the hope that with such a combined approach we may have a functional cure for CHB in the not distant future.

Targeting the PGD2/CRTH2/DP1 Signaling Pathway in Asthma and Allergic Disease: Current Status and Future Perspectives

Maciej Kupczyk, Piotr Kuna

ABSTRACT

Prostaglandin D2 (PGD2) released by degranulating mast cells is believed to play a key role in orchestrating mechanisms of inflammation in allergies and asthma. The biological effects of PGD2 are mediated by D-prostanoid (DP1), CRTH2 (DP2), and thromboxane prostanoid (TP) receptors. The CRTH2 receptor is involved in induction of migration and activation of T helper type 2 (Th2) lymphocytes, eosinophils, and basophils; up-regulation of adhesion molecules; and promotion of pro-inflammatory Th2-type cytokines (interleukin [IL]-4, 5, 13), whereas the DP receptor is associated with relaxation of smooth muscles, vasodilation, inhibition of cell migration, and apoptosis of eosinophils. A number of CRTH2/PGD2 receptor antagonists have been investigated in asthma and allergic diseases. The CRTH2 antagonist (OC000459) or dual CRTH2 and TP receptor antagonist (ramatroban) were effective in reducing eosinophilia, nasal mucosal swelling, and clinical symptoms of allergic rhinitis, with the latter drug registered for clinical use in this indication. OC000459 and setipiprant reduced the late but not early phase of response in an allergen challenge in atopic asthmatics. In persistent asthma, some molecules induced limited improvement in lung function, quality of life, and asthma symptoms (OC000459, BI671800), but in other trials with AMG 853 and AZ1981 these findings were not confirmed. The clear discrepancy between animal studies and clinical efficacy of CRTH2 antagonism in allergic rhinitis, and lack of efficacy in a general cohort of asthmatics, highlight the issue of patient phenotyping. There is no doubt that the PGD2/CATH2/DP1 pathway plays a key role in allergic inflammation and further studies with selective or combined antagonisms in well defined cohorts of patients are needed.

Working Towards an Appropriate Use of Ibuprofen in Children: An Evidence-Based Appraisal

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ABSTRACT

Ibuprofen is the most widely used non-steroidal anti-inflammatory drug (NSAID) for the treatment of inflammation, mild-to-moderate pain and fever in children, and is the only NSAID approved for use in children aged ≥3 months. Its efficacy and safety profile have led to its increasing use in paediatric care, even without medical prescription. However, an increase of suspected adverse reactions to ibuprofen has been noted in concomitance with the raised, often medically unsupervised, consumption of the drug. The purpose of this work was a critical review of the paediatric literature over the last 15 years on side effects and adverse events associated with ibuprofen, in order to highlight circumstances associated with higher risks and to promote safe and appropriate use of this drug. The literature from 2000 to date demonstrates that gastrointestinal events are rare, but (when they occur) include both upper and lower digestive tract lesions. Dehydration plays an important role in triggering renal damage, so ibuprofen should not be given to patients with diarrhoea and vomiting, with or without fever. Likewise, ibuprofen should never be administered to patients who are sensitive to it or to other NSAIDs. It is contraindicated in neonates and in children with wheezing and persistent asthma and/or during varicella. Most of the analysed studies reported adverse events when ibuprofen was being used for fever symptoms or flu-like syndrome. Ibuprofen should not be used as an antipyretic, except in rare cases. Ibuprofen remains the drug of first choice in the treatment of inflammatory pain in children.

Neoadjuvant Therapy for Breast Cancer: Established Concepts and Emerging Strategies

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ABSTRACT

In the last decade, the systemic treatment approach for patients with early breast cancer has partly shifted from adjuvant treatment to neoadjuvant treatment. Systemic treatment administration started as a 'one size fits all' approach but is currently customized according to each breast cancer subtype. Systemic treatment in a neoadjuvant setting is at least as effective as in an adjuvant setting and has several additional advantages. First, it enables response monitoring and provides prognostic information; second, it downstages the tumor, allowing for less extensive surgery, improved cosmetic outcomes, and reduced postoperative complications such as lymphedema; and third, it enables early development of new treatment strategies by using pathological complete remission as a surrogate outcome of event-free and overall survival. In this review we give an overview of the current standard of neoadjuvant systemic treatment strategies for the three main subtypes of breast cancer: hormone receptor-positive, triple-negative, and human epidermal growth factor receptor 2-positive. Additionally, we summarize drugs that are under investigation for use in the neoadjuvant setting.

Therapeutic Utility of Opioids for Restless Legs Syndrome

Susan E. Mackie, John W. Winkelman

ABSTRACT

Restless legs syndrome (RLS) is a sensorimotor neurologic disorder characterized by an unpleasant urge to move the legs, often accompanied by leg dysesthesias. Symptoms predominate in the evening or at night and often cause significant distress and disruption of sleep. Several non-opioid classes of drugs provide initial relief from the symptoms of RLS. Among these, however, the efficacy of dopamine agonists can wane over time or even paradoxically 'augment' the severity of symptoms during the course of long-term treatment. Opioids can alleviate RLS symptoms, even in patients who have become refractory to, or do not tolerate, other drugs. In a carefully selected group of patients with severe RLS that has not been effectively managed with other therapies, opioids may be an appropriate treatment.

Early Use of Ceftaroline Fosamil in the United States Veterans Health Care System

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ABSTRACT

Background: Ceftaroline fosamil is US Food and Drug Administration-approved for acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia, but it is not known how ceftaroline is being used in real-world settings or how adverse effects (AEs) and mortality compare to clinical trials.

Objective: This study describes ceftaroline use, AEs, and mortality in US Veterans Health Administration (VHA) hospital patients.

Methods: This phase IV, population-based, epidemiologic study analyzed patients ≥18 years old who received one or more ceftaroline doses within 14 days of admission to 69 VHA hospitals in 41 US states/territories from 1 October 2010 to 30 September 2014. VHA repository data were linked using unique patient identifiers. Diagnoses and AEs were determined using ICD9-CM and CSS codes. Demographics, AEs within 30 days of therapy initiation, and all-cause in-hospital mortality were summarized using descriptive statistics.

Results: 764 Patients met study criteria. Patients were 97% male and 56% White, with a median age of 61 years and a Charlson score of 6. Diagnoses included skin (40%), sepsis (30%), osteomyelitis (25%), diabetic foot (22%), pneumonia (16%), bacteremia (11%), endocarditis (6%), meningitis (2%), and device (2%) infections. Ceftaroline was used first-line (37%), second-line (56%), and third-line or greater (7%). Patients received ceftaroline a median of 3 days after hospital admission. All-cause in-hospital mortality rates were: overall (5%), skin (2%), sepsis (9%), osteomyelitis (3%), diabetic foot (1%), pneumonia (13%), bacteremia (6%), endocarditis (11%), meningitis (6%), and device (13%). Eosinophilia, leukopenia, leukocytosis, fibromyalgia, myalgia and myositis, and polymyalgia rates were <1% each.

Conclusions: Ceftaroline is used in VHA hospitals for various diagnoses. Mortality was low and comparable with rates from clinical trials. Additional studies comparing ceftaroline to other drugs used in similar situations are needed.

Insulin Glargine/Lixisenatide: A Review in Type 2 Diabetes

Lesley J. Scott

ABSTRACT

Subcutaneous insulin glargine/lixisenatide (Suliqua™) is a titratable, fixed-ratio combination of a long-acting basal insulin analogue and a glucagon-like peptide-1 (GLP-1) receptor agonist for the treatment of adult patients with inadequately controlled type 2 diabetes. Once-daily insulin glargine/lixisenatide, in combination with metformin, provided effective glycaemic control and was generally well tolerated in the 30-week, multinational, phase 3 LixiLan-O and LixiLan-L trials in insulin-naive and -experienced adult patients with inadequately controlled type 2 diabetes. Although long-term clinical experience with this fixed-ratio combination is currently lacking, given its convenient once-daily regimen and beneficial effects on glycaemic control and bodyweight loss in the absence of an increase in the incidence of hypoglycaemia, insulin glargine/lixisenatide is an emerging option for the treatment of adult patients with type 2 diabetes to improve glycaemic control when this has not been provided by metformin alone or metformin combined with another OAD or basal insulin.

Abaloparatide: First Global Approval

Matt Shirley

ABSTRACT

Abaloparatide (Tymlos™) is a synthetic peptide analogue of human parathyroid hormone-related protein that was developed by Radius Health as an osteoanabolic agent for the treatment of postmenopausal osteoporosis. Abaloparatide acts through selective activation of the parathyroid hormone type 1 receptor signalling pathway. In April 2017, subcutaneous abaloparatide received its first global approval, in the USA, for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. A Marketing Authorization Application for subcutaneous abaloparatide for the treatment of postmenopausal women with osteoporosis was accepted by the European Medicines Agency and is currently under review. Radius is also developing a transdermal formulation of abaloparatide, with administration via a microneedle patch. This article summarizes the milestones in the development of abaloparatide leading to this first approval for the treatment of women with postmenopausal osteoporosis.

Durvalumab: First Global Approval

Yahiya Y. Syed

ABSTRACT

Intravenous durvalumab (Imfinzi™; AstraZeneca) is a fully human monoclonal antibody that blocks programmed cell death ligand-1 binding to its receptors (PD-1 and CD80), resulting in enhanced T-cell responses against cancer cells. The US FDA has granted durvalumab accelerated approval for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Durvalumab ± tremelimumab is under phase III clinical trials in urothelial carcinoma, non-small cell lung cancer, small cell lung cancer and head and neck squamous cell carcinoma. The drug is also being evaluated in phase I or II clinical trials in a wide range of solid tumours and haematological malignancies. This article summarizes the milestones in the development of durvalumab leading to this first approval for urothelial carcinoma.

Nerve Growth Factor Antagonists: Is the Future of Monoclonal Antibodies Becoming Clearer

Bernard Bannwarth, Marie Kostine

ABSTRACT

Although there is an unmet need for pain medications that are both effective and safe, virtually no novel analgesics have been approved over the past two decades. In view of both experimental and clinical evidence of a major role for nerve growth factor (NGF) in the generation and maintenance of a wide range of pain states, the clinical development of humanised anti-nerve growth factor monoclonal antibodies (anti-NGF mAbs) aroused particular interest. However, the US Food and Drug Administration (FDA) placed a clinical hold on anti-NGF mAb clinical studies in late 2010, first because of reports of serious joint-related adverse events, and afterwards because of sympathetic nervous system safety concerns. The development programmes of tanezumab and fasinumab resumed after the FDA lifted its hold in March 2015, whereas other anti-NGF mAbs were dropped by their sponsors. This article provides an updated review on the analgesic efficacy and safety of anti-NGF agents based on data from fully published studies and public information from websites, and discusses the possible future role of these agents in managing chronic pain. The efficacy of anti-NGF mAbs was highly variable depending on the chronic pain condition studied. The most consistent and convincing results were obtained in patients with symptomatic osteoarthritis of the knee and/or hip. Conversely, studies in non-specific lower back pain and peripheral neuropathic pain generated mixed results. Finally, there was no conclusive evidence of the effectiveness of anti-NGF mAbs in cancer pain and urological chronic pelvic pain syndromes. Treatment-emergent adverse events were similar across anti-NGF mAbs, thus being suggestive of 'class-specific effects'. Although most patients tolerated anti-NGF agents well, neurosensory symptoms occurred frequently, and some patients developed new or worsened peripheral neuropathies. However, the most problematic safety issue was rapidly destructive arthropathies, leading to joint replacement surgery. To date, the aetiologies of joint-related side effects and their pathophysiology have not been clearly elucidated. However, some risk factors have been identified, such as higher doses of anti-NGF mAbs and longer drug exposure, concurrent nonsteroidal anti-inflammatory drug use and pre-existing subchondral insufficiency fractures. Taken together, the present data suggest that low-dose anti-NGF mABs may exhibit a favourable risk-benefit ratio in selected patients with certain chronic pain conditions, especially symptomatic osteoarthritis.

Phosphodiesterase 4 Inhibitor Therapies for Atopic Dermatitis: Progress and Outlook

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ABSTRACT

Phosphodiesterase 4 (PDE4) is a cyclic AMP degrading enzyme in leukocytes. Several decades ago, increased PDE activity was demonstrated in patients with atopic dermatitis (AD). Currently, several PDE4 inhibitors in both topical and oral formulation have been developed to target the inflammatory cascade of AD. This review shows the pathogenic rationale behind these inhibitors, and discusses multiple PDE4 inhibitors that are under evaluation or in the market. PDE4 inhibitors may be considered as favorable agents in the repertoire of current interventions for AD.

Inhaled Antimicrobials for Ventilator-Associated Pneumonia: Practical Aspects

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ABSTRACT

Positive experience with inhaled antibiotics in pulmonary infections of patients with cystic fibrosis has paved the way for their utilization in mechanically ventilated, critically ill patients with lower respiratory tract infections. A successful antibiotic delivery depends upon the size of the generated particle and the elimination of drug impaction in the large airways and the ventilator circuit. Generated droplet size is mainly affected by the type of the nebulizer employed. Currently, jet, ultrasonic, and vibrating mesh nebulizers are marketed; the latter can deliver optimal antibiotic particle size. Promising novel drug-device combinations are able to release drug concentrations of 25- to 300-fold the minimum inhibitory concentration of the targeted pathogens into the pulmonary alveoli. The most important practical steps of nebulization include pre-assessment and preparation of the patient (suctioning, sedation, possible bronchodilation, adjustment of necessary ventilator settings); adherence to the procedure (drug preparation, avoidance of unnecessary tubing connections, interruption of heated humidification, removal of heat-moisture exchanger); inspection of the procedure (check for residual in drug chamber, change of expiratory filter, return sedation, and ventilator settings to previous status); and surveillance of the patient for adverse events (close monitoring of the patient and particularly of peak airway pressure and bronchoconstriction). Practical aspects of nebulization are very important to ensure optimal drug delivery and safe procedure for the patient. Therefore, the development of an operational checklist is a priority for every department adopting this modality.

Benefits and Risks of Non-Approved Injection Regimens for Botulinum Toxins in Spasticity

Andrea Santama, Francesco Panza

ABSTRACT

Spasticity with muscle paresis and loss of dexterity is a common feature of upper motor neuron syndrome due to injuries or the pyramidal tract in several neurological conditions. Botulinum toxin type A has been considered the gold standard treatment for spasticity and movement disorders, with efficacy, reversibility, and low prevalence of complications. During the last 30 years, thousands of studies of its use have been performed, but few guidelines are available. Therefore, there is great variability in both the doses and intervals of administration and the approaches taken by clinicians with considerable experience in spasticity and movement disorder treatment. In the present review article, we provide a short overview of the benefits and risks of non-approved injection regimens and doses for botulinum toxins, focusing on the treatment of post-stroke spasticity, where there is great interest in the potential for increasing the number of treatment/years and the dose of botulinum toxin treatment for subjects with upper and lower limb spasticity. However, many doubts exist regarding antibody development and possible adverse effects.

Treatment for Negative Symptoms in Schizophrenia: A Comprehensive Review

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ABSTRACT

Negative symptoms (such as amotivation and diminished expression) associated with schizophrenia are a major health concern. Adequate treatment would mean important progress with respect to quality of life and participation in society. Distinguishing primary from secondary negative symptoms may inform treatment options. Primary negative symptoms are part of schizophrenia. Well-known sources of secondary negative symptoms are psychotic symptoms, disorganisation, anxiety, depression, chronic abuse of illicit drugs and alcohol, an overly high dosage of antipsychotic medication, social deprivation, lack of stimulation and hospitalisation. We present an overview of reviews and meta-analyses of double-blind, controlled randomised trials, in which the efficacy of pharmacological and non-pharmacological interventions for negative symptoms was assessed. Unfortunately, there have been very few clinical trials focusing on primary negative symptoms and selecting chronically ill patients with predominant persistent negative symptoms. An important limitation in many of these studies is the failure to adequately control for potential sources of secondary negative symptoms. At present, there is no convincing evidence regarding efficacy for any treatment of predominant persistent primary negative symptoms. However, for several interventions there is short-term evidence of efficacy for negative symptoms. This evidence has mainly been obtained from studies in chronically ill patients with residual symptoms and studies with a heterogeneous study population of patients in both the acute and chronic phase. Unfortunately, reliable information regarding the distinction between primary and secondary negative symptoms is lacking. Currently, early treatment of psychosis, add-on therapy with aripiprazole, antidepressants or topiramate, music therapy and exercise have been found to be useful for unspecified negative symptoms. These interventions can be considered carefully in a shared decision-making process with patients, and are promising enough to be examined in large, well-designed long-term studies focusing on primary negative symptoms. Future research should be aimed at potential therapeutic interventions for primary negative symptoms since there is a lack of research in this field.

Lenalidomide: A Review in Newly Diagnosed Multiple Myeloma as Maintenance Therapy after ASCT

Yahiya Y. Syed

ABSTRACT

Lenalidomide (Revlimid®) is an immunomodulatory drug with multiple mechanisms of action against multiple myeloma. It is a thalidomide analogue, with improved potency and reduced toxicity compared with thalidomide. In the EU and USA, lenalidomide monotherapy is indicated for the maintenance treatment of patients with newly diagnosed multiple myeloma who have undergone autologous stem-cell transplantation (ASCT). In the pivotal, phase 3 IFM 2005-02 and CALGB 100104 trials, lenalidomide maintenance therapy after ASCT administered until disease progression significantly prolonged progression-free survival (PFS; primary endpoint) relative to placebo in patients with newly diagnosed multiple myeloma. These results are generally supported by those of the phase 3 GIMEMA and Myeloma XI trials. Lenalidomide maintenance therapy significantly prolonged overall survival in CALGB 100104 but not in IFM 2005-02. However, a meta-analysis of patient-level data from IFM 2005-02, CALGB 100104 and GIMEMA showed an overall survival benefit with this therapy. Lenalidomide maintenance therapy had a manageable tolerability profile in the pivotal trials. Grade 3/4 haematological adverse events and grade 3 nonhaematological adverse events were more common with lenalidomide than with placebo. Lenalidomide increased the risk of a second primary cancer, but the survival benefits outweigh this risk. In conclusion, lenalidomide maintenance therapy after ASCT until disease progression prolongs PFS and overall survival in patients with newly diagnosed multiple myeloma. Therefore, lenalidomide offers a valuable maintenance treatment option for this population.

Factors Contributing to the Efficacy-Effectiveness Gap in the Case of Orphan Drugs for Metabolic Diseases

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ABSTRACT

Introduction: Authorization of orphan medicinal products (OMPs) is often based on studies with several methodological shortcomings. Hence, data are difficult to interpret and efficacy does not always correspond to real-world effectiveness. We investigated to what extent an efficacy-effectiveness gap exists for OMPs for metabolic diseases and set out to explore which factors contribute to it.

Methods: We included all OMPs for rare metabolic diseases authorized in the EU up to 1 January 2016. Efficacy data were obtained from European Public Assessment Reports, relative effectiveness data from the Dutch National Healthcare Institute website, and real-world effectiveness data from literature and interviews with experts and patients. Efficacy and effectiveness were scored as 'no effect', 'unclear' or 'good' based upon a prespecified scoring system.

Results: We identified 31 authorized OMPs, of which 21 had post-marketing studies available, thus making it possible to score real-world effectiveness. Eight of 21 (38%) OMPs had a 'good' real-world effectiveness. The use of a clinical or validated surrogate primary endpoint and a representative study population seemed to be related to good effectiveness in the real world, as were type of marketing authorization, study population and disease prevalence.

Conclusions: This study revealed that less than half of the authorized OMPs are effective in the real world. Since the type of primary endpoint used in the pivotal study seems to be associated with good real-world effectiveness, it is important to agree upon study endpoints through early dialogues among relevant stakeholders.

Delafloxacin: First Global Approval

Anthony Markham

ABSTRACT

Delafloxacin (Baxdela™) is a fluoroquinolone antibacterial with activity against both gram-positive and gram-negative pathogens being developed by Melinta Therapeutics. The drug is being investigated or considered as a treatment for various bacterial infections and in June 2017 received approval in the USA for the treatment of acute bacterial skin and skin structure infections. This article summarizes the milestones in the development of delafloxacin leading to this first global approval for the treatment of acute bacterial skin and skin structure infections.

Guselkumab: First Global Approval

Anthony Markham

ABSTRACT

Guselkumab (Tremfya™) is a human monoclonal IgG1λ antibody being developed by Janssen Biotech, Inc. that has been approved in the USA as a treatment for moderate-to-severe plaque psoriasis. Guselkumab inhibits the binding of interleukin 23 (IL-23) to its cell surface receptor, disrupting the type 17 helper T cell/IL-17 pathway. This article summarizes the milestones in the development of guselkumab leading to this first approval for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Selective Interleukin-23 p19 Inhibition: Another Game Changer in Psoriasis? Focus on Risankizumab

Tiago Torres

ABSTRACT

The history of psoriasis treatment has been marked by several milestones. Corticosteroids, cyclosporine, tumor necrosis factor alpha (TNF-α) inhibitors and, more recently, interleukin (IL)-17A inhibitors have revolutionized the treatment of psoriasis, each in its own way and time. The IL-23/IL-17 axis is currently considered to be crucial in the pathogenesis of psoriasis and selective IL-23p19 inhibition may bring several advantages with respect to IL-12/23p40 inhibition, or distal blockade of IL-17A or its receptor. In fact, IL-12 axis inhibition does not appear to be essential in psoriasis and IL-12 inhibition may even have a negative effect in the treatment of psoriasis and have potential risks in tumor immune surveillance and in host defense against intracellular pathogens. On the other hand, contrary to IL-17 inhibition, IL-23p19 blockade does not increase the risk of candida infection, nor is it associated with inflammatory bowel disease worsening. Several IL-23p19 inhibitors are currently being developed for the treatment of psoriasis, such as tildrakizumab, guselkumab, and risankizumab. Although clinical data on risankizumab is still scarce, it has shown characteristics that signify a major advance in the treatment of this disease, offering comparable or higher efficacy than IL-17 inhibitors, without the safety concerns of this therapeutic class, combined with the excellent dosing regimen of ustekinumab. Currently, only phase II trial data is available; thus, the results of the large phase III trials will be essential to establish the efficacy and safety profile of risankizumab and its value in the biological armamentarium for the treatment of psoriatic patients.

Drugs in Clinical Development for Fungal Infections

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ABSTRACT

Despite increasing rates of invasive fungal infections being reported globally, only a single antifungal drug has been approved during the last decade. Resistance, toxicity, drug interactions and restricted routes of administration remain unresolved issues. This review focuses on new antifungal compounds which are currently in various clinical phases of development. We discuss two azoles with a tetrazole moiety that allows selective activity against the fungal CYP: VT-1161 for Candida infections and VT-1129 for cryptococcal meningoencephalitis. We also discuss two glucan synthesis inhibitors: CD101, an echinocandin with an increased half-life, and SCY-078 with oral bioavailability and increased activity against echinocandin-resistant isolates. Among the polyenes, we discuss MAT023, an encochleated amphotericin B formulation that allows oral administration. Two novel classes of antifungal drugs are also described: glycosylphosphatidylinositol inhibitors, and the leading drug APX001, which disrupt the integrity of the fungal wall; and the orotomides, inhibitors of pyrimidine synthesis with the leading drug F901318. Finally, a chitin synthesis inhibitor and progress on human monoclonal antifungal antibodies are discussed.

Pharmacotherapy of Anal Cancer

Jane E. Rogers, Cathy Eng

ABSTRACT

Anal squamous cell carcinoma (SCCA), among other malignancies, is associated with the human papillomavirus (HPV) and its incidence continues to rise. Anal SCCA will likely remain an existing healthcare concern given compliance issues with the HPV vaccination seen in the US. Localized disease is predominantly treated with standard of care (SOC) definitive chemoradiation that has remained unchanged for decades. Clinical and molecular prognostic factors have emerged to characterize patients unresponsive to SOC, revealing the need for an alternate approach. Metastatic disease is an extremely small subset and understudied population due to its rarity. Recent prospective trials and mutational analysis have opened treatment options for this subset in need. Our review details the pharmacotherapeutic treatment in localized and metastatic anal SCCA chronologically, while also describing future outlooks.

Current and Emerging Options for the Management of Inherited von Willebrand Disease

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ABSTRACT

Von Willebrand disease (VWD) is the most common inherited bleeding disorder with an estimated prevalence of ~1% and clinically relevant bleeding symptoms in approximately 1:10,000 individuals. VWD is caused by a deficiency and/or defect of von Willebrand factor (VWF). The most common symptoms are mucocutaneous bleeding, hematomas, and bleeding after trauma or surgery. For decades, treatment to prevent or treat bleeding has consisted of desmopressin in milder cases and of replacement therapy with plasma-derived concentrates containing VWF and Factor VIII (FVIII) in more severe cases. Both are usually combined with supportive therapy, e.g. antifibrinolytic agents, and maximal hemostatic measures. Several developments such as the first recombinant VWF concentrate, which has been recently licensed for VWD, will make a more "personalized" approach to VWD management possible. As research on new treatment strategies for established therapies, such as population pharmacokinetic-guided dosing of clotting factor concentrates, and novel treatment modalities such as aptamers and gene therapy are ongoing, it is likely that the horizon to tailor therapy to the individual patients' needs will be extended, thus, further improving the already high standard of care in VWD in most high-resource countries.

Pharmacotherapy of Myelofibrosis

Douglas TremblayBridget MarcellinoJohn Mascarenhas

ABSTRACT

Myelofibrosis (MF) is a myeloproliferative neoplasm that is pathologically characterized by bone marrow myeloproliferation, reticulin and collagen fibrosis, and extramedullary hematopoiesis. Constitutive activation of the Janus associated kinase (JAK)-signal transducers and activators of transcription signaling pathway with resultant elevation in pro-inflammatory cytokine levels is the pathogenic hallmark of MF. JAK inhibitors, namely ruxolitinib, have been successful in alleviating symptoms and reducing splenomegaly, but therapy-related myelosuppression has led to the further development of highly selective JAK2 inhibitors. Additionally, ruxolitinib does not appear to affect the malignant hematopoietic clone substantially, evidenced by lack of molecular remissions, bone marrow histopathologic responses, and a proportion of treated patients developing progressive disease and leukemic transformation while receiving therapy. A number of other pharmacotherapeutic strategies are currently being explored in the clinic. Non-JAK inhibitor strategies being evaluated in MF include non-JAK signaling pathway inhibitors, epigenetic-directed therapies, immune-modulating agents, anti-fibrotic agents, and telomerase inhibitors. This review highlights the current landscape of MF pharmacotherapy and explores therapeutic advances underway.

Abiraterone Acetate: A Review in Metastatic Castration-Resistant Prostrate Cancer

Lesley J. Scott

ABSTRACT

Oral abiraterone acetate (Zytiga®) is a selective inhibitor of CYP17 and thereby inhibits androgen biosynthesis, with androgen signalling crucial in the progression from primary to metastatic prostate cancer (PC) and subsequently, in the development of metastatic castration-resistant PC (mCRPC). In large phase 3 trials and in the clinical practice setting, oral abiraterone acetate in combination with prednisone was an effective treatment and had an acceptable, manageable tolerability and safety profile in chemotherapy-naive and docetaxel-experienced men with mCRPC. In the pivotal global phase 3 trials, relative to placebo (+prednisone), abiraterone acetate (+prednisone) prolonged overall survival (OS) at data maturity (final analysis) and radiographic progression-free survival (rPFS) at all assessed timepoints. Given its efficacy in prolonging OS and its convenient once-daily oral regimen, in combination with prednisone, abiraterone acetate is an important first-line option for the treatment of mCRPC.

Canagliflozin: A Review in Type 2 Diabetes

Emma D. Deeks, André J. Scheen

ABSTRACT

Canagliflozin (Invokana®) is a sodium-glucose co-transporter-2 (SGLT2) inhibitor indicated in various countries worldwide for the once-daily oral treatment of type 2 diabetes (T2D). Canagliflozin lowers blood glucose levels independently of insulin, with the inhibition of SGLT2 reducing renal reabsorption of glucose and increasing excretion of glucose in the urine. In well-designed clinical trials, canagliflozin (as first-line monotherapy or add-on therapy to other antihyperglycaemic agents) improved glycaemic control in adults with T2D, including those of older age and/or at high cardiovascular (CV) risk, and also had beneficial effects on their bodyweight and blood pressure (BP). CV risk reduction, as well as possible renal benefits, were also seen with canagliflozin in T2D patients at high CV risk in the CANVAS Program, an integrated analysis of two large CV outcomes studies. Canagliflozin was generally well tolerated, had a low risk of hypoglycaemia and was most commonly associated with adverse events such as genital and urinary tract infections and increased urination, consistent with its mechanism of action. Although the amputation and fracture risk observed among recipients of the drug require further investigation, canagliflozin is an important option for T2D management in adults.

Fampridine Prolonged Release: A Review in Multiple Sclerosis Patients with Walking Disability

Esther S. Kim

ABSTRACT

Oral fampridine prolonged release (PR) [Fampyra®] is a lipid-soluble selective potassium channel blocker that is approved in the EU for the improvement of walking in adult multiple sclerosis (MS) patients with walking disability (expanded disability status scale score of 4–7). In clinical trials (MS-F203 and MS-F204) using an objective measure of walking improvement [the timed 25-foot walk (T25FW)], more than one-third of patients receiving fampridine PR achieved a consistent on-treatment improvement in walking speed (i.e. became TW responders) over 9–14 weeks of treatment. Fampridine PR recipients who fulfilled the definition of TW responder had mean improvements of ≈25% from baseline in T25FW walking speed. In a clinical trial (ENHANCE) that used a patient-rated measure of walking improvement [12-item MS walking scale (MSWS-12)], a significantly greater proportion of fampridine PR recipients than placebo recipients achieved a ≥8-point improvement on the MSWS-12 with 24 weeks of treatment. Where reported, adverse events were mostly mild or moderate in severity, and generally consistent with the underlying disease or mechanism of action of fampridine PR. Fampridine PR is a useful treatment option to consider in adult MS patients with walking disability.

Inotuzumab Ozogamicin: First Global Approval

Yvette N. Lamb

ABSTRACT

Intravenous inotuzumab ozogamicin (Besponsa®; Pfizer) is an anti-CD22 monoclonal antibody-calicheamicin conjugate that binds to CD22-expressing tumour cells. Upon binding, the complex is internalised and the cytotoxic calicheamicin derivative is released inside the cell, inducing double-strand DNA breakage and subsequent cell death. In June 2017, the EMA granted inotuzumab ozogamicin approval as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia (ALL). The use of inotuzumab ozogamicin in adult patients with Philadelphia chromosome-positive, relapsed or refractory CD22-positive B-cell precursor ALL is restricted to those who have failed treatment with at least one tyrosine kinase inhibitor. Inotuzumab ozogamicin was granted priority review for the treatment of relapsed or refractory B-cell precursor ALL by the US FDA in February 2017. In the USA, a phase III trial evaluating inotuzumab ozogamicin in combination with frontline chemotherapy in adults with newly diagnosed B-cell ALL has recently been initiated and inotuzumab ozogamicin is under phase II evaluation in childhood CD22-positive B-cell ALL. Inotuzumab ozogamicin combination therapies are also being evaluated in the phase I/II or II setting in ALL and chronic myeloid leukaemia and in the phase I setting in Burkitt's lymphoma. This article summarises the milestones in the development of inotuzumab ozogamicin leading to this first approval for ALL.

Potential Role of Thyroid Receptor β Agonists in the Treatment of Hyperlipidemia

Tomas JakobssonLise-Lotte VedinPaolo Parini

ABSTRACT

Thyroid hormones have important effects on cellular development, growth, and metabolism and are necessary for the healthy function of almost all tissues. Hyperthyroid patients with excess thyroid hormone levels experience tachycardia, fatigue, muscle wasting, and osteoporosis. However, although high thyroid hormone levels have adverse effects, efforts have been made to harness the beneficial effects, such as reduced serum low-density lipoprotein (LDL) cholesterol levels, elevated basal metabolic rate, and weight loss. Thyroid hormones interact with nuclear thyroid hormone receptors (TRs), and cholesterol levels are reduced through TRβ, whereas extrahepatic adverse actions are primarily connected to TRα. Thus, to develop a useful compound for clinical use, efforts have been focusing on developing compounds with isomer-specific functions based on the structure of thyroid hormones, i.e., thyromimetics that are liver and/or TRβ specific. In this short review, we discuss the development of the early thyromimetics that enabled, through modern molecular techniques, the progress towards improved design of TRβ-selective thyromimetics. We also address the early promise shown in human clinical trials and the current status of these drugs and other emerging compounds.

Clinical Assessment and Management of Delirium in the Palliative Care Setting

Shirley Harvey Bush, Sallyanne TierneyPeter Gerard Lawlor

ABSTRACT

Delirium is a neurocognitive syndrome arising from acute global brain dysfunction, and is prevalent in up to 42% of patients admitted to palliative care inpatient units. The symptoms of delirium and its associated communicative impediment invariably generate high levels of patient and family distress. Furthermore, delirium is associated with significant patient morbidity and increased mortality in many patient populations, especially palliative care where refractory delirium is common in the dying phase. As the clinical diagnosis of delirium is frequently missed by the healthcare team, the case for regular screening is arguably very compelling. Depending on its precipitating factors, a delirium episode is often reversible, especially in the earlier stages of a life-threatening illness. Until recently, antipsychotics have played a pivotal role in delirium management, but this role now requires critical re-evaluation in light of recent research that failed to demonstrate their efficacy in mild- to moderate-severity delirium occurring in palliative care patients. Non-pharmacological strategies for the management of delirium play a fundamental role and should be optimized through the collective efforts of the whole interprofessional team. Refractory agitated delirium in the last days or weeks of life may require the use of pharmacological sedation to ameliorate the distress of patients, which is invariably juxtaposed with increasing distress of family members. Further evaluation of multicomponent strategies for delirium prevention and treatment in the palliative care patient population is urgently required.

Anti-PD-1 Antibodies as a Therapeutic Strategy in Classical Hodgkin Lymphoma

Michael D. JainJohn Kuruvilla

ABSTRACT

Classical Hodgkin lymphoma (cHL) is defined by malignant Reed–Sternberg (RS) cells that recruit non-malignant immune cells into a supportive tumour microenvironment. In cHL, this is driven, in part, by genomic alterations of the 9p24.1 locus encoding the immune checkpoint ligands PD-L1 and PD-L2. Therapeutic anti-PD-1 antibodies have been developed that competitively inhibit the interaction between PD-1 and its ligands. Clinical trials of anti-PD-1 antibodies in cHL demonstrate high overall response rates but relapses still occur and new clinical challenges exist for toxicity management and response assessment. This review discusses the biological and clinical features of anti-PD-1 antibody therapy in cHL.

Bezlotoxumab: A Review in Preventing Clostridium difficile Infection Recurrence

Emma D. Deeks

ABSTRACT

Bezlotoxumab (Zinplava™) is a fully human monoclonal antibody against Clostridium difficile toxin B indicated for the prevention of C. difficile infection (CDI) recurrence in patients with a high recurrence risk. It is the first agent approved for recurrence prevention and is administered as a single intravenous infusion in conjunction with standard-of-care (SoC) antibacterial treatment for CDI. In well-designed, placebo-controlled, phase 3 trials (MODIFY 1 and 2), a single infusion of bezlotoxumab, given in combination with SoC antibacterial therapy for CDI in adults, was effective in reducing CDI recurrence in the 12 weeks post-treatment, with this benefit being seen mainly in the patients at high recurrence risk. Bezlotoxumab did not impact the efficacy of the antibacterials being used to treat the CDI and, consistent with its benefits on CDI recurrence, appeared to reduce the need for subsequent antibacterials, thus minimizing further gut microbiota disruption. Longer term, there were no further CDI recurrences over 12 months' follow-up among patients who had received bezlotoxumab in MODIFY 2 and entered an extension substudy. Bezlotoxumab has low immunogenicity and is generally well tolerated, although the potential for heart failure in some patients requires consideration; cost-effectiveness data for bezlotoxumab are awaited with interest. Thus, a single intravenous infusion of bezlotoxumab during SoC antibacterial treatment for CDI is an emerging option for reducing CDI recurrence in adults at high risk of recurrence.

Ulipristal Acetate: A Review in Symptomatic Uterine Fibroids

Karly P. Garnock-Jones, Sean T. Duggan

ABSTRACT

Oral ulipristal acetate (Esmya®; Fibristal®), a synthetic selective progesterone receptor modulator, is the first selective progesterone modulator to be approved for the treatment of uterine fibroids. It was initially approved for the preoperative treatment of moderate to severe uterine fibroid symptoms in women of reproductive age. Recently, the indication was extended in the EU to include the intermittent treatment of moderate to severe uterine fibroid symptoms. This narrative review summarizes pharmacological, efficacy and tolerability data relevant to the preoperative and intermittent use of ulipristal acetate in patients with symptomatic uterine fibroids. Ulipristal acetate is an effective and generally well tolerated treatment for patients with symptomatic uterine fibroids, both as preoperative, single-course treatment and as intermittent, longer-term treatment. It is noninferior in efficacy to intramuscular leuprolide acetate, as a preoperative treatment, and is associated with a lower rate of hot flashes, a common adverse event with gonadotropin-releasing hormone analogues. Thus, ulipristal acetate is an effective option for both preoperative and intermittent treatment of moderate to severe, symptomatic uterine fibroids in women of reproductive age.

Lonoctocog Alfa: A Review in Haemophilia A

Zaina T. Al-Salama, Lesley J. Scott

ABSTRACT

Lonoctocog alfa (rVIII-SingleChain; Afstyla®) is a novel single-chain recombinant factor VIII (FVIII) molecule, with a truncated B-domain and the heavy and light chains covalently linked to form a stable and homogenous drug that binds with high affinity to von Willebrand factor (VWF). Intravenous lonoctocog alfa is approved for the prophylaxis and treatment of bleeding in patients with haemophilia A in several countries worldwide. In two pivotal, multicentre trials, lonoctocog alfa was effective in the treatment of bleeding episodes and as prophylaxis, including for perioperative management in adults, adolescents and children. In terms of haemostatic efficacy in controlling bleeding episodes, overall treatment and investigator-assessed success rates were high across all age groups, with the majority of these bleeds controlled with a single injection of lonoctocog alfa. Low median spontaneous, overall and traumatic annualized bleeding rates were evident with prophylactic lonoctocog alfa regimens in both trials. Lonoctocog alfa was generally well-tolerated, with very low rates of injection-site reactions. No previously treated patient experienced an anaphylactic reaction or developed an inhibitor. In conclusion, lonoctocog alfa is an effective and generally well-tolerated alternative to conventional FVIII products for the treatment and prophylaxis of bleeding, including in the surgical setting, in adults, adolescents and children with haemophilia A.

Rolapitant: A Review in Chemotherapy-Induced Nausea and Vomiting

Young-A Heo, Emma D. Deeks

ABSTRACT

Oral rolapitant (Varubi™; Varuby®), a long-acting neurokinin-1 (NK1) receptor antagonist (RA), is indicated in the USA and EU as part of an antiemetic regimen to prevent delayed chemotherapy-induced nausea and vomiting (CINV) in adults receiving highly or moderately emetogenic chemotherapy (HEC or MEC). In randomized, phase III trials, a single oral dose of rolapitant 180 mg was effective in preventing delayed CINV compared with placebo, when each was used in combination with a 5-HT3 RA plus dexamethasone, in adults receiving their first course of HEC or MEC. The benefits of rolapitant were maintained over multiple cycles of chemotherapy. The tolerability profile of rolapitant is similar to that of placebo and consistent with that of other NK1 RAs. However, rolapitant differs from other existing NK1 RAs in that it does not interact with CYP3A4, thereby negating the need for dexamethasone dose adjustments and potentially making rolapitant a more suitable option for patients receiving CYP3A4 substrates. Thus, oral rolapitant is an effective and well tolerated NK1 RA that expands the treatment options for preventing delayed CINV in adults receiving HEC or MEC.

Enasidenib: First Global Approval

Esther S. Kim

ABSTRACT

Enasidenib (Idhifa®) is an oral isocitrate dehydrogenase-2 (IDH2) inhibitor developed by Celgene Corporation under a global, exclusive license from Agios Pharmaceuticals. Enasidenib has been approved in the USA for the treatment of adults with relapsed or refractory acute myeloid leukaemia (AML) and an IDH2 mutation as detected by an FDA-approved test. It is at various stages of development in other countries for AML, myelodysplastic syndromes and solid tumours. This article summarizes the milestones in the development of enasidenib leading to this first global approval in the USA for the treatment of adults with relapsed or refractory IDH2-mutated AML.

Neratinib: First Global Approval

Emma D. Deeks

ABSTRACT

Neratinib (Nerlynx™) is an oral, irreversible inhibitor of the human epidermal growth factor receptors HER1 (EGFR), HER2 and HER4. The drug originally arose from research by Wyeth (now Pfizer) and is now being developed by Puma Biotechnology primarily for the treatment of HER2-positive (HER+) breast cancer. Neratinib is approved in the USA for the extended adjuvant treatment of patients with HER2+ early-stage breast cancer who have been previously treated with a trastuzumab-based adjuvant regimen, and is in the preregistration phase for this indication in the EU. Neratinib, as monotherapy and/or combination therapy, is also in phase 3 development for metastatic breast cancer and in phase 1/2 development for advanced breast cancer and other solid tumours, including non-small cell lung cancer, colorectal cancer and glioblastoma. This article summarizes the milestones in the development of neratinib leading to this first approval for breast cancer.

Volume 77, Issue 16, October 2017

Pharmacological Management of Chronic Rhinosinusitis: Current and Evolving Treatments

Daniel M. BeswickStacey T. GrayTimothy L. Smith

ABSTRACT

Chronic rhinosinusitis (CRS) is an inflammatory sinonasal condition with multiple etiologic factors that is associated with a vast economic cost. Treatment is most frequently pharmacologic and has centered on agents that ameliorate inflammation, decrease bacterial or pathogen load, and facilitate egress of mucus or purulence from the sinonasal cavity. Nasal saline irrigations, topical nasal steroids, certain antibiotics, and systemic steroids have shown some efficacy in the management of CRS. Recently, biologic therapeutics that target specific inflammatory pathways associated with subsets of CRS have been developed and evaluated. Early data evaluating these biologic treatments suggest a potential role in treating a subset of CRS with refractory, poorly controlled disease. Additional studies are necessary to identify which patients would benefit most from biologic therapies and to assess the cost of these therapies compared with the benefit they provide. This review describes the pathophysiology of CRS and summarizes both established and novel biologic pharmacologic treatments.

Pemafibrate: First Global Approval

Hannah A. Blair

ABSTRACT

Pemafibrate (Parmodia®) is a novel, highly selective peroxisome proliferator-activated receptor (PPAR)-α modulator (SPPARM). It acts by binding to PPAR-α and regulating the expression of target genes that modulate lipid metabolism, thereby decreasing plasma triglyceride levels and increasing high-density lipoprotein cholesterol levels. Developed by Kowa Company, Ltd., oral pemafibrate has been approved in Japan for the treatment of hyperlipidaemia (including familial hyperlipidaemia). This article summarizes the milestones in the development of pemafibrate leading to this first global approval for hyperlipidaemia.

Pharmacological Management of Gestational Diabetes Mellitus

Geetha MukerjiDenice S. Feig

ABSTRACT

Gestational diabetes mellitus (GDM) is associated with an increased risk of adverse pregnancy outcomes in the setting of poor glycemic control. The initial management for GDM includes intensive lifestyle modification, which often requires behavioral and nutritional changes to optimize glycemic control. Pharmacotherapy for GDM is initiated when glycemic targets are not met. The rapid-acting bolus analogues aspart and lispro achieve postprandial targets with less hypoglycemia compared to regular insulin, with similar fetal outcomes. The long-acting insulin analogues glargine and detemir appear safe with similar maternal/fetal outcomes compared to NPH. While insulin has been the mainstay therapy for women with GDM to improve glycemic control when lifestyle modifications are insufficient, certain oral antihyperglycemic drugs (OADs) can be considered as alternative treatment options for GDM but continue to be controversial for use as first-line treatment options compared to insulin by many professional bodies. Metformin has good efficacy and short-term safety data but it freely crosses the placenta and long-term safety data are lacking. Glyburide has good efficacy and short-term data but it also crosses the placenta and may be associated with increased rates of large-for-gestational-age (LGA) infants and neonatal hypoglycaemia when compared with insulin. This review aims to give an overview of the pharmacological treatment for women with GDM including some of the known safety profiles of current therapeutic options.

Dual Antiplatelet Therapy Duration: Reconciling the Inconsistencies

Francesco CostaStephan WindeckerMarco Valgimigli

ABSTRACT

Dual antiplatelet therapy (DAPT) prevents recurrent ischemic events after an acute coronary syndrome (ACS) as well as stent thrombosis (ST) in patients with prior stent implantation. Nevertheless, these benefits are counterbalanced by a significant bleeding hazard, which is directly related to the treatment duration. Although DAPT has been extensively studied in numerous clinical trials, optimal treatment duration is still debated, mostly because of apparent inconsistencies among studies. Shortened treatment duration of 6 or 3 months was shown to mitigate bleeding risk compared with consensus-grounded 12-month standard duration, without any apparent excess of ischemic events. However, recent trials showed that a >12-month course of treatment reduces ischemic events but increases bleeding compared with 12 months. The inconsistent benefit of a longer DAPT course compared with shorter treatment durations is puzzling, and requires a careful appraisal of between-studies differences. We sought to summarize the existing evidence aiming at reconciling apparent inconsistencies among these studies, as well as thoroughly discuss the possible increased risk of fatal events associated with long-term DAPT. Benefits and risks of prolonging or shortening DAPT duration will be discussed, with a focus on treatment individualization. Finally, we will provide an outlook for possible future directions in the field.

Benefit–Risk Profile of Sphingosine-1-Phosphate Receptor Modulators in Relapsing and Secondary Progressive Multiple Sclerosis

Giancarlo Comi, Hans-Peter HartungRajesh BakshiIan M. WilliamsHeinz Wiendl

ABSTRACT

Since the approval of fingolimod, several selective sphingosine-1-phosphate receptor modulators have entered clinical development for multiple sclerosis. However, side effects can occur with sphingosine-1-phosphate receptor modulators. By considering short-term data across the drug class and longer term fingolimod data, we aim to highlight the potential of sphingosine-1-phosphate receptor modulators in multiple sclerosis, while offering reassurance that their benefit–risk profiles are suitable for long-term therapy. Short-term fingolimod studies demonstrated the efficacy of this drug class, showed that cardiac events upon first-dose administration are transient and manageable, and showed that serious adverse events are rare. Early-phase studies of selective sphingosine-1-phosphate receptor modulators also show efficacy with a similar or improved safety profile, and treatment initiation effects were reduced with dose titration. Longer term fingolimod studies demonstrated sustained efficacy and raised no new safety concerns, with no increases in macular edema, infection, or malignancy rates. Switch studies identified no safety concerns and greater patient satisfaction and persistence with fingolimod when switching from injectable therapies with no washout period. Better outcomes were seen with short than with long washouts when switching from natalizumab. The specific immunomodulatory effects of sphingosine-1-phosphate receptor modulators are consistent with the low observed rates of long-term, drug-related adverse effects with fingolimod. Short-term data for selective sphingosine-1-phosphate receptor modulators support their potential effectiveness in multiple sclerosis, and improved side-effect profiles may widen patient access to this drug class. The long-term safety, tolerability, and persistence profiles of fingolimod should reassure clinicians that sphingosine-1-phosphate receptor modulators are likely to be suitable for the long-term treatment of multiple sclerosis.

Overlapping Effects of New Monoclonal Antibodies for Severe Asthma

Christian Domingo

ABSTRACT

Among the monoclonal antibodies (mAbs) developed for severe asthma treatment, three have already been marketed. Omalizumab was the first, more than 10 years ago; today, mepolizumab and reslizumab are also available in the European Union and the US. Omalizumab blocks free immunoglobulin E (IgE), mepolizumab and reslizumab block an interleukin (IL-5). In the near future, dupilumab and benralizumab are expected to emerge as two new alternatives. Benralizumab blocks the receptor for IL-5 (IL5-Rα) and has a direct cytotoxic effect on eosinophils, and dupilumab blocks the α-unit of the heterodimeric receptor for IL-4 and IL-13 (IL-4Rα); as a result, dupilumab can block both IL-4 and IL-13. The purpose of this manuscript is to present the pathophysiology of some immunological aspects of severe asthma, describe the adaptive and innate immunity arms as well as their interrelations (stressing the subordination of the adaptive arm to the innate arm), outline the pharmacologic effects of these mAbs, clarify the overlapping effects of the different mAbs, and discuss the differences between mAbs based on their target molecules. Based on the data presented, I propose omalizumab for patients with an allergic phenotype regardless of their peripheral eosinophilic count, and anti-IL-5 as an alternative in allergic patients with blood eosinophilia in which omalizumab has failed; anti-IL5 for patients with an eosinophilic phenotype and omalizumab as an alternative in patients in whom anti-IL5 fails and IgE ≥30 IU/mL (compassionate use). Omalizumab is also proposed for patients with severe chronic asthma allergic to seasonal allergens.

Raltegravir Once-Daily Tablet: A Review in HIV-1 Infection

Emma D. Deeks

ABSTRACT

A once-daily tablet formulation (Isentress® HD; Isentress® 600 mg) of the integrase strand transfer inhibitor raltegravir is now available for the treatment of HIV-1 infection. The 600 mg tablet has improved bioavailability versus the existing twice-daily 400 mg tablet (due, at least in part, to differences in tablet dissolution) and the recommended dosage is 1200 mg (i.e. two 600 mg tablets) once daily. In combination with emtricitabine/tenofovir disoproxil fumarate in treatment-naïve adults, once-daily raltegravir 1200 mg provided virological suppression non-inferior to that seen with twice-daily raltegravir 400 mg over 48 and 96 weeks in the phase 3 ONCEMRK trial. The once-daily raltegravir regimen was also generally well tolerated in this study, displaying a tolerability profile similar to that of the twice-daily regimen. The once-daily tablet simplifies and improves the convenience of raltegravir regimens, although its impact on adherence has yet to be determined. Thus, once-daily raltegravir tablets are a convenient alternative to twice-daily raltegravir tablets for the treatment of HIV-1, further expanding the therapeutic options available to meet the diverse needs of this patient population.

Glecaprevir/Pibrentasvir: First Global Approval

Yvette N. Lamb

ABSTRACT

A fixed-dose combination tablet of the hepatitis C virus (HCV) NS3/4A protease inhibitor (PI) glecaprevir and the HCV NS5A inhibitor pibrentasvir [glecaprevir/pibrentasvir; MAVIRET™ (EU); MAVYRET™ (USA)] has been developed by AbbVie. Oral glecaprevir/pibrentasvir 300 mg/120 mg (three 100 mg/40 mg tablets) taken once daily has been approved by the EMA for the treatment of all major genotypes (genotypes 1–6) of chronic HCV infection in adults. It has also been approved by the US FDA for the treatment of adult patients with chronic HCV genotype 1–6 infection without cirrhosis and with compensated cirrhosis, and for the treatment of adult patients with HCV genotype 1 infection who previously have been treated with a regimen containing either an HCV NS5A inhibitor or an NS3/4A PI, but not both. This article summarizes the milestones in the development of glecaprevir/pibrentasvir leading to its first global approval in the EU and subsequent approval in the USA for chronic HCV infection.

Elsulfavirine: First Global Approval

Zaina T. Al-Salama

ABSTRACT

Elsulfavirine (Elpida®) is a new-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) being developed by Viriom for the treatment and prevention of human immunodeficiency virus (HIV) infections. It is the prodrug of the active compound VM-1500A, a small molecule selective NNRTI, which prevents HIV replication. In June 2017, elsulfavirine received its first global approval in Russia for the treatment of HIV-1 infections in combination with other antiretroviral medicines. Other formulations of this drug are also being evaluated in preclinical and phase II studies for the treatment of HIV infections and/or pre-exposure and post-exposure prophylaxis. This article summarizes the milestones in the development of elsulfavirine leading to this first approval in HIV-1 treatment.

A Review of Food–Drug Interactions on Oral Drug Absorption

Jianyuan DengXiao ZhuZongmeng ChenChun Ho FanHim Shek KwanChi Ho WongKa Yi ShekZhong ZuoTai Ning LamEmail author

ABSTRACT

Food effect, also known as food–drug interactions, is a common phenomenon associated with orally administered medications and can be defined as changes in absorption rate or absorption extent. The mechanisms of food effect and their consequences can involve multiple factors, including human post-prandial physiology, properties of the drug, and how the drug is administered. Therefore, it is essential to have a thorough understanding of these mechanisms when recommending whether a specific drug should be taken with or without food. Food–drug interactions can be clinically relevant, especially when they must be avoided to prevent undesirable effects or exploited to optimize medication therapy. This review conducts a literature search that examined studies on food effect. We summarized the literature and identified and discussed common food effect mechanisms. Furthermore, we highlighted drugs that have a clinically significant food effect and discussed the corresponding mechanisms. In addition, this review analyzes the effects of high-fat food or standard meals on the oral drug absorption rate and absorption extent for 229 drugs based on the Biopharmaceutics Drug Disposition Classification System and demonstrates an association between Biopharmaceutics Drug Disposition Classification System class and food effect.

Deutetrabenazine: A Review in Chorea Associated with Huntington's Disease

Young-A Heo, Lesley J. Scott

ABSTRACT

Oral deutetrabenazine (Austedo™), a reversible inhibitor of vesicular monoamine transporter type 2 (VMAT2) that is structurally related to tetrabenazine is approved for the treatment of chorea symptoms associated with Huntington's disease (HD). In the pivotal 12-week phase III FIRST-HD trial (n = 90), deutetrabenazine, at doses titrated for optimal chorea control and tolerability (maintenance dosage range 12–48 mg/day), was significantly more effective for controlling chorea in HD patients than placebo. In the ongoing phase III ARC-HD trial, a preliminary analysis demonstrated that deutetrabenazine treatment was associated with improvements in chorea control at 54 weeks in patients who had completed FIRST-HD (i.e. ≤ 66 weeks' treatment; rollover cohort) or switched overnight from tetrabenazine to deutetrabenazine. The tolerability profile of deutetrabenazine is similar to that of placebo, with most treatment-emergent adverse events of mild or moderate severity. In both trials, with the exception of somnolence, individual neuropsychiatric adverse events typically occurred in < 7% of deutetrabenazine recipients; in FIRST-HD, there was no significant difference in the incidence of individual neuropsychiatric events between the deutetrabenazine and placebo groups. The favourable pharmacokinetic (PK) profile of deutetrabenazine permits a lower dosage than tetrabenazine, thereby potentially improving the safety profile of deutetrabenazine versus tetrabenazine, whilst maintaining its efficacy. Long-term clinical experience will assist in fully defining the safety profile of deutetrabenazine. Current evidence, albeit relatively limited, indicates that deutetrabenazine provides an effective and potentially better tolerated option than tetrabenazine for controlling chorea symptoms associated with HD.

Tocilizumab: A Review in Rheumatoid Arthritis

Lesley J. Scott

ABSTRACT

Intravenous (IV) and subcutaneous (SC) tocilizumab (RoActemra®), an IL-6 receptor antagonist, are approved (± methotrexate) in numerous countries throughout the world, for the treatment of adults with moderate to severe active rheumatoid arthritis (RA). Extensive clinical experience has firmly established the short- and long-term efficacy and safety of tocilizumab [monotherapy or in combination with conventional synthetic DMARDs (csDMARDs)] in adults with early-stage and longer-duration established RA. In the clinical trial and real-world settings, tocilizumab monotherapy or combination therapy provided rapid and sustained improvements in clinical and radiographic outcomes and health-related quality of life. The safety profile of tocilizumab is consistent over time and, in general, is consistent with that of other immunomodulatory agents. This narrative review, written from an EU perspective, summarizes the clinical use of IV and SC tocilizumab in RA. Given its low risk of immunogenicity, the flexibility of IV and SC administration and the convenience of the once-weekly, self-administered, SC regimen, tocilizumab provides an effective treatment for severe, active and progressive RA in adults not previously treated with methotrexate and an effective biologic first- or subsequent-line treatment for moderate to severe active RA in adults who have either responded inadequately to or were intolerant of previous therapy with ≥ 1 csDMARD or TNF inhibitor.

Meningococcal Quadrivalent Tetanus Toxoid Conjugate Vaccine (MenACWY-TT; Nimenrix®): A Review

Sohita Dhillon, David Pace

ABSTRACT

MenACWY-TT (Nimenrix®) is a quadrivalent meningococcal tetanus toxoid conjugate vaccine licensed in Europe for active immunisation of individuals aged ≥ 6 weeks against invasive disease caused by Neisseria meningitidis capsular groups A, C, W and Y. MenACWY-TT is the first quadrivalent conjugate vaccine to be approved in Europe for use in infants as young as 6 weeks of age. Numerous phase II–IIIb clinical studies showed that intramuscular MenACWY-TT administered as primary or booster vaccination was highly immunogenic for all four vaccine capsular groups and had an acceptable reactogenicity profile in individuals aged 6 weeks to ≥ 56 years. MenACWY-TT is as immunogenic and safe as other previously licensed monovalent capsular group C or quadrivalent capsular groups A, C, W and Y meningococcal vaccines and can be coadministered with other routine vaccines without adversely affecting the immunogenicity or safety profiles of either vaccine. Current data indicate that primary and booster vaccination with MenACWY-TT is a valuable and safe option for broadening meningococcal protection against four capsular groups across a broad age range, starting as early as 6 weeks of age.

Pomalidomide: A Review in Relapsed and Refractory Multiple Myeloma

Sheridan M. Hoy

ABSTRACT

Pomalidomide (Imnovid®; Pomalyst®), an analogue of thalidomide, is an immunomodulatory agent, with several mechanisms of action (both direct and indirect) thought to be involved in its anti-myeloma activity. Oral pomalidomide is available in several countries for use in combination with low-dose dexamethasone in adults with relapsed and refractory multiple myeloma. In multinational, phase II or III studies in patients with refractory, or relapsed and refractory multiple myeloma who had received ≥ 2 prior treatment regimens (including ≥ 2 cycles of both lenalidomide and bortezomib), pomalidomide plus low-dose dexamethasone was associated with prolonged progression-free survival (PFS) and overall survival and an improved overall response rate. Pomalidomide plus low-dose dexamethasone had a manageable tolerability profile, with neutropenia, infections, anaemia and thrombocytopenia being the most frequently reported grade 3 or 4 treatment-emergent adverse events. In conclusion, pomalidomide plus low-dose dexamethasone extends the treatment options available for the management of relapsed and refractory multiple myeloma in a patient population that has very limited treatment options.

Ciclosporin Ophthalmic Emulsion 0.1%: A Review in Severe Dry Eye Disease

Sheridan M. Hoy

ABSTRACT

Ciclosporin ophthalmic emulsion 0.1% (hereafter referred to as ciclosporin 0.1%) [Ikervis®] is an unpreserved cationic emulsion formulation containing an 0.1% concentration of ciclosporin. It has been approved in various countries worldwide, including those of the EU, for the treatment of severe keratitis in adults with dry eye disease, which has not improved despite treatment with tear substitutes. In a multinational, phase III study in this patient population, once-daily ciclosporin 0.1% was associated with statistically significant and clinically relevant improvements in the signs (corneal surface damage and ocular surface inflammation) of dry eye disease relative to vehicle during the first 6-month treatment period. These beneficial effects were maintained or improved in a subsequent 6-month period, with data suggesting sustainability following treatment discontinuation in a 24-month, phase III extension study. Ciclosporin 0.1% was well tolerated in these studies, with instillation-site pain (which was mostly mild in severity) being the most frequently reported ocular treatment-related adverse event. There were no findings to suggest the systemic absorption of ciclosporin. Thus, once-daily ciclosporin 0.1% is an effective and well tolerated option for the treatment of severe keratitis in adults with dry eye disease.

Tivozanib: First Global Approval

Esther S. Kim

ABSTRACT

Tivozanib (Fotivda®) is an oral, potent and highly selective vascular endothelial growth factor receptor (VEGFR) inhibitor that has been approved in the EU, Iceland and Norway for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR and mammalian target of rapamycin (mTOR) pathway inhibitor-naive following disease progression after one prior treatment with cytokine therapy for advanced RCC. Tivozanib is at various stages of development in other countries for advanced RCC and advanced solid tumours. This article summarizes the milestones in the development of tivozanib leading to this first global approval in Europe for the treatment of adults with advanced RCC.

Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome: Current Therapeutic Options and Potential Targets for Novel Therapies

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ABSTRACT

No specific antivirals are currently available for two emerging infectious diseases, Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). A literature search was performed covering pathogenesis, clinical features and therapeutics, clinically developed drugs for repurposing and novel drug targets. This review presents current knowledge on the epidemiology, pathogenesis and clinical features of the SARS and MERS coronaviruses. The rationale for and outcomes with treatments used for SARS and MERS is discussed. The main focus of the review is on drug development and the potential that drugs approved for other indications provide for repurposing. The drugs we discuss belong to a wide range of different drug classes, such as cancer therapeutics, antipsychotics, and antimalarials. In addition to their activity against MERS and SARS coronaviruses, many of these approved drugs have broad-spectrum potential and have already been in clinical use for treating other viral infections. A wealth of knowledge is available for these drugs. However, the information in this review is not meant to guide clinical decisions, and any therapeutic described here should only be used in context of a clinical trial. Potential targets for novel antivirals and antibodies are discussed as well as lessons learned from treatment development for other RNA viruses. The article concludes with a discussion of the gaps in our knowledge and areas for future research on emerging coronaviruses.

Progress in Elucidating Biomarkers of Antidepressant Pharmacological Treatment Response: A Systematic Review and Meta-analysis of the Last 15 Years

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ABSTRACT

Background: Antidepressant drugs are widely prescribed, but response rates after 3 months are only around one-third, explaining the importance of the search of objectively measurable markers predicting positive treatment response. These markers are being developed in different fields, with different techniques, sample sizes, costs, and efficiency. It is therefore difficult to know which ones are the most promising.

Objective: Our purpose was to compute comparable (i.e., standardized) effect sizes, at study level but also at marker level, in order to conclude on the efficacy of each technique used and all analyzed markers.

Methods: We conducted a systematic search on the PubMed database to gather all articles published since 2000 using objectively measurable markers to predict antidepressant response from five domains, namely cognition, electrophysiology, imaging, genetics, and transcriptomics/proteomics/epigenetics. A manual screening of the abstracts and the reference lists of these articles completed the search process.

Results: Executive functioning, theta activity in the rostral Anterior Cingular Cortex (rACC), and polysomnographic sleep measures could be considered as belonging to the best objectively measured markers, with a combined d around 1 and at least four positive studies. For inter-category comparisons, the approaches that showed the highest effect sizes are, in descending order, imaging (combined d between 0.703 and 1.353), electrophysiology (0.294–1.138), cognition (0.929–1.022), proteins/nucleotides (0.520–1.18), and genetics (0.021–0.515).

Conclusion: Markers of antidepressant treatment outcome are numerous, but with a discrepant level of accuracy. Many biomarkers and cognitions have sufficient predictive value ($d \geq 1$) to be potentially useful for clinicians to predict outcome and personalize antidepressant treatment.

Tofacitinib: A Review in Rheumatoid Arthritis

Sohita Dhillon

ABSTRACT

Tofacitinib (Xeljanz®) is a potent, selective JAK inhibitor that preferentially inhibits Janus kinase (JAK) 1 and JAK3. In the EU, oral tofacitinib 5 mg twice daily is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant of, one or more DMARDs. Several clinical studies of ≤ 24 months' duration showed that tofacitinib monotherapy (as first- or second-line treatment) and combination therapy with a conventional synthetic DMARD (csDMARD; as second- or third-line treatment) was effective in reducing signs and symptoms of disease and improving health-related quality of life (HR-QOL), with benefits sustained during long-term therapy (≤ 96 months). Tofacitinib monotherapy inhibited progression of structural damage in methotrexate-naïve patients during ≤ 24 months' treatment, with beneficial effects also seen in patients receiving tofacitinib plus methotrexate as second-line therapy for 12 months. Tofacitinib was generally well tolerated during ≤ 114 months' treatment, with most adverse events of mild or moderate severity. The tolerability profile of tofacitinib was generally similar to that of biological DMARDs (bDMARDs), with infections and infestations the most common adverse events (AEs) in tofacitinib recipients. However, the incidence of herpes zoster (HZ) was higher with tofacitinib than in the general RA population, although infections were clinically manageable. When added to background methotrexate, tofacitinib was noninferior to adalimumab in terms of efficacy, and both combination therapies had generally similar tolerability profiles. Although additional comparative studies are needed to more definitively position tofacitinib relative to bDMARDs and other targeted synthetic DMARDs, current evidence indicates that oral tofacitinib is a useful option for the treatment of patients with RA.

Nonacog Beta Pegol: A Review in Haemophilia B

Yahiya Y. Syed

ABSTRACT

Nonacog beta pegol [Refixia® (EU)] is an intravenously-administered, glycoPEGylated recombinant factor IX (FIX), with an extended terminal half-life. It is approved in the EU for the treatment and prophylaxis of bleeding in patients aged ≥ 12 years with haemophilia B. The therapeutic efficacy and safety of nonacog beta pegol was demonstrated in the phase 3 Paradigm trials in previously treated adolescents and adults with haemophilia B. In Paradigm 2, nonacog beta pegol showed good haemostatic effects when treating bleeds on-demand, and reduced annualized bleeding rates when used as a once-weekly prophylaxis. It also improved some health-related quality of life measures in adult patients. The longer-term efficacy of nonacog beta pegol was demonstrated in the open-label extension Paradigm 4 trial. In Paradigm 3, nonacog beta pegol effectively maintained intraoperative and postoperative haemostasis. Nonacog beta pegol was well tolerated in phase 3 clinical trials in patients with haemophilia B, with no evidence of FIX inhibitor formation, allergic reactions or thromboembolic complications. In conclusion, nonacog beta pegol is effective and well tolerated in the on-demand, prophylaxis and perioperative settings in adolescent and adults with haemophilia B. Its extended half-life allows for once-weekly prophylaxis. Therefore, nonacog beta pegol is a useful additional treatment option for patients with haemophilia B.

Daratumumab: A Review in Relapsed and/or Refractory Multiple Myeloma

Hannah A. Blair

ABSTRACT

Intravenous daratumumab (DARZALEX®) is a first-in-class human IgG1κ monoclonal antibody against CD38 available for use in patients with relapsed and/or refractory multiple myeloma. In phase I/II and II trials and a pooled analysis of these studies, daratumumab monotherapy induced an overall response (partial response or better) in approximately one-third of patients; responses were rapid, deep and durable. An overall survival (OS) benefit was seen with daratumumab monotherapy, including in patients with a minimal response or stable disease. In phase III trials, daratumumab in combination with either bortezomib plus dexamethasone or lenalidomide plus dexamethasone significantly prolonged progression-free survival and induced deep and durable responses compared with bortezomib plus dexamethasone or lenalidomide plus dexamethasone. An OS benefit with daratumumab triple combination therapy is yet to be demonstrated (as the OS data were not mature at the time of the last analysis). Daratumumab was generally well tolerated when used as monotherapy and had a generally manageable tolerability profile when used in combination therapy. Infusion-related reactions (IRRs) were the most common adverse events; these were predominantly grade 1 or 2 and mostly occurred during the first infusion. The most common grade 3–4 adverse events associated with daratumumab triple combination therapy were thrombocytopenia, neutropenia and anaemia. Although final OS data are awaited, current evidence indicates that daratumumab is a valuable addition to the treatment options currently available for patients with relapsed or refractory multiple myeloma.

Ticagrelor: A Review in Long Term Secondary Prevention of Cardiovascular Events

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ABSTRACT

Ticagrelor (Brilique®) is an orally administered P2Y12 inhibitor. A long-term (maintenance) regimen of ticagrelor 60 mg twice daily is indicated in the EU for coadministration with low-dose aspirin 75–150 mg/day for the secondary prevention of atherothrombotic events in high-risk patients with a history of myocardial infarction (MI) of at least 1 year. Approval is based on the results of the PEGASUS-TIMI 54 trial that compared ticagrelor with placebo (in conjunction with low-dose aspirin) in stable patients who had had a spontaneous MI 1–3 years prior to enrolment and were at high risk of atherothrombotic events. At 3 years, the composite primary efficacy endpoint of cardiovascular (CV) death, MI or stroke occurred in significantly fewer ticagrelor 60 mg twice daily than placebo recipients. Long-term ticagrelor had a manageable tolerability and safety profile. The risk of TIMI major bleeding (primary safety endpoint) was significantly increased in ticagrelor 60 mg twice daily versus placebo recipients; however, the risk appeared to decline after the first year of therapy. Landmark analyses have demonstrated that patients with a history of MI remain at a persistent high risk of the composite primary endpoint up to 5 years after the event. Furthermore, these analyses demonstrated that the efficacy of ticagrelor 60 mg twice daily was maintained over time, with less excess in bleeding after the first year. Thus, long-term dual antiplatelet therapy with ticagrelor 60 mg twice daily and low-dose aspirin is a valuable new option for the secondary prevention of atherothrombotic events in stable, high-risk patients with a history of MI of at least 1 year.

Triptorelin: A Review of its Use as an Adjuvant Anticancer Therapy in Early Breast Cancer

James E. Frampton

ABSTRACT

A 1-month formulation of the gonadotrophin-releasing hormone agonist (GnRHa) triptorelin (Decapeptyl®) has been approved in the EU as an adjuvant treatment in combination with tamoxifen or an aromatase inhibitor (AI), of endocrine-responsive, early-stage breast cancer in women at high risk of recurrence who are confirmed as premenopausal after completion of chemotherapy. This indication reflects the results of the 5-year SOFT and TEXT studies, especially SOFT, in which ovarian function suppression (OFS; mainly achieved with triptorelin) added to tamoxifen provided a significant benefit in the overall study population of premenopausal patients only after adjusting for prognostic factors. It emerged that adding OFS to tamoxifen produced more pronounced benefits in terms of disease control and, furthermore, increased overall survival in the cohort of higher-risk patients who had previously received chemotherapy. Also, compared with tamoxifen alone, the combination of OFS plus exemestane produced more pronounced benefits in terms of disease control than OFS plus tamoxifen. OFS induces premature menopause; when combined with either tamoxifen or exemestane, it increased the endocrine symptom burden. Nonetheless, the two combinations had distinct tolerability profiles (e.g. vasomotor symptoms and thromboembolic events were more frequent with OFS plus tamoxifen, whereas musculoskeletal symptoms, decreased libido, osteoporosis and fractures were more frequent with OFS plus exemestane). Thus, the combinations of OFS (with triptorelin) plus either tamoxifen or an AI are valid options for the adjuvant treatment of endocrine-responsive, early-stage breast cancer in women at sufficiently high risk of relapse to warrant receiving chemotherapy and who remain premenopausal thereafter. Individualized weighing of the potential benefits and adverse effects of treatment is required.

Aripiprazole Lauroxil: A Review in Schizophrenia

James E. Frampton

ABSTRACT

Aripiprazole lauroxil long-acting injectable (LAI) [Aristada®] is an intramuscularly administered, extended-release prodrug of aripiprazole, an established atypical antipsychotic agent that, in terms of its relative position within the class, is at the low end of the risk spectrum for metabolic side effects. In the USA, aripiprazole lauroxil LAI is indicated for the treatment of schizophrenia; approved doses of the drug can be injected once-monthly (q4w), every 6 weeks (q6w) or every 2 months (q8w). The efficacy of the 441 and 882 mg q4w dosages in the treatment of acute exacerbations of schizophrenia and as long-term maintenance therapy in stable schizophrenia has been directly demonstrated in a phase III clinical trial and extension, while the efficacy of the 662 mg q4w, 882 mg q6w and 1064 mg q8w dosing regimens has been established on the basis of pharmacokinetic bridging studies. Aripiprazole lauroxil LAI therapy was generally well tolerated, with an adverse event profile consistent with that of oral aripiprazole (with the exception of injection-site reactions), including a low propensity to cause metabolic disturbances. Thus, aripiprazole lauroxil LAI extends the treatment regimen options for patients with schizophrenia; as with other LAI formulations of antipsychotic agents, it can be particularly recommended for patients with recurrent relapses related to nonadherence to oral preparations and for those who prefer this mode of administration. Moreover, unlike aripiprazole monohydrate LAI, the only other commercially available long-acting formulation of aripiprazole, aripiprazole lauroxil LAI offers more than one dosing interval option, which may be a potential advantage in terms of tailoring therapy to the needs of individual patients.

Copanlisib: First Global Approval

Anthony Markham

ABSTRACT

Bayer are developing copanlisib (Aliqopa™)—a pan-class I phosphoinositide 3-kinase (PI3K) inhibitor—as a treatment for various haematological and solid malignancies. The US FDA has granted copanlisib accelerated approval for the treatment of adults with relapsed follicular lymphoma who have received at least two prior systemic therapies based on the results of a phase II trial. Phase III trials are underway evaluating copanlisib as treatment for relapsed/refractory diffuse large B-cell lymphoma and in combination with rituximab or rituximab-based chemotherapy or standard immunochemotherapy in patients with relapsed indolent B-cell non-Hodgkin's lymphoma. Phase I/II studies are underway in relapsed or refractory peripheral T-cell or NK/T-cell lymphoma, advanced cholangiocarcinoma, hormone receptor-positive HER2-negative stage I-IV breast cancer, HER2-positive breast cancer and recurrent and/or metastatic head and neck squamous cell carcinomas harbouring a PI3KCA mutation/amplification and/or a PTEN loss. This article summarizes the milestones in the development of copanlisib leading to this first approval for relapsed follicular lymphoma.

Abemaciclib: First Global Approval

Esther S. Kim

ABSTRACT

Abemaciclib (Verzenio™) is an orally administered inhibitor of cyclin-dependent kinases 4 and 6 that is being developed by Eli Lilly and Company. Abemaciclib has been approved in the USA for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, in combination with fulvestrant in women with disease progression following endocrine therapy, and as monotherapy in adult patients with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. In addition, abemaciclib is in various stages of development internationally for a variety of cancers. This article summarizes the milestones in the development of abemaciclib leading to its first approval for the treatment of patients with HR-positive, HER2-negative advanced or metastatic breast cancer.

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