Medical and Maintenance Treatments for Vitiligo

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KEYWORDS

• Vitiligo • Medical treatments • Topical steroids • Calcineurin inhibitors • Sytemic steroids • Methotrexate

KEY POINTS

- Medical treatments alone, or in combination with phototherapy, are key approaches for treating nonsegmental vitiligo and, to a lesser extent, for treating segmental vitiligo.
- The treatments can be useful for halting disease progression and have proved effective for inducing repigmentation and decreasing the risk of relapses.
- Although the treatments have some side effects and limitations, vitiligo often induces a marked decrease in the quality of life of affected individuals and in most cases the risk:benefit ratio is in favor of an active approach.
- Systemic and topical agents targeting the pathways involved in the loss of melanocytes and in the differentiation of melanocyte stem cells should provide even more effective approaches in the near future, thanks to the increased knowledge of the pathophysiology of vitiligo.

INTRODUCTION

There are 3 aims needed for the optimal care of vitiligo patients: first, halting the disease progression; then, allowing complete repigmentation of lesional areas; and, finally, preventing relapses. There is still no therapeutic panacea for vitiligo but current options can lead to significant improvement of vitiligo lesions. Some areas, such as the face, usually respond well to therapies whereas they remain mostly ineffective for others, such as hands and feet. Recent advances in the understanding of the pathophysiology of vitiligo foster new therapeutic opportunities. One of the most promising is the demonstration of the key role of the interferon gamma (INF-γ)/Janus kinase (JAK)/CXCL10 pathway in the depigmentation process of vitiligo.[1] Targeting this pathway might provide effective therapeutic approaches, as suggested by recent cases reports (discussed later).[2,3] The immune reaction is absent of complete depigmented lesions, however, and repigmentation may be difficult in lesions of some patients while their vitiligo remains inactive for years. Recent transcriptomic analysis showed an impaired Wnt signaling pathway in vitiligo lesions preventing the differentiation of melanocyte stem cells.[4] Fibroblasts of some areas, such as hands and feet, produce Wnt inhibitors.[5] This might contribute to a defect in melanocyte differentiation and could explain the difficulties for repigmenting those localizations. So far the best way to stimulate the differentiation of melanocytes is ultraviolet (UV) radiation. Recent data have shown that the action of UV on melanocyte stem cells is mediated by Wnt proteins.[6] Thus, stimulating the Wnt pathway by using topical agents might allow repigmenting even difficult-to-treat areas. Although phototherapy and surgery remain useful approaches for vitiligo, systemic or topical medical therapies are important alone or combined for optimal treatment of most vitiligo cases

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and, in light of recent pathophysiologic advances, they offer encouraging options for the near future.

HALTING DISEASE PROGRESSION

The course of vitiligo is unpredictable. An active phase, however, can be clinically detected. Medical history of the vitiligo, reporting a rapid onset and ongoing extension of depigmented lesions, is highly suggestive of active disease. Wood lamp examination is of great importance because it can show blurred and hypochromic borders of lesions that are associated with ongoing depigmenting process.[7] The presence of a confetti sign was recently reported to be also associated with a marked spreading of vitiligo lesions within the following months.[8] Several medical approaches have been proposed for halting or decreasing the progression of active vitiligo.

Systemic Steroids

Systemic corticosteroids (high-dose pulsed therapy, minipulsed regimen, or daily oral low dose) have been reported to rapidly arrest spreading vitiligo and to induce repigmentation.[9] Low-dose oral prednisolone (0.3 mg/kg) taken daily for 2 months[10] and a high dose of intravenous methylprednisolone (8 mg/kg) administered on 3 consecutive days[11] were evaluated in open-label clinical studies. Both regimens were reported to halt disease progression in more than 85% of cases and to induce some repigmentation in more than 70% of cases. Most studies have evaluated oral minipulse (OMP) betamethasone or dexamethasone using 5 mg twice a week on 2 consecutive days usually for 3 months[12] to 6 months.[13] The progression of disease was stopped in more than 85% of cases but a marked repigmentation was observed in less than 7% of cases. Side effects included weight gain, insomnia, acne, agitation, menstrual disturbance, and hypertrichosis. The prevalence of side effects ranged from 12%[12] to 69%.[13] A large retrospective study confirmed these results, showing an arrest of disease activity in 91.8% of cases.[14] Adverse reactions, such as weight gain, lethargy, and acneiform eruptions, were observed in 9.2% of patients. Relapses after discontinuation of the treatment are not rare. In 138 children treated with OMP of methylprednisolone for 6 months, 34.8% had relapses over a period of 1 year. The rate of relapses was higher in children below 10 years of age (47.4%). Thus, systemic corticosteroids seem to halt disease progression in most cases. No prospective randomized trial against placebo, however, has been performed yet. Given the significant potential for side effects and the high rate of relapses, the use of such an approach remains controversial.

Methotrexate

The first case supporting the use of methotrexate in vitiligo was reported in a woman treated with 7.5 mg per week for rheumatoid arthritis. She had a 6-month history of rapidly progressing vitiligo. She stopped developing new lesions after 3 months of treatment.[15] More recently, the efficacy of methotrexate (10 mg per week) was compared with OMP dexamethasone (5 mg per week with 2.5 mg taken on 2 consecutive days) in a prospective randomized open-label study in 52 vitiligo patients.[16] After 6 months of treatment, 6 of 25 patients developed new lesions with methotrexate compared with 7 of 25 patients with OMP. Both groups had also a similar reduction in vitiligo disease activity score. The investigators concluded that both drugs are equally effective in controlling the disease activity of vitiligo. The data evaluating the use of methotrexate in vitiligo, however, remain limited.

Minocycline

Minocycline was proposed for treating vitiligo because of its anti-inflammatory, immunomodulatory, and free-radical scavenging properties. An initial open-label study reported an arrest in disease progression in 29 of 32 patients treated with 100 mg per day of minocycline.[17] The same group further reported a prospective randomized trial comparing OMP (5 mg per week) with minocycline (100 mg per day)[18]; 50 patients with active vitiligo were included. After 6 months of treatment, both groups showed a significant decrease in vitiligo disease activity score from 4.0 to 1.64 $\pm$ 0.86 (P<.001) and from 4.0 to 1.68 $\pm$ 0.69 (P<.001), for minocycline and OMP, respectively. The difference between the 2 groups was not statistically significant (P = .60). Minocycline (100 mg per day) was also compared with narrow-band (Nb)-UVB (twice weekly) in a prospective comparative trial performed in 42 patients with active vitiligo.[19] After 3 months of treatment, only 23.8% of patients still had active lesions with Nb-UVB compared with 66.1% with minocycline (P<.05). Patients in the Nb-UVB group also showed significantly higher repigmentation compared with those in minocycline group. Both studies lacked an untreated group to assess the evolution of vitiligo without treatment. These results need further evaluation, but Nb-UVB seems more important for halting disease progression and has the main advantage of also promoting more efficient repigmentation of vitiligo lesions.

REPIGMENTATION THERAPIES

Corticosteroids

Intralesional corticosteroids were first reported for use in vitiligo 30 years ago. The pain associated with injection and the risk of cutaneous atrophy (observed in approximately one-third of patients) was against further use of this approach.[20] Recently, a series of 9 patients with localized vitiligo were successfully treated with intralesional injections of triamcinolone acetonide, 3 mg/mL (0.05–0.1 mL for each site), every 4 to 6 weeks with an average duration of the treatment of 4 months (maximum 7 months).[21] Skin atrophy was seen in 1 patient and menstrual irregularity reported in 2 patients. A meta-analysis of nonsurgical approaches for treating vitiligo reported equal efficacy of intralesional and topical steroids.[22] Taking into account the side effects of intralesional steroids, the use of topical forms should thus be preferred. Systemic steroids can be beneficial for halting systemic progression of active vitiligo but they have limited efficacy in repigmenting the lesions.[13]

Topical corticosteroids are useful for small, localized areas and remain one of the gold standard treatments for vitiligo. Meta-analyses confirmed their effectiveness for localized vitiligo.[23] Steroid-induced repigmentation occurs within 1 to 4 months of treatment in a perifollicular pattern and from the margins of the lesions. Side effects include epidermal atrophy, steroid-induced acne, rosacea, telangiectasia, ecchymoses, and striae. Atrophy was observed in 14% and 21%, respectively (mean), of patients treated with potent versus very potent corticosteroids.[24] Corticosteroids of low potency, however, show no therapeutic effect at all. Furthermore, suppression of the hypothalamic-pituitary-adrenal axis may occur after prolonged applications on large areas. To minimize the incidence of these side effects, it is recommended to use topical steroids on limited skin areas; to avoid prolonged use on sensitive areas, such as face and body folds; and to use them once daily for only 6 to 8 weeks followed by a treatment-free interval of several weeks because mild steroid-induced skin atrophy is reversible. Other schedules of intermittent therapy (3 weeks on and 1 week off and 5 days a week) have also been proposed.[25] To minimize side effects, treatment should be discontinued if there is no visible improvement after 3 months.

Topical Calcineurin Inhibitors

Early observations suggested that tacrolimus and pimecrolimus may be effective treatments for both localized and generalized vitiligo.[26,27] A 2-month double-blind randomized trial compared 0.1% tacrolimus and 0.05% clobetasol propionate in children with vitiligo.[28] This study confirmed that tacrolimus stimulates vitiligo repigmentation; however, tacrolimus ointment was not superior to clobetasol in extent of repigmentation. These results were confirmed by a prospective randomized trial comparing tacrolimus 0.1%, clobetasol propionate, and placebo.[29] Tacrolimus and clobetasol propionate showed similar efficacy and both provided significantly better repigmentation compared with placebo. Facial lesions responded faster and better compared with nonfacial lesions. Twice-daily application of 0.1% tacrolimus provided better results compared with once-daily applications.[30] The same results were obtained in an open intraindividual study performed with 1% pimecrolimus cream.[31] Again, 0.05% clobetasol propionate induced a comparable rate of repigmentation to a topical calcineurin inhibitor. The best results were observed on sun-exposed areas. An intraindividual prospective comparative study has shown that tacrolimus monotherapy in the absence of UV has little or no repigmenting potential in vitiligo.[32] An open randomized study compared topical pimecrolimus and topical tacrolimus to Nb-UVB for treating vitiligo.[33] The investigators did not find statistically significant differences in repigmentation among the 3 groups. It is now demonstrated, however, that best results are achieved when phototherapy is combined with these topical treatments (**Fig. 1**) (See Samia Esmat and colleagues article, "Phototherapy and Combination Therapies for Vitiligo," in this issue).

Other Topical Medical Treatments

Topical vitamin D analogs have been proposed alone or combined with phototherapy for treating vitiligo. A prospective, right/left comparative, open-label study showed that calcipotriol in monotherapy is not effective for vitiligo.[34]

There are several conflicting results on the use of topical antioxidants for treating vitiligo. In most cases, however, topical antioxidants are used in combination with phototherapy. One prospective intraindividual study compared 0.05% betamethasone to topical catalase/dismutase superoxide.[35] After 10 months of treatment, there was no statistical differences between the 2 groups ($P = .79$), with mean repigmentation of 18.5% with betamethasone and 12.4% with topical catalase/dismutase superoxide. Although the rationale for using topical antioxidants in vitiligo is strong, the data remain limited and controversial. One possible explanation is the difficulty of delivering active antioxidants into the skin. Double-blind

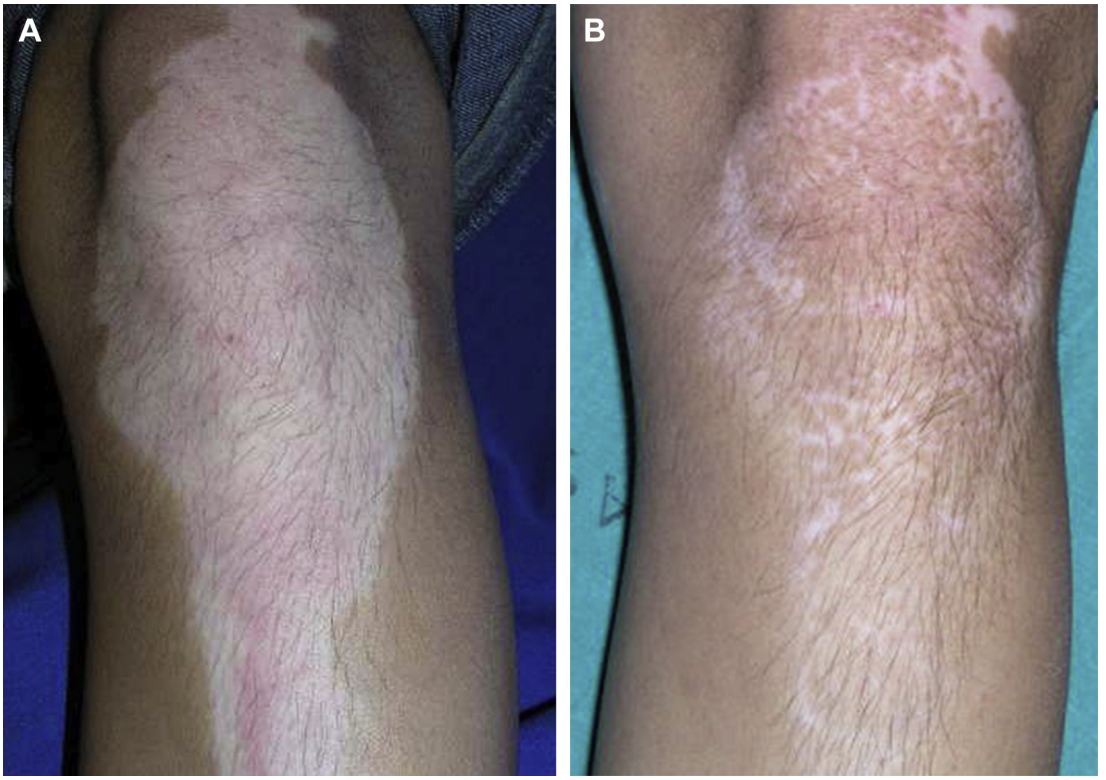

Fig. 1. Vitiligo of the leg and knee (*A*) before treatment and (*B*) after 30 sessions of 308-nm excimer laser combined with twice-daily applications of 0.1% of tacrolimus ointment.

placebo-controlled studies are mandatory to further investigate the real efficacy of such an approach for treating vitiligo.

INDICATIONS AND LIMITATIONS OF USING MEDICAL APPROACHES FOR TREATING VITILIGO

The use of systemic treatments, such as systemic corticosteroids or methotrexate, can induce potential serious side effects. The limited data actually available for their efficiency in treating vitiligo should prompt caution on their use in current practice. Their use remains controversial and should be limited to active vitiligo to halt the disease. Periodic monitoring of their efficacy and tolerance are important. Although comparative data are limited, the good safety profile of Nb-UVB, its ability to decrease disease progression, and its effectiveness for also inducing repigmentation should make Nb-UVB the first-line option for halting disease progression.

Vitiligo usually requires several months for repigmentation and patients have to be informed about the length of the treatment to avoid premature discontinuation of the treatment; many expect to observe rapid repigmentation. Potent topical steroids and calcineurin inhibitors have proved their efficacy and are the best options for repigmenting localized vitiligo.[36,37] Topical steroids or calcineurin inhibitors can also be proposed for segmental vitiligo, although they are less effective than in nonsegmental forms.[38] They can be useful before surgical approaches, however, because they can reduce the size of the area to graft and sometimes completely repigment the lesions (**Fig. 2**).

Due to the risk of atrophy when using potent or very potent topical steroids for a long period, their efficacy has to be assessed after 3 months. Although data remain limited, intermittent therapy with application 5 days a week can be proposed to decrease the risk of atrophy. On sensitive areas, such as folds, neck, and face (and mostly eyelids), twice-daily application of topical calcineurin inhibitors are preferred.[28] Calcineurin inhibitors are significantly more effective on sun-exposed areas or when combined with phototherapy (See Samia Esmat and colleagues article, "Phototherapy and Combination Therapies for Vitiligo," in this issue). Avoidance of UV light is suggested, however, by the package insert. This recommendation was

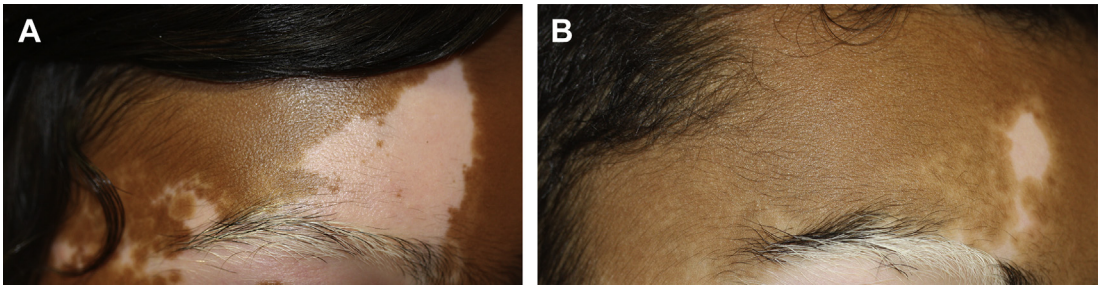

Fig. 2. (*A*) Segmental vitiligo affecting the V1 segment of the face before treatment and (*B*) partial repigmentation after 1 year of twice-daily applications of 0.1% of tacrolimus ointment and sun exposures. The repigmentation remains incomplete but allows decreasing the size of the surgical graft.

based on mouse models and on the immunosuppression that can be induced when a high quantity of calcineurin inhibitors penetrates through the skin and reaches systemic levels. The mouse models have strong limitations, however, when drawing definitive conclusions, and reassuring data on the use of topical calcineurin inhibitors have since been reported.[39,40] Moreover, penetration of high quantities of calcineurin inhibitors can mostly be observed when used over large surfaces in atopic dermatitis patients where the skin barrier is altered, which is not the case for vitiligo skin. Topical calcineurin inhibitors have been used for vitiligo alone or combined with phototherapy for more than 10 years without any indication of risk. Taken together, these data are reassuring concerning the use of topical calcineurin inhibitors combined with UV exposures in vitiligo patients; however, a total follow-up of 20 to 25 years may be required to be completely reassured concerning a potential increased risk of skin cancers. Thus, the risk:benefit ratio needs to be discussed with patients when topical calcineurin inhibitors are proposed. A treatment algorithm is proposed in **Fig. 3**.

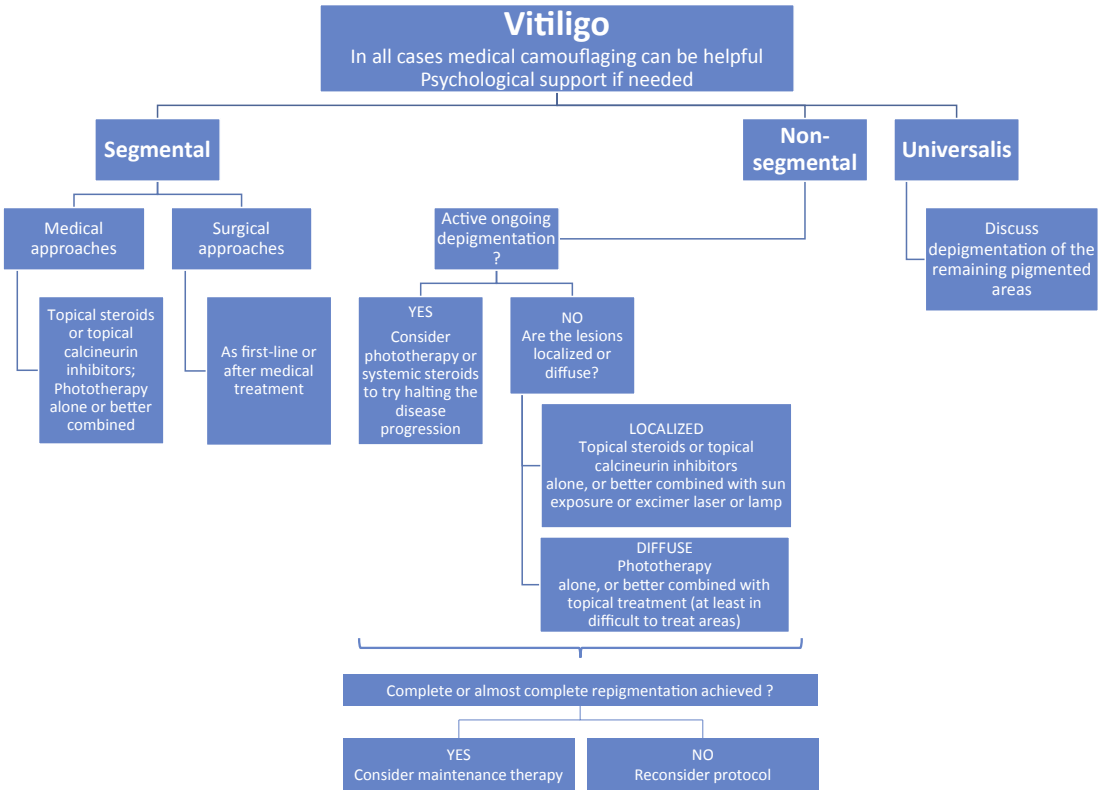

Fig. 3. Treatment algorithm.

PREVENTING VITILIGO RELAPSES

After successful repigmentation, the rate of relapse in vitiligo patches is approximately 40%.[41] In atopic dermatitis, proactive treatment with topical steroids or calcineurin inhibitors has demonstrated efficacy to decrease flares of the disease.[42] In a 2-center, prospective randomized study, the use of biweekly application of 0.1% tacrolimus ointment was compared with placebo[43]; 35 patients with 72 nonsegmental vitiligo lesions who achieved at least 75% of repigmentation after phototherapy, topical treatment, or a combination approach were included. After 6 months, 40% of lesions showed depigmentation in the placebo group compared with 9.7% with tacrolimus ($P = .0075$). The tolerance was good and the side effects limited to transient erythema and stinging or burning sensations. This study shows that twice-weekly applications of 0.1% of tacrolimus are effective for decreasing vitiligo relapses.

According to the data available in atopic dermatitis and the comparable efficacy of topical steroids and tacrolimus for treating vitiligo, it may be hypothesized that topical steroids could also be effective for preventing vitiligo relapse. Many questions remain. How long should this preventive treatment be continued? Are applications 3 times per week more effective than only 2 times per week and thus could they further reduce the risk of relapse? The author proposed this maintenance treatment only in patients with active vitiligo or patients who already had relapses after having achieved repigmentation and continues this proactive approach for at least 6 months without any sign of disease activity. Further studies are clearly required, however, to answer to these questions.

POTENTIAL EMERGING MEDICAL TREATMENTS

Topical Prostaglandins

Prostaglandin E2 can stimulate the proliferation of melanocytes and melanogenesis.[44] Two open-label prospective studies tested twice-daily application of topical prostaglandin E2 in the treatment of localized and stable vitiligo; 15 of the 24 patients in the first study[45] and 20 of the 56 patients in the second trial[46] achieved repigmentation of greater than 75% after 6 months of treatment. The tolerance was good in both studies. Those results need confirmation but they are potentially interesting because the mechanism of action of prostaglandins probably differs from the current therapeutic approaches and may be combined with them to enhance the repigmentation rate.

Afamelanotide

Afamelanotide is a melanocortin-1 receptor agonist. A prospective randomized trial provided encouraging results when afamelanotide, administrated monthly by subcutaneous implants, was combined with UVB (repigmentation rate of 48.64% at day 168) compared with UVB alone (repigmentation rate of 33.26%).[47] Only 17 of 28 patients completed the study in the combination arm (39.3% dropout) compared with 24 of 27 patients (11.1% dropout) in the UVB-only arm. The most frequent side effects were nausea (18%) and fatigue (11%). Better results were obtained, however, in dark-skinned patients. The potent tanning of the nonlesional skin is also a limitation in fair-skinned patients because it increases the contrast between healthy and lesional skin. Additional studies are clearly required to determine the indications and the limitations of this approach.[48]

Janus Kinase Inhibitors

The IFN-γ/JAK/CXCL10 pathway seems to play a key role in the depigmentation process of vitiligo.[1] Every component of this pathway represents a potential therapeutic target.[49] For now, clinical data are limited to 2 case reports using JAK inhibitors. IFN-γ signals through its receptor, which activates JAK1 and JAK2 to induce the transcription of CXCL10, which is important in vitiligo pathogenesis. The first clinical response was reported using a JAK1/JAK3 inhibitor, called tofacitinib, which is Food and Drug Administrant approved for the treatment of rheumatoid arthritis.[2] A 50-year-old woman with vitiligo nonresponsive to topical treatments was treated with 3 mg per day of tofacitinib for 3 weeks and then 5 mg per day (daily dose for rheumatoid arthritis is 10 mg). An almost-complete repigmentation was achieved after 5 months of treatment. The second case was a 35-year-old man with vitiligo and alopecia areata.[3] He received oral ruxolitinib during a phase 2 trial for alopecia areata. Ruxolitinib is a JAK1/JAK2 inhibitor approved for treating myelofibrosis and polycythemia vera. After 20 weeks of treatment, he repigmented from 0.8% to 51% on his face. Unfortunately, the repigmentation was completely gone 12 weeks after the discontinuation of the treatment. Prospective randomized trials are now required for assessing the long-term efficacy and the safety of such approaches but they seem of great interest, especially for active vitiligo.

SUMMARY

Medical treatments alone or in combination with phototherapy are key approaches for treating

nonsegmental vitiligo and to a lesser extent for treating segmental vitiligo. They can be useful for halting disease progression and have proved effective for inducing repigmentation and more recently to decrease the risk of relapses. They have some side effects and limitations that have to be discussed with patients. Vitiligo often induces a marked decreased in the quality of life of affected individuals, however, and the risk:benefit ratio is in favor of an active approach in most cases. Thanks to increased knowledge of the pathophysiology of vitiligo, systemic and topical agents targeting more specifically the pathways involved in the loss of melanocytes and also in the differentiation of melanocyte stem cells should provide in the near future even more effective approaches.

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