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REVIEW ARTICLE

What's new in hypochromy

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Abstract
Hypochromy is a common dermatological disorder. However, its treatment still gives unsatisfactory results. Interesting clues into the understanding of the pathophysiology of hypochromy have been recently brought about thanks to the pigmentary side effects reported with the new tyrosine kinase inhibition treatments. New therapeutic approaches to hypochromy are further discussed.

Key words: *Hypochromy, tyrosine kinase inhibitors, vitiligo*

Introduction

People affected by hypochromy have a vast reduction in their quality of life, caused by the colour contrast between healthy pigmented skin and the hypopigmented or depigmented lesions. It is now demonstrated that such lesions can lead to psychological problems (1,2). Unfortunately, up to the present time, no treatment provides truly satisfactory results. In recent months, interesting reports have brought new clues into the understanding of the pathophysiology of hypochromy and new therapeutic approaches have provided encouraging results, especially in the treatment of vitiligo.

Hypomelanosis induced by tyrosine kinase inhibition treatments

Imatinib mesylate (STI 571) is a new treatment option for cancer and especially for chronic myeloid leukaemia. It is a tyrosine kinase inhibitor that targets the BCR-ABL protein, c-kit (KIT) and platelet-derived growth factor (PDGF) receptors. The c-kit ligand, stem cell factor (SCF), is involved in the proliferation and survival of melanoblasts (3). In vitiligo, the expression of c-kit and its downstream effector, MITF, is reduced and may be associated with the dysfunction and/or loss of melanocytes in the epidermis of vitiligo patients (4).

Interestingly, we have observed a marked progression of vitiligo that had been stable over many years after treatment with tyrosine kinase inhibitors (5). Previously, some authors have reported cases of skin or hair depigmentations as a new side effect of these treatments. Depigmentation of the penis and distal part of both hands was reported in a 52-year-old man, 6 months after initiation of imatinib treatment for a chronic myeloid leukaemia (6). Another case of hypopigmentation of the distal parts of digits, as well as generalized lightening of skin on the body occurring 3 months after receiving imatinib, was also reported in a black Nigerian male with gastrointestinal stromal tumour (7). At the same time, hair depigmentation was reported in 18 of 28 patients with recurrent or metastatic cancers treated with the novel drug SU11428 (Sugen) during a phase 1 clinical trial. SU11428 is a new antiangiogenic oxindole that blocks the receptors for vascular endothelial growth factor (VEGF), PDGF, and stem-cell factor (kit ligand) (8). Clinicians must be aware of these new iatrogenic hypopigmentations. Above all, these reports emphasize the key role of the c-kit pathway in melanogenesis, and bring new clues in the understanding of pigmentation disorders such as vitiligo.

New therapeutic approaches for the treatment of vitiligo

Topical treatments

Calcipotriol. Calcipotriol seemed to be an interesting alternative for the treatment of vitiligo. However, new

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additional reports have showed that calcipotriol, alone or with PUVA, is not effective in vitiligo (9,10).

Calcineurin inhibitors. Preliminary observations have suggested that 0.1% tacrolimus ointment applied twice daily might be effective treatments for both localized and generalized vitiligo (11,12). A 2-month, double-blind, randomized trial comparing 0.1% tacrolimus and 0.05% clobetasol propionate in children with vitiligo has confirmed the initial observation that tacrolimus stimulates vitiligo repigmentation; however, tacrolimus ointment was not superior to clobetasol in terms of repigmentation (13). The same results were recently obtained in an open intra-individual study performed with 1% pimecrolimus cream (14). Once again, 0.05% clobetasol propionate induces a more comparable rate of repigmentation than topical calcineurin inhibitor. Interestingly enough the best results were observed on sun-exposed areas, suggesting that UV may be involved in tacrolimus- and pimecrolimus-induced repigmentation of vitiligo. Further studies are required to establish the safety and efficacy of topical calcineurin inhibitors in the treatment of vitiligo. Recent personal observations suggest that tacrolimus monotherapy in the absence of UV has little or no repigmenting potential in vitiligo (15).

Antioxidant therapies. The effectiveness of antioxidant agents in the treatment of vitiligo is still discussed (16,17). An interesting double-blind, placebo-controlled trial has evaluated the efficacy of *Ginko biloba* extract in 52 patients with limited and slow-spreading vitiligo. The treatment period was 6 months. A statistically significant cessation of active progression of depigmentation was noted in patients treated with *G. biloba* ($p=0.006$). A repigmentation of at least 75% was observed in 40% of the patients treated with *G. biloba*, whereas only 9% showed similar repigmentation in the control group. Tolerance was good. If these results are confirmed, *G. biloba* extract (40 mg three times daily) could be a quite effective therapy for arresting the progression of vitiligo (18).

Prostaglandin. Prostaglandin has been shown to play a role in melanocyte proliferation and melanogenesis. A pilot study has evaluated the topical applications of prostaglandin E2 (PGE2) in treating localized vitiligo (19). After 6 months of daily applications, 15 of 24 patients presented marked to complete repigmentation. Side effects were limited to two cases of mild irritation. However, these encouraging results have not been confirmed so far.

New UVB phototherapy approaches

Thanks to its relatively good efficacy and its excellent tolerance, the narrow-band UVB (NB-UVB) is now considered as the best treatment for extensive vitiligo vulgaris (20–22). However, treating a vitiligo that has spread on less than 10% of the total body surface by NB-UVB exposes healthy areas unnecessarily to radiation. The 308 nm excimer laser and the 308 nm monochromatic excimer light allow selective treatment of the lesions.

The 308 nm excimer laser. Several prospective studies have now shown the efficacy of this laser in the treatment of vitiligo. Patients are treated twice or three times a week for 1–6 months depending on the series. Low fluencies (50–200 mJ/cm^2) are used. In most studies, the percentage of treated lesions achieving at least 75% repigmentation is about 30% (23–27). The rate of repigmentation varies depending upon the anatomic sites. The rate of repigmentation is very high on UVB-responsive areas such as the face, whereas the extremities and bony prominences show a statistically significant inferior repigmentation rate (27). Sessions can be performed once, twice or three times weekly as repigmentation seems to depend on the total number of treatment, not their frequency (28). The stability of the repigmentation with time has so far been difficult to evaluate, as follow-up of the studies is poor or nil; however, one recent series showed an absence of depigmentation of the treated lesions after 1 year (26). Side effects are limited to mild erythema and uncommon blistering.

Focused microphototherapy. The 308 nm excimer light can also be delivered by lamps. A pilot study using such a device reports that 18 out of 37 vitiligo patients achieved 75% or more repigmentation after 6 months of treatment. This study should be confirmed by a comparative trial (308 nm excimer laser versus 308 nm excimer lamp) in a larger population (29).

Combination therapies

Interest in combination treatments was first clearly demonstrated with the combination of UVA and topical steroids. In this prospective, randomized, controlled, left–right comparison study, it was shown that the combination of UVA and fluticasone propionate was much more effective than UVA or topical steroid alone (30).

The use of calcipotriol with sun or PUVA therapy has provided some interesting rates of repigmentation. However, the results are very controversial (10,31,32). The combination of calcipotriol and UVB also provides controversial data. However, two of the three recent studies clearly showed that the combination of calcipotriol with UVB had no enhancing effect on repigmentation, suggesting the absence of interest of adding calcipotriol to UV (33–35).

Two studies have evaluated whether the combination of 308 nm excimer laser and topical tacrolimus could be synergistic in the treatment of vitiligo. These series have compared the efficiency of the 308 nm excimer combined with 0.1% tacrolimus ointment with 308 nm excimer laser monotherapy (36) or associated with placebo ointment (37). In both cases, a total of 24 sessions were carried out and tacrolimus ointment was applied twice a day. The results were similar and a greater efficiency was shown with the combined treatment compared with laser alone. Tolerance was good and side effects were limited to constant erythema, sticking and rare bullous lesions. However, the increased risk of skin cancers promoted by the association of two immunosuppressive treatments cannot be excluded. While long-term follow-up continues, this association should be reserved to control studies.

The 632.8 nm helium-neon laser

Another laser, the 632.8 nm helium-neon laser, was reported as being able to induce a repigmentation in segmentary vitiligo (38). In vitro studies showed that this laser increased the proliferation then the migration of the melanocytes. Thirty patients were treated one or twice weekly. A repigmentation of at least 75% was obtained in 20% of the patients. No side effects were noted. However, the average number of sessions needed to achieve these interesting results is very high (137 sessions, i.e. 1–2.5 years of treatment). Nevertheless, the 632.8 nm helium-neon laser represents a completely innovating therapeutic approach that is worth studying.

Treatment of mature hypopigmented striae and hypopigmented scars

The 308 nm excimer laser, used in the treatment of vitiligo, has also been evaluated in the treatment of mature hypopigmented striae and post-resurfacing leukoderma (39,40). In the first study, 75 patients with hypopigmented striae were treated. All patients achieved a substantial increase in the darkening of their striae after an average of eight sessions. Clinically evident improvement in the cosmetic appearance of striae was noted by 80% of patients. The latest study was performed on 31 patients with hypopigmented scars or hypopigmented striae. Final pigment correction rates relative to control sites of approximately 60–70% by visual assessment and 100% by colorimetric analysis were noted after nine treatments administered bi-weekly. The 308 nm excimer laser seems to induce significant aesthetic results in mature hypopigmented striae and hypopigmented scars by increasing pigmentation. Although a long-term follow-up is necessary and maintenance treatment is required to sustain the cosmetic benefit, these results are encouraging in a disorder suffering from a dearth of alternative therapies.

Conclusions

The importance of the c-kit pathway in melanogenesis, emphasized by the pigmentary disorders induced by the new tyrosine kinase inhibitors, shows new ways for research, especially for the understanding and treatment of vitiligo. Among the new therapeutic approaches, the 308 nm excimer lamps and excimer lasers appear to be the most attractive. The results achieved with the combined treatments are very encouraging. However, further studies have to be done before using these treatments in common dermatological practice in order to confirm these results and, above all, to watch closely for potential side effects.

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