First step in a new era for treatment of patients with vitiligo

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Vitiligo is an acquired depigmentation of the skin, which affects approximately 1% of the population worldwide. The condition can profoundly affect the wellbeing and the social, sexual, and professional lives of affected individuals and thus induces a strong therapeutic demand.[1] Actual treatments rely on the use of topical steroids or topical calcineurin inhibitors, and are better combined with sun exposure or phototherapy.[1,2] The best results are achieved on the face, while some areas such as bony prominences and hands and feet show a very poor repigmentation rate. Although meta-analyses have confirmed the efficacy of these topical agents, primary studies have been done in relatively small populations and most of the treatments remain unapproved and thus used off-label.[3] Over the past decade substantial progress has been made in the understanding of vitiligo pathogenesis and the key role of the interferon γ pathway in the immune destruction of melanocytes.[4] Targeting this pathway using Janus kinase (JAK) inhibitors appears to be an appealing approach, and case reports and open-label studies have suggested the potential interest of topical or systemic use of JAK inhibitors for treating vitiligo.[5,6] In *The Lancet*, David Rosmarin and colleagues[7] report the largest, to my knowledge, prospective randomised trial done for vitiligo. 157 patients (mean age 48·3 years [SD 12·9]; 73 [46%] men and 84 [54%] women) were randomised, and after 24 weeks of treatment, those receiving ruxolitinib cream at 1·5% twice a day and 1·5% once daily showed a significantly higher rate of repigmentation than did patients in the placebo group. This was measured by a 50% or higher improvement from baseline in the facial Vitiligo Area Scoring Index, which was reached by 15 (45%) of 33 patients (odds ratio [OR] 24·7, 95% CI 3·3–1121·4; p=0·0001) in the 1·5% twice daily group, and 15 (50%) of 30 patients (OR 28·5, 95% CI 3·7–1305·2; p<0·0001) in the 1·5% once daily group, compared with vehicle (one [3%] of 32 patients). Repigmentation continued to increase right up to the end of the study period up to 52 weeks. Not surprisingly, the face was the most responsive area, with a third of all patients obtaining a repigmentation rate higher than 90% on this area. Although a third of patients could appear relatively low, we must take into consideration that the topical ruxolitinib was used as a monotherapy when we know that optimal repigmentation needs concomitant sun exposure or phototherapy.[2,3] Further studies should answer crucial questions which remain, such as what is the rate of response in relation to the duration of the disease and the combined effects with phototherapy. Comparative trials against topical steroids and topical calcineurin inhibitors would also be of great value to help clinicians position topical ruxolitinib against the available therapeutic options. The overall tolerance of topical ruxolitinib appears good, even at the highest concentration of 1·5% twice a day. Acne appears to be the side-effect that will need close follow-up in phase 3 studies. It has a clear dose effect, with almost 20% prevalence at the highest concentration of 1·5% twice a day. However, all the cases reported in Rosmarin and colleagues' study were mild. Nevertheless, as topical ruxolitinib shows promising results for treating the face, such a side-effect might be a potential limitation for the use of this cream. With the high psychological burden of vitiligo, the effect on the quality of life of treated patients will be a key marker in the ongoing phase 3 studies.

Robin Hammond/Panos Pictures

Taken together, the results of Rosmarin and colleagues' study[7] show that topical ruxolitinib is promising as a monotherapy and brings reasonable hope that when combined with phototherapy it will allow higher repigmentation rates. These results also confirm the validity of using JAK inhibitors for treating vitiligo and introduce a new therapeutic era for vitiligo using

compounds targeting the key pathophysiological processes that have been shown to be implicated in the disease. Importantly, for optimal care of vitiligo patients, I emphasise three primary areas of concern: to stop the immune destruction of melanocytes to halt the depigmentation process, to induce the differentiation and proliferation of melanocyte stem cells for promoting repigmentation, and to prevent relapses when the repigmentation is achieved.

JAK inhibitors, used topically or systemically, represent the first-generation treatment in a new therapeutic era, particularly when considering that anti-interleukin-17A[8] or apremilast[9] failed to show efficacy. Targeting stress proteins such as Heat shock 70 kDa protein,[10] natural killer cells and CD8 T cells with anti-NKG2-D type II integral membrane protein antibodies, and Tissue-resident memory T cells with anti-interleukin-15 antibodies;[11] increasing the regulatory T cells, and preventing the initial melanocyte apoptosis with anti-CXC chemokine ligand receptor 3-B antibodies;[12] and promoting melanocyte stem cell differentiation with WNT agonists[13] all represent the potential second generation of vitiligo treatments that will hopefully allow the aformentioned three therapeutic objectives to be attained and provide optimal care for all individuals with vitiligo (appendix). The future of vitiligo treatment has never been so bright, and it starts now with topical ruxolitinib.

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Assessing the lifetime benefit of heart failure therapies

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In a landmark essay redefining world systems analysis, Fernand Braudel observed in 1958 that the perceived crisis in the human sciences at that time was largely a result of their success and the rapid pace of additions to the knowledge base.[1] He encouraged colleagues to incorporate a longer historical view, the *longue durée*, and to embrace multidisciplinary approaches to inform their understanding. Many physicians may be overwhelmed by the success of contemporary heart failure therapeutics, with multiple trials of medicines demonstrating improved survival and decreased morbidity in patients with heart failure with reduced ejection fraction (HFrEF).[2–4] Unfortunately, few patients are treated with the ideal, guideline-directed cocktail of these medications.[5] There is difficulty in translating the trial results into meaningful values for clinicians and patients, and long-term benefits are rarely studied due to cost constraints. There are at least six pharmaceutical classes proven to decrease morbidity or mortality, available clinical trials included multiple permutations of therapies, and many patients in these trials were not taking the full complement of the available