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Apremilast: a step forward in the treatment of psoriasis?

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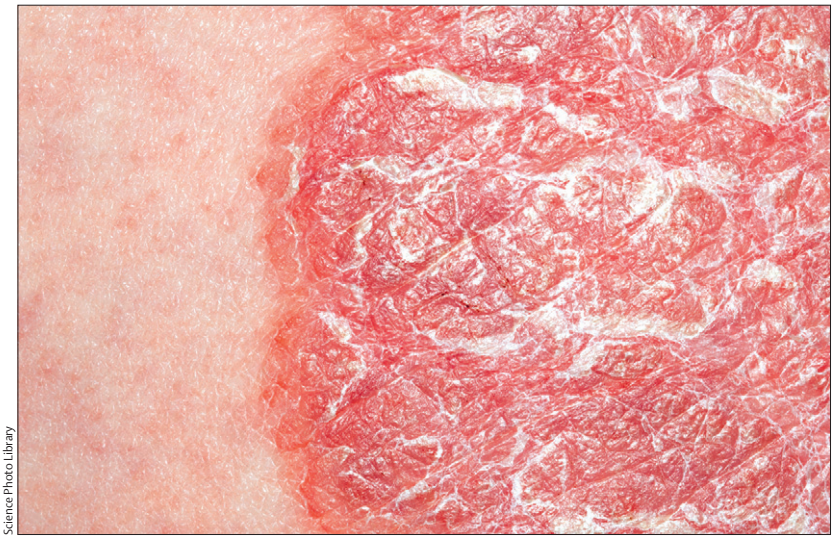
A broad range of treatments for psoriasis are available, including topical treatments (vitamin D, corticosteroids, calcineurin inhibitors, dithranol, and tar), phototherapy and photochemotherapy, classic systemic treatments (methotrexate, ciclosporin, retinoids, and fumarates), and biological agents (targeting tumour necrosis factor α, interleukin 12, or interleukin 23).[1] Guidelines have been developed based on the best available evidence, followed by a consensus process. Evidence-based guidelines help to provide the best treatment for a patient, reconciling individual responsiveness, comorbidities, and side-effects.[2] However, the long-term safe control of psoriasis remains a problem in patients who have unsatisfactory improvement or comorbidities. Long-term effects of psoriasis, including comorbid disorders,[3] impairment of quality of life, and stigmatisation[4] might be prevented by early active treatment; however, evidence from clinical studies about early treatment is scarce, especially with regard to the development of comorbidities. New therapies that are well tolerated and have few cumulative toxic effects could provide a solution for early intervention and long-term management.



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Plaque psoriasis

In the previous century new treatments for psoriasis were discovered by chance. For the past decade, treatment development has been based on mechanisms of pathogenesis. Pathogenesis-based treatments with a selective and focused action are likely to cause fewer side-effects than are treatments with a broad range of effects. Indeed, cumulative toxic effects are a limitation of classic systemic treatments.[5]

Injectable biological drugs such as those that target tumour necrosis factor α or interleukins 12 and 23 were the first generation of pathogenesis-based treatments.[6] Evidence for long-term efficacy and safety of such agents is accumulating.[7] The broad use of biological agents in the treatment of psoriasis has improved management of the disease; inpatient treatment and day-care treatment have decreased substantially.[8] Although long-term controlled studies of the effect of biological agents on quality of life are not available, many patients with severe disease report that their lives have improved substantially with such treatment. The action spectrum of biological agents in psoriasis is still quite wide, because tumour necrosis factor α and interleukins 12 and 23 are cytokines with a broad spectrum of effects. An important development is biological agents targeting interleukin 17.[9,10] Yet the high cost of biological agents is a challenge for their widespread use, especially for early intervention.

New molecules that do not need the expensive production process of biological agents and that have a selective focus on a key step in the pathogenesis of psoriasis have been eagerly awaited. Apremilast (CC-10004) is a small molecule that specifically targets phosphodiesterase 4. By enhancing intracellular accumulation of the second messenger cAMP, the production of inflammatory mediators, such as tumour necrosis factor α, interleukins 2, 12, and 23, and CXCL chemokine 10, is reduced in cells of the

immune system, including dendritic cells, monocytes, neutrophils, and keratinocytes.[11]

In *The Lancet*, Kim Papp and colleagues[12] report a phase 2 trial of the clinical efficacy and safety of apremilast in treatment of moderate to severe plaque psoriasis. In this double-blind trial done at centres in the USA and Canada, 352 patients with moderate to severe psoriasis were randomly assigned to oral placebo or apremilast 10 mg, 20 mg, or 30 mg twice daily. The primary endpoint was the proportion of patients achieving at least a 75% reduction from baseline psoriasis area and severity index (PASI-75) at week 16.

At week 16, PASI-75 was achieved in five (6%) patients assigned placebo, ten (11%) assigned apremilast 10 mg, 25 (29%) assigned apremilast 20 mg, and 36 (41%) assigned apremilast 30 mg. The differences from placebo were significant for both apremilast 20 mg (odds ratio 6·69; 95% CI 2·43–18·5) and apremilast 30 mg (11·5; 4·24–31·2), but not for apremilast 10 mg (2·10; 0·69–6·62).[12] Most (96%) adverse events were mild or moderate; at least 5% of patients had nausea, upper respiratory tract infection, diarrhoea, nasopharyngitis, headache, arthralgia (in patients given placebo), gastroenteritis, or dyspepsia. Eight serious adverse events occurred in the whole study cohort, but these were judged to be unrelated to apremilast.[12]

Papp and colleagues' study was well controlled and the superiority of apremilast compared with placebo seems convincing. However, before firm conclusions about the efficacy of apremilast can be made, further investigations are needed to compare it with other systemic treatments and to examine the safety of long-term treatment for at least a year. In particular, studies comparing the efficacy and safety of apremilast with a classic systemic treatment (such as methotrexate) and one of the biological agents would be worthwhile. Future investigations will tell us whether apremilast will lead clinicians to a new path in the long-term treatment of psoriasis.

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Expansion of the donor lung pool: use of lungs from smokers

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In *The Lancet*, Robert Bonser and colleagues[1] investigate whether the use of lungs from donors with positive smoking histories is justifiable in lung transplantation. On the basis of a study of 1295 adult lung transplants done in the UK between July, 1999 and December, 2010, the authors conclude that use of such lungs has a net benefit to the potential transplant recipient since donors with positive smoking histories provide a substantial proportion of organs for transplantation (nearly 40% of the donor pool), leading to fewer deaths of patients on the waiting list. Benefit was noted in the study despite lower survival for patients who received lung transplants from donors who smoked compared with those who received lungs from donors with negative smoking histories (adjusted hazard ratio for death at 3 years 1·36, 95% CI 1·11–1·67). As expected,