

Dupilumab: a milestone in the treatment of atopic dermatitis

Atopic dermatitis is the most common chronic inflammatory, pruritic skin disease with a high prevalence, both in adults (2–10%) and children (15–30%).^{1,2} From a scientific viewpoint, atopic dermatitis can be attributed to both a genetically mediated epidermal barrier dysfunction and Th2-driven inflammation.^{3,4} Therefore, classic treatment regimens, such as emollients, topical steroids, and calcineurin inhibitors, are still regarded as viable.⁵ For severe cases, systemic use of the immunosuppressant ciclosporin has been approved in many countries, a move that has reduced disease activity by up to 50%.⁶ In view of recent insights into the Th2-driven inflammatory characteristic of atopic dermatitis, it seemed worthwhile to investigate the inhibition of Th2-related molecules, such as the cytokines interleukin (IL)-4 and IL-13, so as to achieve a greater reduction of inflammation. The anti-interleukin-4 receptor (IL-4R) α antibody dupilumab inhibits signalling via IL-4 and IL-13 by inhibiting both IL-4 type 1 and 2 receptors on various immune cells.⁷ Results of four early phase studies (phases 1 and 2) in patients with atopic dermatitis have already shown promising results.⁸

In *The Lancet*, Diamant Thaçi and colleagues⁹ present their novel results from a randomised, double-masked, placebo-controlled, dose-ranging phase 2b study of dupilumab use in adult patients with moderate-to-severe atopic dermatitis. 380 patients, randomly assigned, received 300 mg of dupilumab once a week (n=63), 300 mg every 2 weeks (n=64), 200 mg every 2 weeks (n=62), 300 mg every 4 weeks (n=65), 100 mg every 4 weeks (n=65), or a placebo (n=61). The efficacy data confirm the results from the four early phase studies, with a mean reduction in the Eczema Area and Severity Index (EASI), the trial's primary endpoint, by 73.7% in the highest dosage group (300 mg once a week), 68.2% in the second highest dosage group (300 mg every 2 weeks), and 44.8% in the lowest dosage group (100 mg every 4 weeks), whereas the reduction with the placebo treatment was only 18.1% at week 16. The strong placebo effect could be partly explained by the mandatory use of an emollient, because participating patients were required to use emollients twice a day during the first weeks of the study.

The overall changes and symptom reduction rates that start to occur during the first week of treatment

with dupilumab are remarkable. Furthermore, clinical improvement is so rapid that the greatest amelioration in symptoms can already be achieved in just 4 weeks of treatment. These efficacy data are unique and suggest that dupilumab might even be better than the well-known ciclosporin, both in terms of final efficacy and in rapid achievement of treatment goals (although a direct comparison of these agents has yet to be done). As reported by Thaçi and colleagues,⁹ pruritus, which severely affects patients' quality of life, is thus greatly reduced, as is disease activity.

Additionally, dupilumab seems to be the clear favourite compared with ciclosporin when it comes to safety issues. Generally, ciclosporin has an unfavourable safety profile (eg, nephrotoxic effects, an increase in blood pressure, increased infection rates, and risk of cancers after long-term use). In the trial reported by Thaçi and colleagues,⁹ the dupilumab (81%) and placebo (80%) treatment groups had similar rates of treatment-emergent adverse events. The rate of serious treatment-emergent adverse events was higher in the placebo group (7%) than in the dupilumab groups (4%), with equally low numbers of infectious treatment-emergent adverse events in patients from both groups. Such a safety profile seems to be almost unique in the era of modern targeted treatment. However, Thaçi and colleagues report an increased rate of herpes viral infections in patients given dupilumab (26 [8%] of 318 patients vs 1 [2%] of 61 patients receiving

Published Online
October 8, 2015
[http://dx.doi.org/10.1016/S0140-6736\(15\)00389-X](http://dx.doi.org/10.1016/S0140-6736(15)00389-X)
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placebo), with the highest occurrence in the lowest dosage group (8 [12%] of 65 patients). This finding was not reported in the first four phase 1 and 2 studies⁸ and needs to be attentively monitored in ongoing and future studies of the use of dupilumab; although, in theory, an increased risk for herpes viral infections does not seem to implicate IL-4 and IL-13 signalling specifically.

Dupilumab seems to be an urgently needed milestone for patients with atopic dermatitis. However, because prevalence of this disorder is highest in children and adolescents, the medical community is focusing almost exclusively on studies including patients in that specific age group. A study of dupilumab use in children and adolescents (aged 6–17 years) is currently in progress (NCT02407756). To make a conclusion about treatment stratification, researchers need a direct comparison of dupilumab and ciclosporin.

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AT was an investigator in several clinical trials involving dupilumab, sponsored by Regeneron. SS declares no competing interests.

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