

## Psoriasis and ixekizumab

### Turn first to standard systemic treatments

● In a randomised trial in 108 adults with moderate to severe plaque psoriasis who had never received systemic therapy, subcutaneous *ixekizumab* (an interleukin-17A inhibitor) appeared to have greater efficacy than oral *methotrexate* in achieving short-term clearance of lesions. However, these results are not robust, due to the lack of blinding and the imbalance in patient characteristics between the groups.

In adults with plaque psoriasis who continue to be badly affected by the disease despite topical treatments and phototherapy, a systemically administered drug is an option. The immunosuppressive drugs *methotrexate* or *ciclosporin*, or the retinoid *acitretin*, are the standard treatments in this situation. TNF alpha antagonists such as *adalimumab* or *etanercept* should be reserved for situations in which these systemic drugs have failed. In clinical trials, antibodies directed against interleukins, such as *ixekizumab* (an interleukin-17A inhibitor), had greater efficacy than TNF alpha antagonists. However, as of early 2021, there is less experience with the use of interleukin inhibitors (1,2).

At the time of its evaluation prior to marketing authorisation (MA), *ixekizumab* had not been compared to a standard treatment such as *methotrexate*, *ciclosporin* or *acitretin* (1,2). The results of a randomised trial of *ixekizumab* versus *methotrexate* were published in 2020 (3).

**Possibly more frequent clearance of lesions in the ixekizumab group.** This randomised non-blinded trial included 162 adults with moderate to severe plaque psoriasis who had never received systemic treatment. On average, one-quarter of the patients' body surface was affected. They were randomised to receive, for 24 weeks, either subcutaneous *ixekizumab* (at the dosage recommended in the MA), or oral *methotrexate* (aiming for a weekly dose of at least 15 mg), or a drug based on fumaric acid esters. The results in the fumaric acid esters group are not considered here, since this drug is not marketed in France (3,4).

Despite randomisation, the patient characteristics were not the same in the *ixekizumab* and the *methotrexate* groups. For example, in the *ixekizumab* group, more patients had already received phototherapy (52% versus 24%) (3). The potential influence of these differences is unknown, but it increases the uncertainty surrounding interpretation of the results. The level of evidence is also reduced by the absence of blinding.

After 24 weeks of treatment, 91% of patients in the *ixekizumab* group had a reduction of at least 75% in a score which took into account the extent

and nature of the lesions (erythema, thickness and scaling) – the primary endpoint – compared to 70% in the *methotrexate* group ( $p=0.014$ ). In the *ixekizumab* group, 41% of the patients achieved complete clearance of lesions, versus 13% in the *methotrexate* group ( $p=0.004$ ) (3).

**Infections and injection site reactions.** *Ixekizumab* shares the adverse effect profile of all interleukin-17A inhibitors, with in particular: immunosuppressive effects leading to infections and an increased risk of cancer, injection site and hypersensitivity reactions, and neutropenia (1,5).

During the evaluation of *ixekizumab* prior to MA, cardiovascular events and Crohn's disease were mentioned as adverse effects of this drug (1). After the drug was marketed, severe arterial thrombosis (especially in patients with a history of cardiovascular disorders) and serious colonic pathology (not otherwise specified) have been reported with *ixekizumab* (6).

The trial of *ixekizumab* versus *methotrexate* described above does not provide additional information, due to the small number of patients included and the absence of blinding (3).

**In practice** As of 2021, there is no strong evidence that *ixekizumab* has greater efficacy than *methotrexate* in patients with psoriasis. In addition, its adverse effects are less well established than those of standard treatments, particularly in the long term. When systemic therapy is considered, it seems preferable to turn first to *methotrexate*, *acitretin* or *ciclosporin*, rather than *ixekizumab*.

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#### Literature search up to 9 March 2021

- 1- Prescrire Editorial Staff "Ixekizumab and plaque psoriasis. Effects similar to secukinumab, but no demonstrated advantages" *Prescrire Int* 2018; **27** (192): 93-94.
- 2- Prescrire Editorial Staff "Risankizumab - Skyrizi® and plaque psoriasis" *Prescrire Int* 2021; **30** (222): 13.
- 3- Reich K et al. "A 24-week multicentre, randomized, open-label, parallel-group study comparing the efficacy and safety of ixekizumab vs. fumaric acid esters and methotrexate in patients with moderate-to-severe plaque psoriasis naive to systemic treatment" *Br J Dermatol* 2020; **182**: 869-879 + Suppl: 15 pages.
- 4- Prescrire Editorial Staff "Dimethyl fumarate and psoriasis: Transparency Committee of the French National Authority for Health opposed to its reimbursement" *Prescrire Int* 2020; **29** (213): 68.
- 5- Prescrire Rédaction "Anti-interleukine-17A: sécukinumab, etc." *Interactions Médicamenteuses Prescrire* 2021.
- 6- ANSM "Réunion du comité technique de pharmacovigilance-CT012019053" 18 June 2019: 28 pages.