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Supporting Information

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Building the evidence base for current systemic treatments for severe, chronic atopic dermatitis: methotrexate vs. azathioprine

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Linked Article: Gerbens et al. *Br J Dermatol* 2018; **178**:1288–1296.

This issue of the BJD includes the important paper by Gerbens et al., 'Methotrexate and azathioprine for severe atopic dermatitis: a 5-year follow-up study of a randomized controlled trial', providing first answers on the efficacy and safety of these commonly used drugs for long-term treatment of severe atopic dermatitis (AD).¹

As many as 5–10% of adults suffer from AD, which implies the largest global burden of disability due to skin disease.² Systemic treatments are frequently needed for individuals with severe AD; until recently, only one oral drug was approved for AD although several oral treatments are used off label.³ New treatments are eagerly anticipated and it is therefore essential to gain evidence on all currently used systemic treatments for AD.^{4,5} It is astonishing that no long-term study of oral AD treatment has been performed until now.

The Dutch study was an open-label follow-up of a clinical trial on the treatment of AD with methotrexate (MTX) vs. azathioprine (AZA). In total, the study covers a period of 5 years in adult patients with moderate-to-severe AD; 43 patients were included in the study. The dosing of the study drug, either AZA or MTX, could be adjusted, therapy could be switched and additional treatments could be added. Follow-up was every 3 months; clinical signs, symptoms, quality of life, long-term control and adverse events were assessed.

Gerbens et al.¹ showed that both MTX and AZA seemed to be effective; the mean absolute reduction in total SCORAD (SCORing of Atopic Dermatitis) was 32.1 in both groups. Both MTX and AZA seemed to be safe for the long-term treatment of AD. The most common adverse events were mild-to-moderate infections. Other mild-to-moderate adverse events probably related to the study medication were 'hepatobiliary' and 'gastrointestinal disorders' for MTX, and 'blood and lymphatic system disorders' for AZA. Three serious adverse events possibly related to the study medications were registered.

This study has the strength of being a well-performed longitudinal study: efficacy, safety and tolerability were all assessed using relevant outcome measures regularly.⁶ Choosing a head-to-head design was beneficial for comparing the effect of the two drugs. However, the interpretation of the effectiveness requires caution, as participants were able to change medication, which might have confounded the results. Furthermore, unknown adverse events cannot be excluded as the study involved relatively small numbers.^{7,8} Indeed, only 35 of 43 originally included patients participated, of whom 27 completed follow-up. Survival in both groups was low after 5 years (MTX *n* = 5, AZA *n* = 1), and some patients discontinued due to controlled AD. Thus, it is essential that the results of this study are confirmed in larger future trials.

The findings of this study are of high importance for both clinical management and decision-makers. Until now there was a knowledge gap regarding the effect of treatment with MTX and AZA for a period of several years on the clinical course of severe AD and potential adverse events. As the study provides data for up to 5 years, the effect of long-term treatment could be explored in detail for the first time in an adult population. Furthermore, this study is the longest pragmatic study ever performed on this topic, and investigated two important drugs that are frequently prescribed for this indication. Based on this study, both MTX and AZA seem to be treatment options for patients with moderate-to-severe AD for up to 5 years. However, few patients in both groups remained on their originally allocated drug at the study end. This highlights the urgent need for effective long-term regimens of currently used drugs as well as new drugs. Informed decisions for individualized treatment need evidence on the long-term effect and safety profile of drugs.

The results of the current study stress the importance of more well-designed studies with long-term follow-up to adequately address public health problems. However, these studies are difficult to carry out and expensive, and may be hard to fund. Therefore, the Dutch study, which overcame these

challenges, is a highly valuable step to answer several important questions that otherwise would remain unsolved.¹ Thank you and congratulations to our determined Dutch colleagues!

Conflicts of interest

None to declare.

¹Faculty of Medicine, Lund University, Lund, Sweden

L.B. VON KOBYLETZKI¹
Å. SVENSSON²

²Department of Dermatology, Malmö University Hospital, Malmö University Hospital UMAS, SE-205 02 Malmö, Sweden

E-mail: Laura.vonkobyletzki@skane.se

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Evidence for improving the therapeutic response to ixekizumab: more than just a statistic

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The availability of biotechnological drugs, increasingly targeted to pivotal mediators of pathogenesis of psoriasis, has significantly improved the therapeutic perspectives as well as

the quality of life of patients with psoriasis. The use of this class of molecules for more than a decade allows them to be considered safe, even in long-term, continuous treatment. Sekukinumab, ixekizumab and brodalumab, monoclonal antibodies that selectively target the effect of a crucial mediator in the psoriasis pathomechanism like interleukin-17, are the latest option in the treatment of this disease, providing excellent clinical results.¹

However, some unmet medical needs remain, even after the introduction of biologics. First of all is the possible gradual loss of efficacy over time, which is the main reason for treatment discontinuation.² This undoubtedly represents a limitation in the treatment of a chronic disease like psoriasis, which requires an effective long-term therapy. Moreover, despite the remarkable therapeutic results achieved with biologics, a certain proportion of patients are poorly or only partially responsive to treatment. This can be explained by the extreme complexity of the pathways underlying psoriasis. Thus, drugs that selectively inhibit individual therapeutic targets in some cases may be scarcely effective in suppressing the inflammatory mechanism leading to psoriasis. An immunological re-orchestration induced by biologic therapy has also been hypothesized.³ It has been well established that adjustment of biologic dosage and regimen may restore clinical response and/or improve clinical outcome in patients scarcely responsive to conventional treatment schemes.⁴

The current issue of the *BJD* reports an enlightening multi-centre, randomized, phase III trial with the aim to evaluate the long-term efficacy and safety of an increased dose frequency of ixekizumab in the treatment of moderate-to-severe plaque psoriasis.⁵ In particular, the authors compared an 80 mg every 2-week dosing (Q2W) beyond the first 12 weeks with the current recommended label dose (80 mg every 4 weeks, Q4W). A further group provided for a dose adjustment from 4-week to 2-week administration, based on therapeutic response (Q4W/Q2W dose adjustment). The large size of this study, which included 1227 patients, and its long-term duration represent two notable strengths.

At study completion, high levels of clinical response were achieved and maintained through 52 weeks in all dose groups, but Q2W dosing provided significantly higher response rates than Q4W in terms of both static patient global assessment (sPGA) and Psoriasis Area and Severity Index (PASI) scores. Of note, the occurrence of treatment-emergent adverse events was similar across all three groups. Due to the high rate of responders among the study patients, the authors could not draw statistically reliable conclusions on the benefit of the Q4W/Q2W dose adjustment.

Finding that the increase in dosing frequency significantly improves ixekizumab efficacy without affecting the safety profile of the treatment provides evidence for strengthening its therapeutic potential. This property brings further benefits in the clinical setting. In fact, it may increase the drug retention rate and reduce both biologic switching and multidrug combinations, especially with conventional drugs, where low safety profile in prolonged use is well known.