

EDITORIAL

JAK inhibition and the holy grail for
pain control in early RASofia Pazmino ¹, Patrick Verschueren ^{2,3}, René Westhovens ⁴

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A recent paper by Taylor *et al* in *RMD open*¹ focuses on achieving pain control with baricitinib in early rheumatoid arthritis (RA) compared with methotrexate (MTX) monotherapy based on data from the RA-BEGIN trial. A superior efficacy of baricitinib with regard to more rapid improvement of pain was also brought forward in more advanced RA as well as for other JAK-inhibitors (JAKi) in comparison to TNF blockade or IL-6 inhibition.^{2–3} In other inflammatory diseases, comparable findings have been reported.^{4–5} Pain control is a highly preferred outcome in RA especially in early disease where aspects of chronicity and negative illness behaviour have not had the chance yet to fully develop, as was demonstrated in a study from our group.⁶ The latter qualitative longitudinal prospective study also points to different dimensions of the pain problem in RA: while in the first weeks after disease onset the actual pain is the main issue, 1 year later when these patients have much better disease control they still remember their initial pain experience and it is rather the fear of pain flaring that comes to the forefront in a focus group.

In the RA-BEGIN study, baricitinib was compared with MTX monotherapy without the EULAR recommended⁷ short period of bridging glucocorticoids (GCs). This might be a factor responsible for the observed difference between treatment arms with regard to pain control. GCs in combination with disease-modifying antirheumatic drugs have been proven to not only help control disease activity and inhibit radiographic progression but also improve function and relieve pain.⁸ GCs are especially relevant in the short-to-medium term and as a bridging treatment in early RA given MTX is a slow-acting drug. On the other hand, JAK inhibition rapidly improves symptoms and ideally should be compared with the standard of care as proposed in the EULAR recommendations. We already demonstrated that speed and stability of the initial clinical response

are independently associated with favourable patient-reported health at 1 year based on data from the CareRA trial.⁹ Moreover, in the latter study, it was shown that even in a small group of good prognosis patients, MTX monotherapy (without oral GCs) was associated with more analgesic use over the first 2 years compared with MTX +bridging GCs.¹⁰ Of note is also that some of the DMARD naïve patients participating in the RA-BEGIN trial—as in other JAKi trials in DMARD naïve populations—had a relatively long disease duration: median disease duration of 0.2 years but mean disease duration of over 1.3 years without having been treated with MTX but often already on GCs, that were continued in both treatment arms. The early treat to target recommendation was certainly not implemented in a substantial number of patients entering these trials and this could have had substantial impact on symptoms as pain becoming more chronic.

Nevertheless, there might also be a specific mechanism of action related to JAK inhibition responsible for a particular or more pronounced effect on pain. Besides controlling pain by decreasing articular inflammation, a JAKi might have additional direct or indirect effects on peripheral and/or central sensitisation. This influence on so-called nociceptive pain was recently nicely reviewed by Simon *et al*.¹¹ It is not yet known which JAK/STAT pathway-targeting therapies are the most preferred in treating RA pain and which inhibitory profile of JAKi would be the most effective. Another open question to solve: is the JAKi effect on pain similar in the different inflammatory diseases? This needs more pathophysiological studies; however, there is already a rationale for the clinical therapeutic use of JAKi in psoriatic arthritis also taking into account optimal pain relief.¹² In the meantime, we should not forget that pain sensations engage cognitive brain regions that will be influenced also by psychosocial factors.

A number of recent non-JAKi studies shed light on the issue of remaining non-inflammatory pain even when disease activity is well controlled already early in the disease process. In a post hoc analysis of CareRA, of the 140 patients with early and stable clinical disease control one fifth reported poor health at 1 year.¹³ A cluster analysis revealed three groups: 9.3% of patients belonging to a 'dominant fatigue' and 12.9% to a 'dominant pain and fatigue' cluster. In the remaining patients, health was perceived concordant to the good disease control. Differences in pain reporting between the patients in the three clusters were already found at week 16 and importantly also illness perceptions and coping styles differed, making this an attractive focus for early intervention.

A recent analysis¹⁴ of the early RA SWEFOT trial focuses in detail on unacceptable pain (VAS pain >40 mm) and specifically also on unacceptable pain despite inflammation control (refractory pain; VAS pain >40 plus C-reactive protein (CRP) level <10 mg/L). In this trial, patients with an insufficient response to MTX after 3 months were treated with the addition of infliximab or sulfasalazine combined with hydroxychloroquine. Half of the randomised patients reported unacceptable pain at randomisation, which improved to 29% at 21 months, while refractory pain (unacceptable pain despite inflammation control) constituted 82% of all unacceptable pain at 21 months. There were some differences between the two treatment arms for unacceptable pain, but no between-group differences were observed for refractory pain after the intervention. This recent analysis, 12 years after the report of the primary outcome, is of course a perfect illustration of the increased focus in recent years on specific unmet needs from the perspective of patients, such as pain. One could also speculate if JAKi instead of infliximab would have changed this outcome substantially, but we would argue that the challenge of refractory pain management is likely to be more complex. An interesting post hoc analysis of the titrate trial in the UK, demonstrating the benefit of a more intensive management schedule incorporating psychosocial aspects also in patients with mild to moderate disease, found a high association of baseline anxiety on remaining pain after 1 year as well as an impact of baseline illness perceptions.¹⁵ Of note, this study included patients with approximately 6 years of disease duration who had already had the chance to develop particular illness behaviour and perceptions.

Given all the emerging evidence of the importance of remaining pain in RA despite good disease control it is time to act: first, there is certainly a need for more insight into the pathophysiology of pain. Further studies on the particularities of the JAK/Stat pathway also in nociception as well as studies looking for eventual specificities in the different inhibitory pathways of the different JAKs can be of help. So far, the choice between JAKi and biologics or other treatments in this regard remains open and largely dependent on the experience of the treating physicians. In early DMARD naïve RA this choice is clearly also determined by cost considerations. Second,

the examples discussed in this editorial are also a plea for a better implementation of current EULAR treat to target recommendations specifically in early RA.

Finally, the pain problem in RA has to be taken seriously not the least because of the huge personal and societal impact of remaining symptoms like pain and fatigue, but also related aspects as patients' ability to function and participate in work and leisure activities.¹⁶

We sincerely think efforts will have the most impact if they are focused on early RA, also for preventing high burden of residual pain and chronicity of pain. We need to move to a more comprehensive evaluation of these patients during the follow-up, with more attention to patient-reported outcomes (PROs) already early in the disease to get a complete and holistic picture. Using exploratory factor analysis on CareRA data,¹⁷ our research group recently demonstrated that separately monitoring PROs (patient assessment of global health, pain, fatigue and physical function) for the evaluation of the global disease burden added to our usual clinical assessment (physician global health, swollen and tender joint count) and the laboratory evaluation (ESR/CRP). A discordance between PROs and clinical/laboratory outcomes helps in predicting future disease impact¹⁸ and should initiate a more profound evaluation of specific underlying causes that might benefit from the addition of individualised multidisciplinary non-pharmacological interventions.

In conclusion, pain control in RA is a complex task and probably multifactorial. Benefits might be expected the most in early diseases.

Correction notice This article has been amended since it was first published online. Reference 1 has been updated.

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