TARGETED THERAPIES

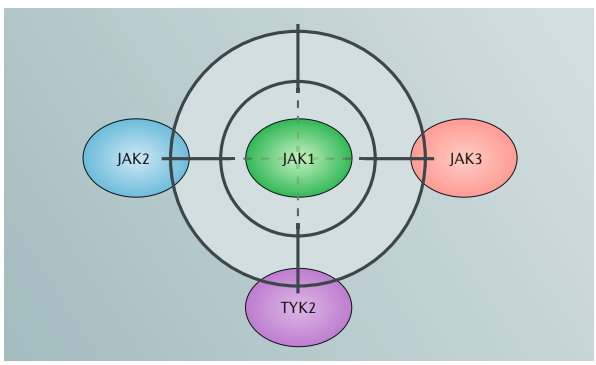
# Selective inhibition of JAK1 shows promise for RA

> positive results … offer hope for patients who have responded inadequately to multiple other therapies

The ability to target cytokine signalling pathways by inhibiting Janus kinases (JAKs) has been a major advance in the treatment of several rheumatic diseases. However, concerns remain about the safety of these inhibitors owing to their wide-ranging effects. Now, two phase III clinical trials published in *The Lancet* reveal the results up to 24 weeks of selective inhibition of a single JAK.

In both the SELECT-NEXT and SELECT-BEYOND studies, researchers investigated the use of upadacitinib (a JAK inhibitor that is selective for JAK1 over JAK2, JAK3 and non-receptor tyrosine-protein kinase TYK2) as a therapy for different sub-populations of patients with rheumatoid arthritis (RA).

"Upadacitinib is a selective (albeit not specific) inhibitor of JAK1 that has a key role in interferon-α/β and interferon-γ signal transduction, as well as in the signal transduction of IL-6," explains Gerd Burmester, lead author of the SELECT-NEXT study. Although still affecting a wide range of cytokine signalling pathways, theoretically, selective inhibition of JAK1 should reduce unwanted adverse events in patients, although fully integrated safety analysis from these trials is still awaited.




Credit: Susanne Harris/ Springer Nature Limited

In SELECT-NEXT, the authors enrolled 661 patients who had previously failed therapy with conventional synthetic DMARDs (csDMARDs), most of whom were biologic DMARD (bDMARD)-naive. By contrast, the authors of SELECT-BEYOND recruited 499 patients who had previously failed therapy with csDMARDs and with more than one bDMARD. "This difficult to treat population of patients with RA has the greatest need of newer therapies," says Roy Fleischmann, co-author of the SELECT-BEYOND study.

Both studies followed the same protocol, in which patients were treated with 15 mg upadacitinib, 30 mg upadacitinib or placebo once daily for 12 weeks, followed by once daily upadacitinib (15 mg or 30 mg). Patients were able to continue with csDMARDs, NSAIDs and low-dose glucocorticoids for the first 24 weeks of the studies. The primary outcomes for both trials at 12 weeks were a 20% improvement in ACR criteria (ACR20) and a 28-joint disease activity score (as measured by C-reactive protein) of ≤3.2.

For both clinical end-points, both studies found statistically significant improvements in patients receiving either dose of upadacitinib over placebo at 12 weeks. Patients receiving 30 mg upadacitinib in the SELECT-BEYOND study and both doses of upadacitinib in the SELECT-NEXT study had higher numbers of adverse events overall than patients receiving placebo at 12 weeks. These adverse events were mostly infections, but one incidence of pulmonary embolism and cardiac failure that resulted in death was reported in SELECT-BEYOND.

"The results of SELECT-NEXT support the evidence that JAK inhibitors could be considered as an alternative treatment option for patients with long-term disease who have an inadequate response to csDMARDs, or those for whom bDMARDs are not a good option," says Burmester. "Treatment with JAK inhibitors could help these patients achieve rapid responses and disease control."

Likewise, the positive results of SELECT-BEYOND offer hope for patients who have responded inadequately to multiple other therapies. Subgroup analysis of 154 patients who had previously failed ≥3 bDMARDs revealed that 71% of patients receiving 15 mg upadacitinib achieved an ACR20 response at week 12.

However, the results of these studies need to be interpreted with care. In an independent commentary also published in *The Lancet*, Tore Kvien and Guro Goll from Diakonhjemmet Hospital in Oslo, Norway commented, "We do not yet know which selective JAK inhibitor offers the maximum efficacy with the optimal side-effect profile. No head-to head studies between JAK inhibitors have been done and comparisons between the different therapeutic compounds remain tenuous."

*Joanna Collison*

**ORIGINAL ARTICLES** Burmester, G. R. et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* **391**, 2503–2512 (2018) | Genovese, M. C. et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. *Lancet* **391**, 2513–2524 (2018)