The extending scope of kinase inhibition in immune diseases

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Functional mutation analyses in patients with immune deficiencies identified Janus kinases (JAKs) as plausible regulators of the immune response. Thereafter, elegant signalling biology generated a compelling rationale for the use of small molecule inhibitors to recapitulate the cytokine blocking activities of biologics. JAK inhibitors have thus emerged as novel immune modifiers that target cytokines via blockade of intracellular cytokine receptor signalling pathways. Four members of the family (JAK1, JAK2, JAK3, and TYK2) can form a variety of heterodimers (eg, JAK1/JAK2 and JAK1/JAK3) and transmit signals from the cell membrane to the nucleus (via cytosolic shuttling proteins) to activate leucocytes and stromal cells and drive inflammation[1]. In the past 5 years, JAK inhibitors were developed for the treatment of rheumatoid arthritis[1]; now attention has turned to their wider use across immune-mediated inflammatory diseases.

Spondyloarthritis comprises a group of clinically and pathogenetically related immune-mediated inflammatory diseases, including psoriatic arthritis and axial spondyloarthritis. These conditions impair quality of life and, by virtue of accelerated comorbidity, reduce life expectancy[2,3]. Although novel biological therapies, including inhibitors of tumour necrosis factor (TNF), interleukin (IL)-12/IL-23 p40, IL-17A, and IL-23 p19, have transformed the management of psoriatic arthritis[2,4,5], and TNF and IL-17A inhibitors the management of axial spondyloarthritis[6], unmet need remains for these lifelong, incurable conditions. Patients with psoriatic arthritis with articular and entheseal disease often only partly respond or do not respond at all to treatment, with few patients reaching sustained minimal disease activity. Moreover, pain control is suboptimal, and therapeutic tapering and drug-free remission remain challenging and rarely achieved goals. Orally bioavailable therapeutics are intriguing in this context. A phosphodiesterase type 4 inhibitor, apremilast, is approved for use in patients with psoriatic arthritis. More recently, tofacitinib (an inhibitor of JAK1/JAK3) showed efficacy in patients with psoriatic arthritis and ankylosing spondylitis, offering the first clue that JAK family inhibition might offer general benefits to patients with spondyloarthritis[7,8].

In *The Lancet*, two phase 2 studies of filgotinib offer the first insight into the potential of a highly selective JAK1 inhibitor in two different spondyloarthritis conditions. The first, by Philip Mease and colleagues[9], is the multicentre, randomised, placebo-controlled EQUATOR study in patients with active psoriatic arthritis. In this study, patients with moderate to severe disease who had not responded to or tolerated conventional disease-modifying antirheumatic drugs or TNF inhibitors were randomly assigned 1:1 to receive oral filgotinib 200 mg or placebo. 52 (80%) of 65 patients in the filgotinib group and 22 (33%) of 66 in the placebo group achieved the primary endpoint of 20% improvement in American College of Rheumatology response criteria at week 16 (treatment difference 47% [95% CI 30·2 to 59·6], p<0·0001). Significant improvements in other clinical and patient-reported outcomes were observed in those who received filgotinib. In the second trial, Désirée van der Heijde and colleagues[10] present the multicentre, randomised, placebo-controlled TORTUGA study of filgotinib in patients with ankylosing spondylitis. In that trial, patients with active disease and an inadequate response to at least two non-steroidal anti-inflammatory drugs were randomly assigned 1:1 to oral filgotinib (n=58) or placebo (n=58). The primary endpoint was the change from baseline to week 12 in the ankylosing spondylitis disease activity score, which was –1·47 (SE 0·14) in the filgotinib group and –0·57 (0·11) in the placebo group, with a least squares mean difference between groups of –0·85 (95% CI –1·17 to –0·53; p<0·0001). In addition to achieving the primary endpoint, significant improvements were also observed with filgotinib compared with placebo in most secondary and patient-reported outcomes. Therapeutic onset was rapid, evident within 1 week of therapy in both studies. Treatment-emergent adverse events were similar between filgotinib and placebo within studies but were higher in the psoriatic arthritis study (57% for filgotinib and 59% for placebo) than in the ankylosing spondylitis study (31% in both groups). In both studies, one case of pneumonia was reported in the filgotinib group, which was fatal in the psoriatic arthritis study. One case of uncomplicated herpes zoster occurred in the psoriatic arthritis study, and a non-serious deep vein thrombosis occurred in an

at-risk participant with ankylosing spondylitis. No new safety concerns beyond those reported in the rheumatoid arthritis studies[11] were observed, although longer follow-up is needed.

The results of these studies should be interpreted with caution pending robust phase 3 studies that include active comparators. However, they offer encouraging evidence that selective inhibition of JAK1, rather than broader inhibition across JAKs, might suffice in the management of spondyloarthritis. In theory, this strategy might limit toxic effects in patients with spondyloarthritis—for example, through sparing JAK2-dependent and JAK3-dependent immune processes and bone marrow homoeostatic activities. However, these distinctions of clinical significance have not yet been shown in practice, nor is it an entirely convincing prediction given that JAK1 can form a functional heterodimer with JAK3. The magnitude of articular response is high in these studies compared with previous studies; head-to-head comparisons are needed to consolidate the findings, as are larger sample sizes, longer follow-up, and more detailed exploration of clinically relevant patient subgroups (eg, those with a history of treatment with biological therapies). The authors selected a single dose of filgotinib (200 mg) on the basis of the highest dose being tested in phase 3 studies of rheumatoid arthritis[9]. We do not know whether this dose is the optimal dose in patients with spondyloarthritis, and understanding optimal dosing regimens, including short-term flexibility, for JAK inhibitors in immune-mediated inflammatory diseases will be potentially important in future. Similarly, the effects on pain are interesting and suggest that JAK inhibition could confer independent benefits beyond immune modulation.

The proportion of patients in the filgotinib group who achieved a 75% reduction in the Psoriasis Area and Severity Index in the EQUATOR trial was only 45% at week 16[9]. This rate is lower than expected for modern biological inhibitors (eg, those targeting the IL-23 p19/IL-17 pathway) but is consistent with the emerging pattern of tissue-specific magnitudes of responses to different drugs across the spondyloarthritis domains (eg, skin, synovium, or enthesis). This pattern might reflect a tissue-dependent hierarchy of immune pathogenetic pathways within spondyloarthritis[12]. Thus, IL-17A blockade is superior to TNF blockade in treatment of inflammatory disorders of cutaneous psoriasis, but equivalent in the musculoskeletal compartment in patients with psoriatic arthritis and inferior in the gastrointestinal tract in patients with inflammatory bowel disease[13]. IL-23 p19 inhibitors are effective for the treatment of cutaneous psoriasis and for peripheral arthritis in patients with psoriatic arthritis but inactive in patients with ankylosing spondylitis[14,15]. Quite how JAK1-dependent pathways drive spondyloarthritis pathogenesis requires re-evaluation—we believe that experimental medicine studies will be essential to discern such mechanistic detail and to thereby inform future drug development and therapeutic strategies focused on pathogenetically defined clinical unmet need.

Several other JAK inhibitors are under investigation for the treatment of immune-mediated inflammatory diseases, including baricitinib (JAK1/2) and upadacitinib (JAK1)[16-18], with others to come (figure). As our armamentarium expands, so more questions arise. At what stage in the therapeutic pathway will JAK inhibition provide optimal benefit? Can the broader spectrum of cytokines blocked by these drugs, compared with monospecific biologics, confer deeper immune modulatory effects? Will selective inhibition within the JAK family, or indeed targeting of other JAK members (eg, TYK2), confer within-class therapeutic advantage? How will these drugs modulate comorbidities that are prevalent in patients with spondyloarthritis? These are exciting times in the immune-mediated inflammatory disease field and for spondyloarthritis.

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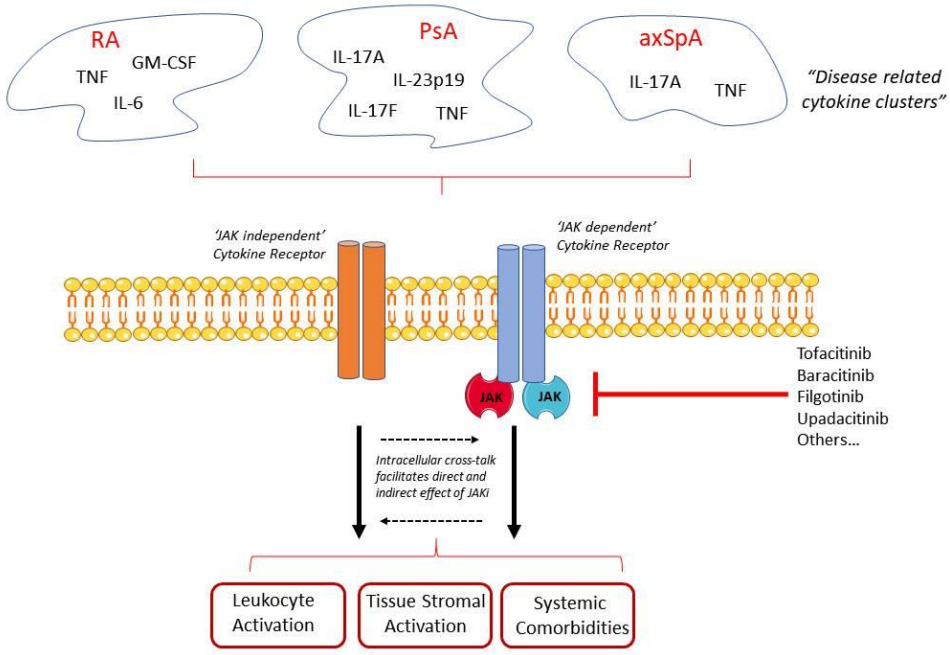

Figure: **JAK inhibitory pathways in spondyloarthritis**
Increasingly, immune-mediated inflammatory diseases are being associated with distinct cytokine clusters. JAK inhibitors might affect the biological mechanisms mediated by these clusters, either directly by inhibiting receptors that require JAK for their downstream signalling (eg, common γ-chain cytokines) or indirectly by inhibiting JAKs and thereby altering intracellular crosstalk between JAK-dependent and JAK-independent receptor signalling pathways. Through these mechanisms, JAK inhibition can regulate broad cytokine function in disease. JAK=Janus kinase. GM-CSF=granulocyte-macrophage colony-stimulating factor. IL=interleukin. TNF=tumour necrosis factor.