Janus kinase inhibitors for autoimmune disorders

STEVE CHAPLIN

Three janus kinase (JAK) inhibitors – baricitinib (Olumiant) and tofacitinib (Xeljanz) for rheumatoid arthritis, and ruxolitinib (Jakavi) for myelofibrosis – have already been launched in the UK and others are currently being evaluated in a diverse range of autoimmune disorders and cancers. This article provides an overview of the properties and potential of this new class of drugs.

Understanding of the mechanisms by which cytokines alter cellular behaviour as part of the immune response has been evolving since the 1960s. The kernel of this complex multistranded system is reversible protein phosphorylation, a function executed within the cell that activates or deactivates pathways that change gene expression. Several hundred protein kinases have been identified. Recognition that they are major drivers of pro- and anti-inflammatory pathways has opened a fruitful avenue of research, culminating in the development of new classes of drugs with a potentially profound therapeutic impact.

Protein kinase inhibitors have been available for the treatment of various cancers since the early 2000s – examples include imatinib for leukaemia and gastrointestinal tumours, sorafenib for hepatic and renal cell cancer, sunitinib for gastrointestinal and renal cell cancer, and trametinib for melanoma and non-small cell lung cancer (NSCLC). One pathway in particular, the janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, has been the target of intense research effort in recent years and novel drugs are now in the final stages of development or have been introduced for the treatment of autoimmune disorders including rheumatoid arthritis, psoriasis and inflammatory bowel disease.

Janus kinases and the JAK-STAT signalling pathway
Cytokines are a large and diverse group of proteins that influence cellular activity. They are secreted by many cell types and include the interleukins (IL), interferons (IFN), tumour necrosis factors (TNF) and growth factors. In general, cytokines bind with cell surface receptors to activate intracellular pathways. Again, there is a multiplicity of pathways, each responsive to specific cytokines, that lead to changes in intracellular targets.

Figure 1. Simplified overview of the JAK-STAT signalling pathway

1. Cytokine binds to receptor
2. Receptor dimerisation activates JAK phosphorylation of receptor
3. STAT binds phosphorylated receptor
4. JAK phosphorylates STAT
5. STAT dimer is formed
6. STAT dimer travels to the nucleus
7. STAT dimer binds DNA and activates gene transcription
**Janus kinase inhibitors**

Janus kinase (JAK) proteins are transmembrane and intracellular protein kinases that are critical for cytokine signaling. Over 30 JAKs have been identified, with the protein kinases including four JAKs—JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2)—each associated with different cytokine receptors. The STATS, of which there are seven, bind to the phosphorylated cytokine-receptor complex and, after phosphorylation by a JAK, they translocate to the nucleus, bind DNA and activate target gene transcription (Figure 1). Table 1 includes examples of cytokines, the JAKs and STATS involved in their signalling pathways, and their functional roles.

The JAK-STAT signalling pathway is important for cytokines that regulate the cellular immune response (type I cytokines such as IL-2 and related interleukins) and the antibody-mediated response (type II cytokines such as the interferons, IL-10 and related interleukins). However, some other cytokines with a major role in inflammatory disorders do not use the JAK-STAT pathway; examples include TNF, IL-1 and IL-17.

Gene mutations that affect JAK or STAT function have been implicated in several disorders. Examples include severe combined immunodeficiency (JAK3), systemic lupus erythematosus (TYK2, STAT4), rheumatoid arthritis (STAT4), atopy (STAT6), Crohn’s disease (TYK2, STAT3) and Behcet’s disease (JAK2, STAT3).

**Properties of JAK inhibitors**

The JAK inhibitors (also known as jakinibs) are small molecules; they are orally active and have a straightforward daily dosing regimen. For many people, this will be an advantage over the biological disease-modifying drugs, many of which are monoclonal antibodies that require subcutaneous injection or intravenous infusion (albeit much less frequently, at intervals of weeks or months). JAK inhibitors will therefore avoid the need to train patients or carers to administer the dose, or for patients to attend a clinic for treatment.

Imatinib and other early protein kinase inhibitors introduced for the treatment of cancer were not selective for a single class of protein kinases. Similarly, the JAK inhibitors available to date are selective but not specific for a single JAK. Given the overlap between JAKs in their interactions with STATS and their association with more than one cytokine (see Table 1), it is evident that each agent is likely to affect several immunological pathways. Furthermore, a JAK inhibitor can block mediators of cytokines not dependent on the JAK-STAT signalling pathway—for example, indirectly affecting TNF by blocking interferons. And not all cytokines are pro-inflammatory—some interleukins, such as IL-2 and IL-10, have anti-inflammatory actions—so the wider impact of inhibition may be complex.

The immunological effects of JAK inhibitors are influenced by their selectivity for JAK subtypes but whether such differences will be associated with clinically significant differences in efficacy or safety is not yet clear. Adverse effects that are potentially associated with inhibition of each JAK are summarised in Table 2.

JAK inhibitors are currently being evaluated in a diverse range of disorders (see www.clinicaltrials.gov), of which rheumatoid arthritis, psoriasis, inflammatory bowel disease and myeloproliferative disorders account for the greatest number. Many more trials are underway in other autoimmune disorders (juvenile idiopathic arthritis, ankylosing spondylitis, systemic lupus erythematosus, Sjögren’s syndrome), chronic kidney disease and diabetic nephropathy, breast cancer, lymphoma and the prevention of graft rejection.

**Rheumatoid arthritis**

Two JAK inhibitors, baricitinib (Olumiant) and tofacitinib (Xeljanz), have been introduced in the UK for the treatment of rheumatoid arthritis. Baricitinib is selective for JAK1 and 2 and tofacitinib preferentially inhibits JAK1 and JAK3. Both are licensed as monotherapy or in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in adults who have responded inadequately to, or are intolerant to, one or more disease-modifying antirheumatic drug (DMARDs). Several other JAK inhibitors are undergoing clinical trials for similar indications, including the JAK1-selective filgotinib and upadacitinib.

There is strong evidence that JAK inhibitors, combined with methotrexate, improve the symptoms of rheumatoid arthritis in patients who did not experience benefit from treatment with a biological DMARD plus methotrexate. Defining a response as the ACR20 (a ≥20% improvement in tender and swollen joint counts, plus a ≥20% improvement in at least three of: visual analogue pain scale, disability, acute phase reactants, and patient and physician global assessment), a key phase 3 trial of baricitinib reported response rates of 55% compared with 27% with placebo after 12 weeks in patients with refractory disease (see Figure 2); similar response rates have been reported for tofacitinib. After failure of methotrexate therapy (but before

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>JAK</th>
<th>STAT</th>
<th>Functional/role</th>
</tr>
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<tbody>
<tr>
<td>IL-2</td>
<td>JAK1, JAK3</td>
<td>3, 5</td>
<td>Enhances effector and regulatory responses</td>
</tr>
<tr>
<td>IL-9</td>
<td>JAK1, JAK3</td>
<td>1, 3, 5</td>
<td>Atopic disease, inflammatory bowel disease</td>
</tr>
<tr>
<td>IL-3</td>
<td>JAK2</td>
<td>3, 5, 6</td>
<td>Differentiation of multipotent haematopoietic stem cells, proliferation of myeloid cells</td>
</tr>
<tr>
<td>IL-5</td>
<td>JAK2</td>
<td>3, 5, 6</td>
<td>Allergies, asthma, eosinophilic disease</td>
</tr>
<tr>
<td>IL-6</td>
<td>JAK1, JAK2, TYK2</td>
<td>1, 3</td>
<td>Prototypic proinflammatory cytokine implicated in many autoimmune disorders</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>JAK2</td>
<td>5</td>
<td>Erythropoiesis</td>
</tr>
<tr>
<td>IFN-gamma</td>
<td>JAK1, JAK2</td>
<td>1</td>
<td>Enhanced immunity against infection, drives autoimmunity</td>
</tr>
<tr>
<td>IL-19</td>
<td>JAK1, JAK2, TYK2</td>
<td>3</td>
<td>B cell activation, antibody production</td>
</tr>
</tbody>
</table>

Table 1. Examples of cytokines, the JAKs and STATS involved in their signalling pathways, and their functions
treatment with a biological DMARD), tofacitinib and baricitinib have been shown to be non-inferior\(^7\) or superior\(^8\) to the TNF inhibitor adalimumab and to slow disease progression.\(^8\,^9\)

Because long-term safety is currently uncertain, European management guidance recommends that JAK inhibitors should be reserved for use when a biological DMARD proves unsatisfactory.\(^10\) NICE has now appraised both baricitinib and tofacitinib, and recommends them for use only when disease is severe and has responded inadequately to a combination of conventional DMARDs, or if the patient has responded inadequately to or cannot take a biological DMARD.\(^11\,^12\) A month’s treatment with tofacitinib or baricitinib costs £690 or £805, which is close to the cost of biological DMARDs.

**Dermatology**

JAK inhibitors are being evaluated as treatments for psoriasis, alopecia areata, vitiligo and atopic dermatitis.\(^13\)

NICE recommends systemic biological agents as an alternative to the PDE4 inhibitor apremilast for the treatment of severe psoriasis when phototherapy, methotrexate and ciclosporine have proved unsuccessful.\(^14\) The options are the TNF inhibitors adalimumab and etanercept, the interleukin (IL)-12 and IL-23 inhibitor ustekinumab, the IL-17A inhibitors secukinumab and ixekizumab, and (for very severe psoriasis) the TNF inhibitor infliximab.

Most clinical trials of JAK inhibitors for psoriasis have been of tofacitinib.\(^13\) In patients with moderate to severe plaque psoriasis who were eligible for conventional systemic therapy, who had not responded to it, or in whom it was contraindicated or poorly tolerated, the proportion of patients with a PASI 75 response (\(\geq 75\%\) reduction in Psoriasis Area and Severity Index score) was 40–46\% with 5mg tofacitinib twice daily and 59–60\% with 10mg tofacitinib twice daily compared with 6–11\% with placebo after 16 weeks (see Figure 3).\(^15\) The higher dose of tofacitinib was non-inferior to etanercept 50mg twice weekly.\(^16\)

In one trial that included 12 patients with psoriatic arthritis, all met the ACR20 response criterion after 12 weeks’ treatment with tofacitinib and this improvement was maintained in most patients after one year, with the 10mg twice daily dosage possibly superior to 5mg twice daily.\(^17\) A phase 2 trial suggests that baricitinib may offer similar efficacy in patients with moderate to severe plaque psoriasis.\(^18\)

Topical formulations of JAK inhibitors have also been evaluated; early trials suggest that ruxolitinib compares well with established topical treatments but trials of topical tofacitinib have been inconclusive.\(^13\)

Other early trials suggest that JAK inhibitors show promise in the treatment of vitiligo and atopic dermatitis. Animal models suggest that JAK inhibitors can activate hair follicles and restore hair growth; several trials indicate that tofacitinib in particular may improve alopecia areata in 30–40\% of patients, though definitive evidence is needed.\(^13\) In one retrospective study, symptom score improved by more than 50\% in 60\% of patients treated for 4–18 months.\(^19\)

**Inflammatory bowel disease**

NICE recommends the alpha-4 beta-7 integrin inhibitor vedolizumab for moderate to severe active ulcerative colitis, TNF inhibitors when treatment with steroids and immunosuppressants has failed, and infliximab for acute exacerbations of ulcerative coli-

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**Table 2. Potential adverse effects associated with JAK inhibition**\(^4\)

<table>
<thead>
<tr>
<th>JAK</th>
<th>Function impaired</th>
<th>Potential adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK1</td>
<td>Severely impaired lymphoid development, Defective cytokine signalling</td>
<td>Infection, hyperlipidaemia</td>
</tr>
<tr>
<td>JAK2</td>
<td>Impaired erythropoiesis, myelopoiesis</td>
<td>Anaemia, neutropenia</td>
</tr>
<tr>
<td>JAK3</td>
<td>Impaired response to gamma chain receptor family of interleukins (eg IL-2)</td>
<td>Natural killer cell lymphopenia, Diminished function of CD8 T cells, Infection, possibly opportunistic infection</td>
</tr>
<tr>
<td>TYK2</td>
<td>Impaired helper T cell (Th)1 responses, Reduction in pathogenic Th17 cells, Blockade of IFN actions</td>
<td>Infection</td>
</tr>
</tbody>
</table>

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**Figure 2.** American College of Rheumatology (ACR) response rates to baricitinib 2mg or 4mg daily or placebo, plus a conventional disease-modifying antirheumatic drug (DMARD), in patients with moderate to severe active rheumatoid arthritis and an inadequate response to a biological DMARD.\(^10\)

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**Figure 3.** ACR20, ACR50, ACR70 response rates to tofacitinib 5mg or 10mg twice daily or placebo.
Janus kinase inhibitors

Similar guidance applies to the treatment of severe active Crohn’s disease that is unresponsive to conventional agents and immunosuppressants, and vedolizumab is a further option if biological agents are unsuitable or ineffective. Early experience with JAK inhibitors in patients with ulcerative colitis has been encouraging. In patients with active ulcerative colitis despite treatment with conventional and biological agents, treatment with tofacitinib induced remission in 17–19% of patients after eight weeks (vs 4–8% with placebo); by 52 weeks, 34% of patients taking a dosage of 5mg twice daily and 41% of those taking 10mg twice daily were in remission (vs 11% with placebo). By contrast, results in patients with Crohn’s disease have been disappointing: one phase 2 trial showed that, after eight weeks, tofacitinib did not significantly increase the proportion of patients with moderate to severe disease in remission (43% vs 38% with placebo), with no significant difference in the proportion of patients with response or remission at six months (56% with 10mg tofacitinib twice daily, 40% with 5mg twice daily) compared with placebo (38%). Filgotinib is currently undergoing evaluation as a treatment for ulcerative colitis and Crohn’s disease in several trials, none of which have been published to date.

Myeloproliferative disorders

The JAK1- and JAK2-selective inhibitor ruxolitinib (Jakavi) is indicated for the treatment of disease-related splenomegaly or symptoms in adults with myelofibrosis, either as a primary disease or after polycythaemia vera or essential thrombocythaemia, and is recommended by NICE for intermediate- or high-risk disease. Treatment reduces splenomegaly, itch and fatigue and improves survival but the newer agents now in phase 3 trials, such as momelotinib and pacritinib, may offer similar efficacy with a lower risk of myelosuppression (though they may have other adverse effects such as, in the case of momelotinib, peripheral neuropathy).

Adverse effects

It is presently uncertain how great the differences in tolerability and toxicity are between the JAK inhibitors. These agents vary in their selectivity for JAK subtypes – for example, baricitinib and ruxolitinib exert greatest inhibition on JAK1 and JAK2 whereas tofacitinib preferentially inhibits JAK1 and JAK3. To what extent these effects selectively induce the potential adverse effects listed in Table 2 is unclear.

As with the biological DMARDs, there are concerns about the risk of serious infection with the JAK inhibitors. A meta-analysis of 66 randomised trials and 22 long-term extension studies in patients with rheumatoid arthritis who had not responded to a biological DMARD found that the risk of serious infection with tofacitinib was similar to that of the biological DMARDs. A second meta-analysis of 45 studies concluded that the rate of treatment discontinuation in clinical trials was similar for tofacitinib and biological DMARDs in patients with rheumatoid arthritis who had not responded to treatment with a conventional DMARD. Tofacitinib and baricitinib are associated with an increased risk of herpes zoster, and upper respiratory tract infections were the most frequent adverse events in clinical trials. Based on premarketing experience, there is no evidence that either of these agents is associated with an increased risk of malignancy in patients with rheumatoid arthritis.

Both tofacitinib and baricitinib raise LDL cholesterol in patients with rheumatoid arthritis but this appears to be at least partly attributable to correction of the low levels caused by inflammation associated with rheumatoid arthritis. This effect is more frequent than with methotrexate or adalimumab but is not associated with a change in the LDL/HDL ratio or, so far (up to eight years for tofacitinib), an increase in cardiovascular events; similar findings have been reported in patients with psoriasis treated with tofacitinib.

Tofacitinib and baricitinib have been associated with anaemia, lymphopenia or neutropenia (and with thrombocytopenia in patients with myelofibrosis treated with ruxolitinib), and with abnormal liver function tests; prescribing cautions require...
monitoring during treatment and interruption of treatment if minimum thresholds are reached.

Summary
The JAK inhibitors offer a new pharmacological strategy for the treatment of a range of autoimmune disorders. Most of the published data are for tofacitinib and baricitinib in the treatment of rheumatoid arthritis. JAK inhibitors have been shown to be effective in the treatment of rheumatoid arthritis, myeloproliferative disease, psoriasis and ulcerative colitis when other treatments have failed. However, a substantial proportion of patients who are running out of other treatment options do not respond to these agents.

The JAK inhibitors appear to be as safe as biological DMARDs though less is known about their long-term effects and about the risk of blood disorders and malignancy in particular. They are currently recommended for the treatment of severe rheumatoid arthritis when established therapies fail; as clinical experience grows, it may be possible to target these agents to improve outcomes further.

References

Declaration of interests
None to declare.

Steve Chaplin is a medical writer specialising in therapeutics