RHEUMATOLOGY

Editorial

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Janus kinase inhibitors clear to land

Janus kinase inhibitors in RA

In Europe, the first two Janus kinase (Jak) inhibitors have just become available. On 15 February, the Jak1/Jak2 inhibitor baricitinib was approved by the European Medicines Agency for patients with RA not responding sufficiently to at least one DMARD. For the same indication, European Medicines Agency approval of the Jak1/Jak2/Jak3 inhibitor tofacitinib, which the US Federal Drug Administration and Swissmedic had approved in 2012 and 2013, respectively, followed on 27 March. How much impact on RA therapy will these two novel oral drugs have?

The picture of the clinical effects of Jak inhibitors is already fairly detailed. In the end, it may be a fitting coincidence that the third DMARD lined up for landing this year is sarilumab, the second IL-6 receptor blocker after the approval of tocilizumab in 2009. After all, the signalling of the IL-6 receptor depends on Jaks, namely on Jak1 (Table 1) [1]. Although Jaks are essential for the signalling of most cytokine receptors, important exceptions include many of the other cytokines targeted by biologic DMARDs (bDMARDs), namely TNF, IL-1 and IL-17 [1].

Jak1 inhibition is indeed essential for the efficacy of the Jak inhibitors in RA, because filgotinib, a Jak1-specific inhibitor, has effects very similar to baricitinib and tofacitinib [2]. Although tocilizumab was originally designed to be a Jak3 inhibitor, the additional Jak3 inhibition in comparison to baricitinib has so far not been apparent in RA. The limited Jak2 inhibition exerted by baricitinib and tofacitinib is visible, with a slight decrease in haemoglobin during therapy [3, 4]. Although manageable, this decrease is in sharp contrast to tocilizumab, which leads to a clear increase in haemoglobin within weeks. This is presumably attributable to reduced erythropoietin signalling, which depends on Jak2. Proving the point, the Jak1-selective inhibitor filgotinib produces an increase in haemoglobin similar to tocilizumab [2].

In line with Jak1 inhibition impacting on IL-6 receptor signalling, the clinical results of the Jak inhibitors are reminiscent of those of the anti-IL-6 receptor antibody tocilizumab. Like tocilizumab, baricitinib and tofacitinib work almost as well without accompanying MTX (or other conventional synthetic DMARDs). Like tocilizumab, both were, in monotherapy, clearly better than MTX in MTX-naïve patients. Similar to tocilizumab, they both rapidly normalize the acute phase response. Although there is no direct comparison so far, most effects are in approximately the same range. Likewise, the increase in cholesterol seen with tocilizumab is repeated in Jak inhibition. Taken together with the mechanistic insights into IL-6 signalling via Jak1, it appears likely that blockade of IL-6 receptor signalling is a main mechanism of Jak inhibitors in RA treatment.

Two clinical adverse events beyond IL-6 receptor blockade probably track to reduced Jak1- and Jak2-dependent (Table 1) IFNγ signalling. Jak inhibition is associated with an increase in tuberculosis reactivation comparable to anti-TNF antibodies [5]. The rate in herpes zoster is even higher than with any of the bDMARDs in use so far [6]. Nevertheless, although the zoster rate is increased, herpes zoster typically stays localized under the Jak inhibitors, and multi-segmental zoster is uncommon. In contrast, pharmacological, and thus incomplete, Jak inhibition might be safer than complete IL-6 receptor blockade with regard to large intestinal perforations. Even though this difference is not significant so far [7], tofacitinib is a candidate therapy for both ulcerative colitis and Crohn's disease [8], where tocilizumab was not developed further because of safety concerns.

While additional Jak inhibitor indications are being tested, RA will remain, for the moment, the area of potential impact of both tofacitinib and baricitinib. This is based on two comprehensive clinical trial programmes. Within these programmes, were tested both drugs in combination with MTX in patients with insufficient response to MTX (ORAL Standard, ORAL Scan and RA-BUILD, respectively), in patients with insufficient response to bDMARDs (ORAL Step and RA-BEACON), and in monotherapy against methotrexate in MTX-naïve patients (ORAL Start and RA-BEGIN). Reduction in radiographic progression was demonstrated (ORAL Scan, RA-BUILD and RA-BEACON), and baricitinib even outperformed the TNF blocker adalimumab in combination with MTX in the RA-BEAM study [9]. There is therefore little doubt that Jak inhibitor efficacy will be comparable to the efficacy of bDMARDs in RA treatment. In fact, the newly updated EULAR RA recommendations list Jak inhibitors with bDMARDS, differentiating by long-term experience only [10].

The last piece missing in this puzzle has been the price. In the USA, tofacitinib entered the market at an annual treatment cost usually associated with bDMARDs. Since then, biosimilars have started to influence bDMARD prizes, and Jak inhibitors will be likely to face significant opposition if they are not competitive with biosimilars. The initial German list prize for baricitinib that was recently been announced, which will be subject to negotiations, gives a first impression of Lilly's strategy. This first list price would mean an annual cost of €18 601. This is

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Table 1 Presumable therapeutic relevance of the inhibition of individual Janus kinases

Cytokine	Effects presumably attributable to Jak inhibition	Jak1	Jak2	Jak3
IL-6	RA; IBD; acute phase response; AE: cholesterol	+		
Epo	AE: (lack of remission in) anaemia		+	
Tpo	AE: mild thrombocytopenia		+	
IFNγ	AE: tuberculosis, herpes zoster	+	+	
IFNα/β	AE: herpes zoster	+		
IL-12	AE: tuberculosis?		+	
IL-23	Psor; PsA; AS		+	
IL-22	Halt in radiographic progression AS?	+		
IL-15	Psor?	+		+

Please note that Tyk-2, which is involved in type I IFN, IL-12/23 and IL-22 receptor signalling, has been left out because this fourth Janus kinase is not targeted by either baricitinib or tofacitinib. AE: adverse event; Epo: erythropoietin; Psor: psoriasis; Tpo: thrombopoietin.

close to the list price-based annual costs of the first available s.c. biosimilar etanercept (Benepali©) at €18 336 and 18% less expensive than the bio-originator Etanercept (Enbrel©) at €22 669.

Although it will need to be seen how the price and the limited experience will influence the reception of this new class of highly effective drugs, oral therapy will add an interesting aspect. Effects on the signal transduction of more than one receptor, but somewhat leakier suppression of the signalling of any given receptor are still difficult to balance. There may be additional chemistry-based toxicity. Nonetheless, it is clear that we will not see secondary loss of efficacy because of anti-drug antibodies. Thus, patients who fared well on tocilizumab, but then experienced secondary failure, should be among those who benefit from baricitinib or tofacitinib.

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