Selected Summaries

Selective Janus kinase inhibitors: Promising drugs for rheumatoid arthritis

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Genovese MC, Fleischmann R, Combe B, Hall S, Rubbert-Roth A, Zhang Y, Zhou Y, Mohamed M-E F, Meerwein S, Pangan AL. (Division of Immunology and Rheumatology, Stanford University School of Medicine, Palo Alto, CA, USA; University of Texas Southwestern, Metroplex Clinical Research Center, Dallas, Texas, USA; Department of Rheumatology, CHU Montpellier, Université de Montpellier, Montpellier, France; Department of Medicine, Monash University, Cabrini Health and Emeritus Research, Malvern, VIC, Australia; Kantonsspital St Gallen, St Gallen, Switzerland; AbbVie Inc, North Chicago, IL, USA; AbbVie Deutschland, Ludwigshafen, Germany.) Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying antirheumatic drugs (SELECT-BEYOND): A double-blind, randomised controlled phase 3 trial. *Lancet* 2018;**391:**2513–24.

SUMMARY

The safety and efficacy of upadacitinib in patients with rheumatoid arthritis (RA) and inadequate response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (SELECT-NEXT) study was a randomized controlled trial (RCT) that showed the efficacy of Janus kinase (JAK)-1 inhibitor upadacitinb at doses of 15 mg and 30 mg over placebo at 12 weeks. Almost two-third patients achieved the American Rheumatology criteria (ACR20) response with the drug as compared to only 36% with placebo ($p<0.01$). In the SELECT-BEYOND trial, patients refractory to biological DMARDs were enrolled, and they also showed similar results (65% response with 15 mg, 56% with 30 mg and 28% with placebo). The most significant finding was the remission rates of 48% in SELECT-NEXT and 43% in SELECT-BEYOND trials with upadacitinb as compared to 14% in placebo. Further, the response started as early as 1 week. Upadacitinib also led to better improvement in functional disability and quality of life as compared to placebo.

As expected, the number of serious adverse events were more frequent in the upadacitinib group especially opportunistic infections such as herpes zoster, lymphopenia and anaemia, but they occurred in a small proportion of patients. These effects were dose-dependent. Four patients developed pulmonary embolism in SELECT-BEYOND trial, and three had a cardiovascular event in the SELECT-NEXT trial. Most of these patients had pre-existing cardiovascular disease risk factors.

COMMENT

The current paradigm of treatment in RA is treat to target so as to achieve remission or low disease activity by 6 months.[1] To achieve this goal, therapies targeted at various molecules in the immune system are being tried in addition to csDMARDs. Among these tumour necrosis factor (TNF)-inhibitors, interleukin-6 inhibitors and B cell depletion therapy, the so-called bDMARDs have become standard of care in the management of RA in patients not responding to csDMARDs. Although the response to these agents is good, it is not uniform and significant proportion of patients still has active disease. Thus, there is a need for newer drugs for this group of patients.

Targeted synthetic DMARDs (tsDMARD) are the new class of drugs that target downstream pathways of cytokine signalling. JAK-STAT pathway is utilised by more than 50 cytokines. There are three different JAK molecules named 1–3. Tofacinitib (JAK-1 and -3 inhibitor) was the first approved JAK inhibitor for the treatment of RA and showed efficacy comparable to anti-TNF agent adalimumab.[2] Head-to-head comparison between baricitinib (JAK-1 and -2 inhibitor) and adalimumab, showed superiority of baricitinib over adalimumab.[3] The SELECT studies show that upadacitinib, a specific JAK-1 inhibitor has excellent short-term benefit in treating RA. Thus, it is evident that JAK inhibitors are highly effective in RA.

Though tsDMARDs are equal or even better than bDMARDs do they have similar toxicity profile? The major toxicity of JAK inhibitors includes increased risk of infections, drop in blood counts and increase in vascular events. JAK-2 is mainly linked to the development of non-lymphoid lineage haematopoiesis and JAK-1 and -3 are mainly linked to lymphoid development. Therefore, selective JAK inhibitors are being developed to improve specificity and reduce haematological toxicity. Tofacitinib long-term safety profile is very similar to bDMARDs, and the short-term data of upadacitinib also suggest that it has similar toxicity profile. We need to wait for the long-term safety data to see if targeting only JAK-1 has reduced toxicity.[4] At present, no head-to-head trials are available comparing different JAK inhibitors.

Another major challenge in the use of JAK inhibitors is the lack of dose-response in most studies. In the SELECT studies, both doses of upadacitinib have shown similar efficacy, but the adverse effects were higher in the higher dose arm. In the baricitinib study, both 2 and 4 mg showed equal clinical efficacy though the 40 mg adalimumab dose showed little better radiological benefit. This resulted in delayed approval by the FDA and that of only the lower dose of 2 mg.[5]

Furthermore, long-term effects on radiographic progression of upadacitinib need to be seen in the next phase of the study. Although the superior efficacy of other tsDMARD such as baricitinib over biological agents has been shown, similar head to head comparative trial between upadacitinib and biological agents is still awaited.

One of the major advantages of upadacitinib is rapid onset of action, within a week. Conventionally, low-dose steroid bridge therapy is used for 12–16 weeks for control of the disease before the DMARDs show their effect. In view of the rapid onset of

action, one can obviate the need for use of prednisolone in patients with RA. This can help reduce pill burden and adverse effects caused by prednisolone.

Another advantage, in the SELECT BEYOND trial of upadacitinib was that 70% of 154 patients who had failed on more than two bDMARDs achieved ACR20 response. This provides a promising therapy to patients who previously had little choice.

Although bDMARD has changed the life of patients with RA, their high cost precludes their use in resource-constrained countries such as India. Despite the development of cheaper biosimilars of these bDMARD they still remain out of reach for most patients in India.[6] In addition, bDMARD need a complex production system and cold chain for transport. With erratic availability of power in different parts of India, their storage is an issue. All biological DMARDs need to be given by the parenteral route and some of them need in-hospital intravenous infusion. This further increases the cost of therapy and makes it inconvenient for the patient. Even for subcutaneous preparations, almost one-third of patients take the help of a family member or physician, and many patients have injection phobia.

In contrast, tsDMARDs are in tablet formulation, so can be easily manufactured, stored, transported and taken by patients. Patients prefer oral medications over injectables with similar efficacy. This leads to better adherence by patients which ultimately translates into better disease control. A recent trial on oral strategy shows that methotrexate and tofacitinib are as good as methotrexate and adalimumab.[7] Although at this time point, tsDMARDs are as expensive as bDMARDs, in the near future, after expiry of the patent, they can be marketed at a nominal cost.

Regardless of some pending issues, JAK inhibitors have opened the door for effective management of patients unresponsive to csDMARD or bDMARD. Considering ease of administration, rapid onset of action, scope for price reduction and probably superior efficacy, JAK inhibitors may supersede bDMARD as the standard of care in patients not responding to conventional DMARDs.

Conflicts of interest. None declared

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