Tapering Janus kinase inhibitors in rheumatoid arthritis with low disease activity or remission: reality or dream?

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In this issue of the journal, Takeuchi *et al* presented results of a baricitinib long-term extension study of patients who received baricitinib 4 mg for ≥15 months and maintained a clinical disease activity index (CDAI) low disease activity (LDA; CDAI <10) or remission (CDAI ≤2.8) for ≥3 months.[1] Patients with rheumatoid arthritis (RA) were randomised to baricitinib tapering to 2 mg daily dose versus continuing the baricitinib 4 mg daily.

Patients in this study had a mean (SD) age of 54 (12) years, 75% were female, 75% were anticyclic citrullinated protein antibody (ACPA) positive, 75% were rheumatoid factor positive, 46% on concomitant glucocorticoids, 82% were on concomitant methotrexate, one-third each had previously failed one or two traditional disease-modifying antirheumatic drugs (DMARDs), but only 13% previously failed a biologic. Patients had one swollen and one tender joint count, and the CDAI score was 3.6 (SD, 2.8), just before tapering.

The rates of LDA (67% vs 80%) and remission (33% vs 40%) at 48 weeks and non-serious infection rates (24.9 vs 30.6) were lower and relapse (CDAI score >10; 37% vs 23%) and rescue rates (18% vs 10%) higher in baricitinib 2 mg (tapering) vs 4 mg (continuing) daily dose groups. Among the rescued patients, most people who lost response (up to two-thirds) could regain the LDA or remission within 24 weeks after rescue to baricitinib 4 mg daily, 67% for the 2 mg group vs 54% for the 4 mg group. Compared with 4 mg daily dosing, baricitinib dose reductions to 2 mg daily were associated with statistically significant increase in CDAI, simplified disease activity, disease activity score (DAS) and earlier relapse. Among DMARD-incomplete responder (IR) patients who had achieved remission at step-down baseline, the majority maintained remission in both dose groups, 56% vs 68% in the baricitinib 2 mg vs 4 mg group. The authors acknowledge major study limitations, including the lack of radiographs, only a 48-week follow-up and smaller numbers for important subgroups of patients (ie, DMARD-naïve, biological DMARD IR).[1] The authors did not perform analyses of specific patient or disease characteristic/s predicting the risk of losing LDA or remission during baricitinib tapering.

SO, WHAT ARE THE STUDY IMPLICATIONS FOR BARICITINIB TAPERING IN RA?

This study showed in patients with RA (primarily with previous conventional DMARD failure) being treated with baricitinib 4 gm daily dose who were concurrently on methotrexate (MTX) (mean dose 15 mg/week) with/without glucocorticoids, tapering to baricitinib 2 mg dose led to statistically significantly lower LDA rates up to 48 weeks follow-up, that is, 10%–13% fewer patients had LDA in the group tapering baricitinib to 2mg dose compared with those continuing at 4mg dose. Up to two-thirds of the patients with RA who relapsed could regain their LDA or remission within 24 weeks after rescue with baricitinib 4 mg dose. In those with previous conventional DMARD failure who were in remission at baseline, 15% fewer and 12% fewer of those being tapered maintained remission at 24 and 48 weeks, respectively, compared with 4 mg dose continuers.

To me, this indicates that patients in remission with baricitinib 4 mg daily dose who have taken this medication for >1 year can attempt baricitinib dose tapering while continuing their MTX (±glucocorticoids) regimen, with some risk (10%–20%) of loss of LDA or remission state, but two-thirds regain that state with baricitinib dose escalation. This is an important finding since patients frequently consider and try RA medication tapering or discontinuation (with and without provider knowledge). The cost of lifelong therapy with biologic or Janus kinase inhibitors in RA is high, and there are few associated risks of treatment. This study provides robust data to support baricitinib tapering in patients who desire it, with some risk of loss of remission state.

WHAT ARE THE STUDY IMPLICATIONS FOR DMARD/BIOLOGIC TAPERING IN RA? WHERE DOES THIS FIT IN THE SPECTRUM OF EVIDENCE?

Edwards *et al* performed a systematic review of 52 papers of biologics across various rheumatic conditions and concluded that remission is typically not sustained in patients who discontinue biologic therapy.[2] The relapse rates and flare in people discontinuing biologic was moderate to high in people with early RA (48%–54%) and established RA (2%–84%).[2] In many cases, an acceptable disease activity could be regained on retreatment; however, 19%–100% of the patients regained disease remission,[2] a very wide range that represents significant clinical uncertainty. In another systematic review of 11 studies of biologics in RA, the authors found that dosing down of biologic may be an option in many patients who have achieved remission or LDA.[3] A key limitation of the current evidence is the inability to predict which patient with RA will succeed in DMARD/biologic tapering without flare and without the loss of current LDA/remission state.

A recent review highlighted potential factors associated with successful tapering, but the evidence for each factor is based on one to few studies. The presence of deep remission state (DAS28 of 2.2 or lower) prior to tapering DMARDs in people with remission, shorter duration of RA (early RA), a longer duration of remission state, a more rapid response to DMARDs, absence of serum markers of inflammation (acute-phase reactants, cytokines and metalloproteinases) and ACPA negativity may each be associated with a higher likelihood or remission maintenance with tapering of biologic and/or synthetic DMARDs.[4] The presence of synovitis detected by the ultrasound was a predictor of failure of successful tapering of biologics in three studies.[5–7]

The 2015 American College of Rheumatology (ACR) guideline for the treatment of RA *conditionally recommended* tapering of biologics, traditional DMARDs or Janus kinase inhibitor (only tofacitinib was approved for RA at the time of guideline formulation) versus not tapering the

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respective medications in patients with RA in disease remission[8] and *conditionally against* tapering these medications in with those with LDA. The ACR RA guideline defined DMARD/biologic tapering as scaling back therapy one medication at a time, by reducing dose or dosing frequency and recommended conducting it slowly and carefully, watching for increased disease activity and flares.[8] The ACR guideline also recommended that even in remission, all the drugs should not be stopped at the same time, a **strong recommendation**.[8] The 2017 European League against Rheumatism (EULAR) recommendations for the management of RA state that if a patient with RA is in deep remission after tapering glucocorticoids, then biologic can be tapered especially if it is combined with a traditional DMARD.[9] Thus, both ACR and EULAR guidelines for RA management allow for gradual tapering of DMARD/biologic in people with remission, watching carefully for disease flare and the loss of remission state.

WHAT IS THE TAKE HOME MESSAGE?

Tapering of DMARDs, biologics and Janus kinase inhibitors in patients with RA is a reality in those in sustained, deep RA remission, and on combination therapy with traditional DMARD. This decision should be made in line with patient values and preferences, balancing cost/safety against the possibility of RA flare and loss of RA remission which can be regained in the majority by restarting or increasing the dose, but not all patients. Thus, the uncertainty of the potential loss of remission must be acceptable to patients attempting Janus kinase inhibitor tapering and a shared decision-making approach is critical, to avoid mismatched expectations. A key factor to consider is that if the patient is on concomitant glucocorticoids, they should be tapered first, considering the risk–benefit ratio. As more evidence is generated with longer follow-up studies, patients and providers can make more informed decisions about tapering biologics and/or DMARDs. But, let's not forget concomitant glucocorticoids, which should be tapered first. More research is need to address if biologic or Janus kinase inhibitor drug holidays would be preferable to their discontinuation.

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