Jack pot! What can we learn about registries with respect to treatment cycling in rheumatoid arthritis?

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An analysis of the Janus kinases (JAK)-pot collaboration of registries, recently reported on the comparative effectiveness of cycling JAK inhibitors (JAKi) compared with switching to a biological disease-modifying antirheumatic drug (bDMARD) in patients with rheumatoid arthritis (RA) after failure to the first JAKi in a nested cohort of patients.1 Of the registries contributing to the pooled data, 15 were from Europe and the remaining 2 were from Canada and Israel.1 A strength of this analysis is that much can be learnt from combining datasets as the sample size allows for more power, more questions may be answered, and, most importantly, generalisability is increased.

The specific patients studied in this analysis were patients with RA in whom the first JAKi failed and who were subsequently switched to either a second JAKi or a bDMARD. Of the 2000 patients who fulfilled these criteria, 365 were switched from a JAKi to a second JAKi while 1635 switched from a JAKi to a bDMARD. The primary outcome was drug retention and secondary outcomes were the reason for stopping the second treatment depending on the reason for discontinuing the first JAKi and the change in the Clinical Disease Activity Index (CDAI) over time. Of note, in this group of patients, the vast majority were older, mean disease duration of 13–15 years and had failed 2–3 bDMARDs before treatment with the first JAKi. The adjusted analysis demonstrated that cycling to a second JAKi was superior to switching to a bDMARD with respect to drug retention (HR of withdrawal 0.82 (95% CI 0.68 to 0.99). With respect to the secondary outcomes, CDAI improvement was similar at 2 years. When the reason for stopping the first JAKi was lack of efficacy, most of the patients in both treatment groups also stopped for this reason (difference between groups: p = 0.59). If the first JAKi was discontinued due to an adverse event (AE) and the reason for stopping the second JAKi was more likely another AE.1

Based on these observations, one could conclude that either strategy is reasonable in the difficult to treat patient with RA who had failed multiple advanced therapies.

This analysis from the JAK-pot collaboration does have several strengths; as, by combining multiple registries, the increased sample size allows for more power, the ability to address more questions, and, importantly, generalisability is increased. In addition, patients enrolled in these registries more likely would with the common comorbidities and disease activity seen in daily practise compared with randomised controlled registry trials which should help clarify the understanding of real-world comparative effectiveness of the medications included.

This analysis also has several significant potential areas of concern. Patients were not prospectively randomised in a blinded manner to the second treatment after failure of the first JAKi. Patients were enrolled and treated according to the preferences of the enrolling physician resulting in the likely occurrence of channelling bias.2 In addition, combining multiple registries could lead to a centre effect because of divergent data from the registries and the many confounders related to the choice of RA treatment.2 In this report, only three of the seventeen registries enrolled 45% of the subjects. Access to medications, and prescriber and patient preferences affects prescribing patterns worldwide; the effects of this may be minimised or maximised in combined registries. To clarify this point, 4 of the 17 registries did not have a single patient who failed a JAKi switched to a second JAKi (all JAKi failures were switched to a bDMARD) whereas in 7 greater than 20% were switched from a JAKi to a JAKi.1 These differences are important, when analysing and interpreting data from pooled registries. A possible solution would be to analyse data with matching within each centre such as using propensity scores but there may have been insufficient sample size within each registry to match patients accurately who switched from one JAK inhibitor to another.

The question asked by the JAK-pot collaborators is currently very germane. There are multiple factors to be considered by the patient and physician when deciding what to prescribe next after failure of a medication for RA. First, what has occurred previously with respect to the patients’ treatment and response is clinically important. The choice of which medication to use depends on factors including patient access to specific medications, governmental and regional prescribing restrictions and requirements, and physician and patient preferences with wide variations in the order of treatment of advanced therapies in RA.3–5

An important factor in the JAK-pot collaboration of registries is that the vast majority (if not all) patients were multiple drug failures. By definition, these patients are difficult to treat.6 It would be expected that patients failing a drug with one mechanism of action (MOA) would be switched to an MOA to which they were not previously exposed. The patients who switched to a second JAKi had previously failed a mean of three bDMARDs while those who switched to a bDMARD had failed a mean of two bDMARDs. The patients with two bDMARD failures would more likely switch to another, untried bDMARD while those who had failed three, would be more likely to switch in the same class as they had failed more MOAs. This would be especially true for the 25%–35% of patients reported who were seronegative as they would be less likely to respond to two of the MOA available, rituximab and abatacept.7–8

As noted in the 2022 EULAR recommendations for the treatment of RA, it has been shown that tumour necrosis factor inhibitor (TNFi) cycling can be effective in the treatment of RA and also in a randomised trial of TNFi cycling.3–5 With the availability of biosimilar bDMARDs with markedly reduced cost in many regions of the world, trying a more cost effective medication, even with the same MOA, may be preferable in many instances than switching to a more costly alternative, even if the MOA is different. Similarly, JAKi cycling can be effective.9–11 Data from the Swiss registry already suggested that after JAK inhibitor treatment, drug retention was superior when switching to another JAKi than to a TNFi.12 Whereas, a study from Belgium demonstrated that
after use of a JAKi in RA demonstrated that IL6i had the largest change in DAS28 (55%) as the next treatment, whereas, all other options had a change in DAS28 of 38%–41%.\textsuperscript{13}

For a patient who does very well on an advanced treatment in RA, but then has a secondary failure (a patient with a long period of remission and then loss of response), there is a temptation to try another molecule within that class; whereas, if a drug was not tolerated or the patient had a clinically meaningful AE which was felt to be MOA related, there is a tendency to try a different MOA. For the uncommon patient who is a primary non-responder or with a minimal response to one MOA, in general, a rheumatologist is far more likely to switch the MOA for one MOA, in general, a rheumatologist is far more likely to switch the MOA for

For instance, a US database found that IST in RA were more likely to be used as mono-

therapy than TNFis.\textsuperscript{15} Questions arise from the data such as: Would retention vary if comparing those with advanced therapies combined with csDMARDs (especially methotrexate) compared with monotherapy; and, if retention was worse with monotherapy, the data would bias against JAKis as there was more mono-

therapy use in these patients. Comorbid-

ities were also higher in the JAKi to JAKi switching group and this could lead to shorter retention as comorbidities may affect retention adversely.\textsuperscript{16 17} It is difficult to know what items to adjust for in analy-

ses as many are inter-related. Likely there were interactions between at least some if not many of the variables. When inter-

preting any large sample size, there may be statistical differences in some variables; but some differences may not be as clini-

cally relevant. In multivariable adjusted analyses, the amount of variance explained by specific factors can add relevance to a clinician interpreting the findings.

We conclude that comparing combined registries, there are inherent limitations. For instance, treatment pathways are dependent on access and reimbursement within a jurisdiction. Lines of therapy may be related to country guidelines and drug reimbursement. As an example, advanced therapy reimbursement is different in Switzerland (virtually all treatments are available after methotrexate inadequate response) compared with the UK where advanced therapies are accessible after combination conventional synthetic DMARDs where the bDMARDs and the JAK inhibitors are tiered. Some countries lack global pharmacare (ie, segments of the population have different or no drug coverage); all these factors affect prescribing. The known and unknown factors of why one treatment is prescribed over another is a form of channelling bias. A statistical way to reduce this bias could be using propensity score matching but within each country/region in order to compare similar types of patients where access may be very different compared with another country. However, with small numbers within each registry where there was switching from one JAKi to another, this technique would not have resolved the potential confounding in this study.

However, the JAK-pot collaboration has provided and will continue to yield insights into comparative effectiveness of advanced therapies in RA including disease activity outcomes and retention which is primarily affected by effective-

ness, safety, tolerability and access of medications. In the future, bias could be eliminated by performing large pragmatic trials where patients can be randomised to current standard of care vs other treatment options. The sample size for these studies needs to be very large if comparisons are assumed to have non-inferiority. Such a large trial has been done in early RA in the NORD-STAR study where csDMARDs were compared with methotrexate with a TNFi, an IL6i or abatacept.\textsuperscript{18} Remission rates were different between csDMARDs and abatacept (the latter was superior) but csDMARDs were non-inferior to the other groups. This study required 29 sites and 8 years to enrol in Nordic countries to randomise 812 patients, suggesting that even a multicountry pragmatic trial takes time to obtain an answer and by the time the answer is found, new questions arise, such as what about if a JAK inhibitor was compared.

We also cannot ignore the potential benefit vs risk when prescribing. Tofa-

citinib has been shown to have small but definite increased incidence risk of cardiovascular events and malignancies than TNFis in active patients with RA when added to methotrexate with differences only becoming apparent after approximately 1.5 years.\textsuperscript{19} The generalisability of these results and how they may affect future prescribing of tofacitinib and other JAK inhibitors in RA is unknown.

On balance there is a great value in combining multiple databases/registries to answer questions that are relevant to clinicians and patients. We applaud the work that was done to answer questions within the JAK-pot consortium.

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