The role of JAK inhibitors in the treatment of PsA

Following their success in rheumatoid arthritis, Janus kinase (JAK) inhibitors are emerging as a promising therapeutic option for psoriatic arthritis (PsA), and the selective JAK1/3 inhibitor tofacitinib is now approved for the treatment of PsA in the USA, Canada, and Europe [1,2]. *medwireNews* speaks to Dafna Gladman, Professor of Medicine at the University of Toronto and Senior Scientist at the Krembil Research Institute in Toronto, Ontario, Canada, about the data so far and how JAK inhibitors may influence PsA treatment.

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Increasing the number of treatment options

Gladman believes that the positive trial results for JAK inhibitors are significant because they may provide an additional treatment choice for PsA.

"The most important thing for us as treating rheumatologists is that there are options for patients," she stresses.

She outlines that "we have had five anti-TNF [tumor necrosis factor] agents that work reasonably well but none of them works for all the patients," meaning that alternatives are needed. A study of the British Society of Rheumatology Biologics Register demonstrated that of 422 PsA patients who were treated with a TNF inhibitor (etanercept, adalimumab, or infliximab) and followed up for at least 1 year, 9.5% discontinued treatment due to lack of effectiveness and 10.0% discontinued due to adverse events [3].

In addition to TNF inhibitors, "we've got the anti-IL [interleukin]-17 agents," including secukinumab and ixekizumab, which have been shown to work in around 60% of patients, while the IL-23/23 inhibitor ustekinumab "works very well for skin but not as well as TNF inhibitors for the joints," notes Gladman. She adds that the IL-23 specific inhibitors guselkumab and tildrakizumab, which are currently approved for the treatment of psoriasis, along with

the IL-23 inhibitors risankizumab and mirikizumab that are presently under investigation, "work very well for skin and their effect on the joints is currently being evaluated."

"Even though these agents do work for some of the patients that don't respond to anti-TNF agents, there is still a large population of patients who don't respond to any of those drugs," says Gladman.

"So there is always a need for a new mechanism of action and the JAK inhibitors provide a different mechanism of action," having a combined effect on multiple cytokines through their effect on the JAK enzymes, she remarks.

And Gladman points out that JAK inhibitors are oral agents, unlike the injectable TNF, IL12/23, IL23, and IL-17 inhibitors, noting that "it is good for patients to have alternatives because many patients don't like needles, so getting an oral medication is an attraction for them."

Encouraging efficacy results

Based on the trial results to date, "there is no doubt that JAK inhibitors will have some impact" on the treatment of PsA, says Gladman.

Click here for a round-up of data from the clinical trials of JAK inhibitors in patients with PsA.

She notes that the JAK1/3 inhibitor tofacitinib "works for both TNF inhibitor-naïve and TNF inhibitor-exposed patients," with efficacy demonstrated in around half of patients taking the drug. And the difference in ACR20 response rates between patients treated with tofacitinib and those given placebo "is similar to what we see with anti-TNF agents, so there is a very good efficacy there."

The selective JAK1 inhibitor filgotinib "showed an even better efficacy" in the phase II EQUATOR trial than tofacitinib did in the phase III studies, she says, with 80% of filgotinib-treated patients achieving an ACR20 response by week 16 [4].

How JAK inhibitors compare with other agents

At present, there are scarce trial data available on the comparative efficacy of JAK inhibitors and other treatments in PsA patients, with only one published clinical trial having an active comparator. OPAL BROADEN, the phase III trial demonstrating efficacy of tofacitinib in patients with an inadequate response to conventional DMARDs, included the active comparator adalimumab at a dose of 40 mg every other week given as a subcutaneous injection, which Gladman notes is how the drug is used to treat PsA patients in everyday clinical practice, that is, as a subcutaneous injection [5].

"The tofacitinib response was comparable to the adalimumab response," she observes, with 3-month ACR20 response rates of 50% for patients given tofacitinib 5 mg twice daily, 61% for those given tofacitinib 10 mg twice daily, and 52% for patients in the adalimumab group. However, she emphasizes that OPAL BROADEN "was not powered as a head-to-head study so you can't do any statistical analysis" to compare tofacitinib and adalimumab.

When JAK inhibitors should be considered

Gladman picks out two considerations for deciding when to initiate treatment with

tofacitinib in PsA patients: the use of other medications and the extent of skin disease.

"Since the trials demonstrated efficacy of tofacitinib in TNF inhibitor-naïve and TNF inhibitor-exposed patients, one could use [the agent] upfront," says Gladman, noting that "in the future it may have a role as a first-line drug."

Nonetheless, she points out that "unfortunately, tofacitinib was tested on a background of methotrexate, so officially we do not have the capacity of using it as a first-line drug because that is not how it is marketed."

She believes that tofacitinib may prove to be effective as monotherapy, citing the results from the recently published SEAM-PsA trial demonstrating that "etanercept is moderately superior to methotrexate, but importantly that the addition of methotrexate to etanercept is not helpful" [6].

Click here to read more about the SEAM-PsA study results, with comments from lead author Philip Mease.

"I suspect it will be the same with tofacitinib," remarks Gladman. "I don't think the presence of methotrexate did anything to the efficacy of tofacitinib [in the OPAL BROADEN and OPAL BEYOND trials]; it is just that these patients were not responsive to methotrexate otherwise they couldn't have gone into the trial."

Gladman also says that "the unfortunate thing is that the dose [of tofacitinib] that has been approved in most countries, 5 mg twice a day, is not as effective for the skin as the TNF inhibitors and the anti-IL-12/23, anti-IL23, and anti-IL-17 agents, even though it works very well for the joints." In the OPAL BROADEN study, 43% of patients treated with tofacitinib at the 5 mg dose experienced a PASI75 response at month 3, as did 44% of those given the 10 mg dose. By the 12-month follow-up, however, there was a clearer difference in PASI75 response rates between the two groups, at 56% for patients given tofacitinib 5 mg and 67% for those given 10 mg [5].

And in OPAL BEYOND, the trial comparing tofacitinib 5 mg or 10 mg twice daily with placebo in patients with an inadequate response to TNF inhibitors, Gladman says that the higher dose "almost doubled the PASI75 response." At 3 months, PASI75 response rates were 21% for patients receiving the 5 mg dose and 43% for the 10 mg group, and the rates at 12 months were 34% and 46%, respectively [7].

Based on these findings, "if patients with psoriatic arthritis have significant joint disease, but mild skin disease, then certainly tofacitinib could be the drug of choice," believes Gladman.

Whereas for patients with severe psoriasis, "I would probably use an IL-17 or an IL-23 inhibitor" rather than a JAK inhibitor, she adds.

Safety considerations

"Overall, tofacitinib has a pretty favorable safety profile and there is a lot of experience with it in the rheumatoid arthritis area," says Gladman, but she outlines two specific adverse events that rheumatologists should be aware of. She says that the JAK inhibitor is associated with a numerically increased infection risk, particularly herpes zoster – reported in four tofacitinib-treated patients in OPAL BROADEN and three in OPAL BEYOND – "so you might not want to give tofacitinib to people that have had shingles."

Gladman says that "there was a concern from the rheumatoid arthritis studies" that tofacitinib treatment may be linked to lipid changes. Indeed, a meta-analysis of randomized controlled trials of tofacitinib in rheumatoid arthritis demonstrated that average percentage increases in high- and low-density lipoprotein cholesterol were significantly higher among patients treated with tofacitinib versus comparator treatments [8], and the US and European labels for tofacitinib recommend routine monitoring of lipids and other cardiovascular risk factors [1,2].

"We did a study looking at lipids in tofacitinib-treated PsA patients," remarks Gladman, noting that "it doesn't look like there is a significant concern with lipid change." She says that "there was no increased incidence of heart attacks or strokes" associated with tofacitinib in PsA patients, and overall "there were very few discontinuations due to side effects" in the clinical trials.

"If in the real world exposure we get the same kind of [efficacy and safety] results that were seen in the clinical trials, then tofacitinib certainly would have a very important role in the treatment of PsA," summarizes Gladman.

Focus for future research

The main priorities for future research regarding tofacitinib in PsA patients are long-term efficacy and safety studies, as well as investigations into its efficacy as monotherapy, believes Gladman.

"The first type of research that needs to be done is to demonstrate its efficacy as monotherapy because even though I say it probably is [efficacious], that is not good enough. We need evidence for its efficacy as monotherapy so that we can use it earlier in the course of the disease."

Gladman also highlights that "at the end of the day we are going to want to know what drug is relevant to what patient," so we need a better understanding of "the concept of personalized medicine in the sense of understanding the mechanism of disease in each patient so that we can provide targeted therapy, both in terms of efficacy and safety."

She believes that "we are still a few years away from there but that is really where we want to be."

For the other JAK inhibitors currently under investigation in PsA, further trial results are awaited before their place in therapy can be established. The authors of the phase II EQUATOR study of filgotinib, led by Gladman, conclude that "global phase 3 trials in psoriatic arthritis are needed to confirm" the positive results of the phase II study, "and to extend [the] observations over a longer period of time" [3].

Two phase III trials of the selective JAK1 inhibitor upadacitinib, SELECT-PsA 1 (NCT03104400) and SELECT-PsA 2 (NCT03104374), are currently underway, with estimated completion dates in 2022 [9,10].

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