Editorial

Of Mice and Men: Defining the Role of Interleukin 17 in Rheumatoid Arthritis

In a recent issue of *The Journal*, Pavelka and colleagues reported on a negative study of brodalumab, the interleukin 17 (IL-17) inhibitor, in rheumatoid arthritis (RA)\(^1\). In addition to the authors’ conclusion that there is no reason to pursue further evaluation of the molecule, an antibody against the IL-17 receptor A (IL-17RA), in this disease, there are a number of other important lessons to be learned from this publication. Combined with previously published data for secukinumab\(^2\) and ixekizumab\(^3\), 2 anti-IL-17A antibodies, the results of this study strongly suggest that the IL-17 pathway is not an appropriate target in RA. This conclusion comes despite both animal data suggesting potential benefit and clinical evidence that IL-17 inhibition is effective in psoriatic arthritis (PsA). The latter observation is instructive, and may provide a clue to important pathogenic differences between 2 outwardly similar forms of inflammatory arthritis.

The study itself compared 3 different dose regimens of brodalumab (70 mg, 140 mg, and 210 mg) and placebo; doses were given every 2 weeks, with an additional loading dose at 1 week. The population studied was a typical methotrexate (MTX) inadequate responder population (~80% female, 7–8 years of disease, Disease Activity Score28 ~6.4, Health Assessment Questionnaire-Disability Index 1.4, and mean dose of MTX 17 mg/week). The primary endpoint selected was the ACR50 (American College of Rheumatology 50% improvement) response rate at Week 12. There was no benefit seen for any of the brodalumab doses over placebo, and no dose response seen for the 3 tested doses. None of the secondary endpoints were achieved either. This was in contrast to the brodalumab data in PsA, where doses of 140 mg and 280 mg were both effective. On the positive side, there were no signals of specific adverse events (AE) or serious adverse events (SAE) with brodalumab in the RA trial, and withdrawals for AE were similar across the 4 groups.

In a previously published study of secukinumab in 237 MTX inadequate responders with RA, the primary endpoint of ACR20 response at Week 16 was not met\(^2\). There was also no statistically significant difference from placebo for any of the secondary endpoints, although there was numerical improvement compared with placebo for several of these secondary endpoints. The authors of this study were a bit more forgiving. They suggested that the trends toward response identified suggested a signal of response that warrants further study, perhaps to identify biomarkers of response to IL-17A inhibition.

In a study of ixekizumab, another IL-17A antibody, 5 doses of the antibody were examined in 448 patients, 260 of whom were biologic naive and 188 of whom were tumor necrosis factor (TNF) inhibitor inadequate responders\(^3\). The doses were similar, but not identical, to the doses studied in psoriasis trials with ixekizumab, and only the 2 highest doses were studied in the latter group\(^4\). This study used a complicated primary endpoint, the dose-response relationship for ixekizumab in the ACR20 response at 12 weeks, and this was met with a p value of 0.031. However, only the middle of the 5 escalating dose groups (30 mg every 2 weeks) actually had an ACR20 response that was statistically greater than placebo at 12 weeks. Most of the ixekizumab dose groups had an ACR50 response rate that was greater than placebo (p < 0.05), but the average rate of response was only 20–30%, compared with 9% for placebo. The 2 doses tested for the TNF inadequate responders generated an ACR20 response that was statistically better than placebo (p < 0.05), but the difference in response rate was < 20%.

Despite these rather modest responses, the authors generously concluded that ixekizumab produced a rapid and significant response in both biologic naive and TNF inhibitor inadequate responder patients, and that this molecule might represent a viable treatment alternative. They did suggest that the fact that brodalumab targets the IL-17 receptor, while ixekizumab (and secukinumab) target the cytokine itself, might explain some of the differences in the trial results. As with brodalumab, the safety profile of secukinumab and ixekizumab in their respective trials was good, with no signals for specific AE or SAE with either agent.

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Two other agents that target the IL-17 pathway, ustekinumab, an IL-12/23 antibody, and guselkumab, an IL-23 antibody, have been studied in a trial of MTX inadequate responders in RA (IL-23 drives Th17 polarization and thus IL-17 production). In this study, which has been reported on clinicaltrials.gov but has not yet been published, neither antibody was significantly more effective than placebo at achieving the primary endpoint of ACR20 response at 28 weeks. In sum, despite the rather positive spin by the authors of the secukinumab and ixekizumab studies, the weight of the evidence suggests that the IL-17 pathway is simply not an attractive target in RA, especially in an era of other highly effective medications. As the authors of the secukinumab trial suggest, the availability of specific biomarkers predicting response might change this conclusion, but such biomarkers have yet to be identified.

What can we learn from such negative studies? It must be noted that none of the antibodies studied are ineffective molecules. Indeed, all 5 of the antibodies above have been demonstrated to be effective in skin psoriasis, and 2 (ustekinumab and secukinumab) have been approved in the United States for this indication. Ustekinumab has also been approved for the treatment of PsA, and there have been studies demonstrating the effectiveness of brodalumab and secukinumab in this disease as well. While disappointing, the results of the trial by Pavelka, et al are important observations, and the authors are to be commended for reporting them. Much has been written about the importance of publishing negative clinical trial data. Doing so gets this information into the public domain, so that others have access to it. It allows for critical peer review of the data, to determine whether the results are truly negative, or perhaps merely underpowered to identify a positive result.

Having the negative results in the public domain also ensures that future metaanalyses can provide a balanced and accurate evaluation.

Finally, the availability of negative results such as these helps to ensure that further effort is not wasted pursuing targets that show little promise for therapy. At the same time, it may inspire more investigation into why the results were negative, potentially generating new insights into disease pathogenesis. In this case, the apparent lack of efficacy of IL-17 inhibition in RA, contrasted with its apparent efficacy in PsA, may inform further research into the unique and distinguishing cellular and molecular aspects of these 2 inflammatory arthropitides. Much has been made of the bench-to-bedside successes achieved by the biologic therapies in rheumatic diseases. Data from this study may help to drive more research back at the bench, so that we may better understand the diseases themselves.

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