RESEARCH DEVELOPMENTS IN PSORIATIC ARTHRITIS

OVERVIEW

The latest research related to the treatment of patients with psoriatic arthritis is often first made public at the American College of Rheumatology (ACR) annual meeting. In this CME activity, Dr. Roy Fleischmann of the University of Texas Southwestern Medical Center at Dallas discusses three posters presented at ACR Convergence 2020. Dr. Fleischmann first summarizes the methods and results of each of these posters, then provides his own thoughts as to the importance of the research findings and implications for clinical practice in the treatment of patients with psoriatic arthritis.

TARGET AUDIENCE

This activity was developed for rheumatologists, primary care physicians and other healthcare providers who manage patients with rheumatoid arthritis.

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Summarize the latest research developments in the treatment of psoriatic arthritis
- Describe how new data and recommendations can impact clinical practices to improve care
- Incorporate evidence-based research into clinical practice

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RESEARCH DEVELOPMENTS IN PSORIATIC ARTHRITIS

Efficacy and safety of guselkumab, a monoclonal antibody specific to the p19-subunit of interleukin-23, through week 52 of a phase 3 randomized, double-blind, placebo-controlled study conducted in biologic-naïve patients with active psoriatic arthritis.

The study results were presented by Dr. Iain McInnes at the American College of Rheumatology Convergence 2020 virtual annual meeting.

Link to abstract: CLICK HERE

Analysis provided by Roy M. Fleischmann, MD

Guselkumab is a monoclonal antibody that specifically binds to the p-19 subunit of IL-23, which has been demonstrated to be an important pathway in the development of psoriatic arthritis. In patients with no previous treatment with a biologic, and who had active psoriatic arthritis defined by at least five swollen and tender joints, with a C-reactive protein (CRP) of greater than or equal to 0.6 milligrams per deciliter. Treatment with guselkumab resulted in sustained improvements in joint and skin symptoms, inhibition of radiographic progression, as well as improvements in physical function and quality of life. The safety profile of guselkumab was similar during the 52 weeks of the study, and was consistent with the safety of guselkumab previously reported in patients with psoriasis.

What's the importance? This report confirmed that the week 24 clinical, functional, and radiographic results were sustained through 52 weeks without a change in safety.

What were the methods? This trial involved adults with biologic-naive psoriatic arthritis who had active psoriatic arthritis as defined previously. Patients were randomized to guselkumab 100 milligrams administered every four weeks, or 100 milligrams administered at weeks zero and four, and then every eight weeks, or to placebo. At week, 24 placebo patients were switched to guselkumab 100 milligrams administered every four weeks.

ACR response rates at week 52 were based on non-responder imputation for missing data, and as observed in patients who continued study agent at week 24. Data for other endpoints were collected at weeks zero, 24, and 52, or at time of treatment discontinuation.

What were the key findings? Of the 739 initial treated patients, 96.3% continued steady treatment through week 24, and 93.2% completed study treatment through week 52. Non-responder imputation imputed ACR20/50/70 response rates were generally maintained, or numerically slightly improved from week 24 to week 52. The ACR20/50/70 response rates for the two different dosing regimens of guselkumab every four or eight weeks were generally similar.

Similar patterns of response were observed in both guselkumab groups for improvement in Health Assessment Questionnaire- Disability Index (HAQ-DI) and SF-36, Psoriasis Area and Severity Index (PASI) responses, achieving minimal disease activity and very low disease activity, as well as dactylitis and enthesitis resolution. Patients switched from placebo to guselkumab at week 24 tended to show similar responses as the patients who were originally treated with guselkumab. Interestingly, radiographic progression was similar in the guselkumab every four weeks group from week 24 through 52, compared with weeks zero through 24, but it was less from week 24 through 52, compared with week zero through 24, in both the guselkumab every eight weeks

group, and the group switched from placebo to guselkumab at week 24.

With respect to safety, 4.2% of the patients treated with guselkumab experienced a serious adverse event, with 1.2% experiencing a serious infection. No patients died, had inflammatory bowel disease, an opportunistic infection, active tuberculosis, or anaphylactic or serum sickness-like reaction.

Here are my thoughts and analysis of this study. So, the main points were guselkumab given as 100 milligrams at week zero and four, and then every eight weeks, has similar clinical, functional, and radiographic efficacy as 100 milligrams weekly, with similar improvements in multiple domains of psoriatic arthritis in patients not previously treated with the biologic. The clinical responses appear to be durable over one year with maintained safety.

How would these results of this study impact the current state of patient management? The approval of guselkumab in psoriatic arthritis gives physicians another effective medication for the treatment of psoriatic arthritis, in addition to inhibitors of IL-17, tumor necrosis factor (TNF), IL-12/23, and Janus kinase (JAKs), as well as traditional conventional synthetic DMARDs. Where this drug will fall within our current therapeutic armamentarium will depend upon patient access, as well as physician and patient preferences considering the domains of psoriatic arthritis involved, the route and frequency of administration, and patient and physician comfort with the molecule.

How do these results impact the future state of patient management? Guselkumab appears to be very effective for skin manifestations, and reasonable for joint manifestations. The question is how well oral medication, still in development, including several JAK inhibitors, will perform and what will be their access?

And then finally, what questions remain unanswered? The main question is how would guselkumab, compare to other currently approved molecules and molecules in development, in properly powered head-to-head studies in patients with the multiple domains of psoriatic arthritis? Would we find that there are mechanisms that are advantageous in some domains versus others, and some molecules with a better safety profile than others?

RESEARCH DEVELOPMENTS IN PSORIATIC ARTHRITIS

Ustekinumab-treated patients with psoriatic arthritis in a real-world study: Similar clinical responses and treatment persistence over one year in elderly and younger patients.

The study results were presented by Dr. Laure Gossec at the American College of Rheumatology Convergence 2020 virtual annual meeting.

Link to abstract: CLICK HERE

Analysis provided by Roy M. Fleischmann, MD

Ustekinumab is a monoclonal antibody that specifically binds to the p40 unit of IL-12/23. In a real-world setting, ustekinumab therapy was maintained to a similar degree whether patients were less than age 60 years or greater than or equal to age 60 years through one year of follow up. Both age groups manifested clinical response by multiple metrics, but younger patients had a numerically better response in most parameters.

What's the importance? It's assumed that treatment interruption is common in patients with chronic diseases, including psoriatic arthritis, often due to adverse events, less efficacy, or other issues such as comorbidities and polypharmacy. For these reasons, older adults are generally at increased risk of treatment interruption. The finding here that treatment persistence was similar in older compared with younger patients over one year of treatment suggests that patient satisfaction was similar in both groups.

What were the methods? This was a post hoc analysis of a multi-national, prospective, observational study in patients with psoriatic arthritis, prescribed either ustekinumab or a tumor necrosis factor inhibitor as first-, second-, or third-line treatment. The effectiveness and safety of ustekinumab was compared by age group. That is, age less than 60 years versus age 60 years or older. Effectiveness was assessed using a variety of validated measures, such as Clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA), minimal disease activity, joint counts, Health Assessment Questionnaire-Disability Index (HAQ-DI), patient's assessment of pain, and C-reactive protein (CRP). Patients were followed over 15 months.

What were the key findings? Of the 930 patients in the entire cohort, 458 were treated with ustekinumab. Three-quarters were age less than 60 years. Baseline demographics were similar in the two age groups, except that the patients in the older age group had a higher incidence of cardiovascular disease and metabolic syndrome (79.4% versus 30.7%), use of glucocorticoids, and a longer duration of psoriatic arthritis (9.54 versus 6.88 years).

Using the measures previously mentioned, effectiveness after treatment with ustekinumab for six months and one year was generally comparable in the two groups, but tended to favor the younger patients. As expected, the incidence of adverse events, but not withdrawal due to an adverse event, were somewhat higher in the older group. Treatment persistence did not differ between older and younger patients, showing a statistically non-significant small increase in risk in the older versus younger group for stop or switch within the first year.

Here are my thoughts and analysis of this study. So, the main highlights, from my perspective, are that ustekinumab was clinically effective in both younger and older patients. Older patients are more likely to have adverse events, for numerous reasons. The adverse event profile

did not cause the older patients to withdraw treatment. Approximately three-quarters of patients in both groups maintained ustekinumab for over one year.

How could the results of this study impact the current state of patient management? Ustekinumab can be used in older patients with the same degree of confidence as a younger patient.

How could the results of this study impact the future state of patient management? With the proliferation of treatments now and in the future for psoriatic arthritis, including oral therapies, ustekinumab will remain a part of the therapeutic armamentarium, but where it will be utilized is hard to predict.

What questions remain unanswered? We did not see the results of the TNF-treated patients. Were they similar? Would the results be similar with an IL-17, IL-23, or a JAK inhibitor?

Impact of upadacitinib on reducing pain in patients with active psoriatic arthritis: Results from two phase 3 trials in patients with inadequate response to non-biologic or biologic DMARDs.

The study results were presented by Dr. Iain McInnes at the American College of Rheumatology Convergence 2020 virtual annual meeting.

Link to abstract: CLICK HERE

Analysis provided by Roy M. Fleischmann, MD

Upadacitinib is a Janus kinase-1 selective inhibitor. This post hoc analysis was of patients with psoriatic arthritis who still had active disease despite non-biologic or biologic disease-modifying anti-rheumatic drug therapy. The results indicated that numerically more patients treated with upadacitinib 15 milligrams a day, the approved dose, compared to placebo-treated patients, achieved clinically meaningful reduction in pain, in some as early as two weeks and sustained to 24 weeks, as assessed with multiple measures of pain. The improvement in pain with 15 milligrams of upadacitinib was generally similar to that achieved with adalimumab, although at some points, using different metrics, upadacitinib was nominally superior to adalimumab.

What's the importance? Pain is a dominant symptom experienced by patients with psoriatic arthritis. Thus, reducing pain is a key treatment objective. The superiority of upadacitinib in reducing pain compared to the placebo is not surprising. But it is surprising that there was similar time to effect and depth of response with upadacitinib 15 milligrams and adalimumab in many of the analyses in contradistinction to the multiplicity-controlled results in SELECT-COMPARE, a head-to-head trial in rheumatoid arthritis.

What were the methods? Adults with active psoriatic arthritis were enrolled in either the SELECT PsA-1 or SELECT PsA-2 study. Patients in SELECT PsA-1 had active psoriatic arthritis, despite treatment with greater than or equal to one non-biologic DMARD, while patients in SELECT PsA-2 had active psoriatic arthritis despite treatment with greater than or equal to one biologic DMARD. Although not mandatory, patients were allowed concomitant treatment with less than or equal to two non-biologic DMARDs. Patients were randomized to upadacitinib 15 milligrams, 30 milligrams, or placebo once daily in both studies. In SELECT PsA-1, a fourth treatment of adalimumab 40 milligrams every other week was included. Treatment was continued for 24 weeks.

So, what were the key findings? 1,704 patients were randomized in SELECT PsA-1 and 641 patients in SELECT PsA-2. The unapproved dose of 30 milligrams upadacitinib achieved nominally significant pain improvements versus placebo and adalimumab, using multiple metrics in both studies. The approved dose of upadacitinib achieved a similar proportion of patients achieving pain reduction of greater than or equal to 30%, greater than or equal to 70%, and patients achieving the minimal clinically important difference (MCID) in pain, as did adalimumab, and both nominally superior to placebo. Upadacitinib was nominally superior to adalimumab in percent of patients achieving greater than or equal to 50% reduction in pain and mean reduction in pain on the Numeric Rating Scale (NRS). In patients treated with upadacitinib or adalimumab, improvements in most pain endpoints occurred as early as week two, and were sustained and increased through

week 24. Improvements in spinal pain, as measured by the Bath Ankylosing Spondylitis Disease Activity Index, were inexplicably reported, as we do not know if any of the patients truly had axial involvement, and thus if the BASDAI pain question would be relevant.

Here are my thoughts and analysis of the study. The main points are that upadacitinib 15 milligrams appears to be efficacious in the treatment of pain in patients with psoriatic arthritis, and mostly comparable to adalimumab with respect to speed of response and depth of response. The results for speed and depth of response are similar in conventional synthetic DMARD and biologic DMARD incomplete responders.

How do the results of the study impact the current state of patient management? Well, these results are not clinically relevant as yet, as upadacitinib is not yet approved in psoriatic arthritis.

How do the results of this study impact the future state of patient management? The results of the SELECT-PsA studies were both very positive, and one would expect that upadacitinib will be approved in psoriatic arthritis.

In that case, where does it fit into our armamentarium? It is attractive as an oral medication, which can be very effective after conventional synthetic DMARDs, probably more effective than apremilast, and possibly more than tofacitinib, but will still require lab monitoring.

Will it replace TNF inhibitors, and how will it compete with IL-17, IL-23 molecules? We don't know.

What questions remain unanswered? How does upadacitinib compare to methotrexate in methotrexate-naive psoriatic arthritis, and how does it compare to IL-17 and IL-23 molecules in conventional synthetic DMARD incomplete responders? And, importantly, how does it compare to tofacitinib, the JAK inhibitor approved in psoriatic arthritis?