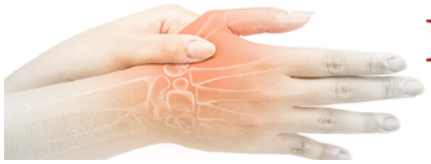

Research Developments in Rheumatoid Arthritis

OVERVIEW

The past decade has provided numerous advances in the treatment of rheumatoid arthritis. As will be discussed, recent evidence of 2 medications from different classes provide reassurance as to their long-term safety and efficacy. Of key importance is that these treatment advances provide a real opportunity to achieve disease remission using a treat-to-target approach. The benefits of achieving long-term disease remission vs low disease activity are presented. Join Dr. Roy Fleischmann as he discusses this recent evidence from the American College of Rheumatology Convergence 2020 virtual annual meeting and the implications for clinical practice.

TARGET AUDIENCE

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

LEARNING OBJECTIVES

At the end of the activity, participants will be better able to:

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

FACULTY

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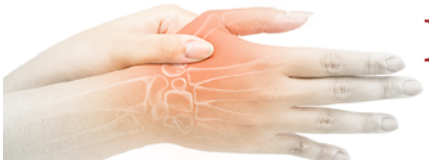

Research Developments in Rheumatoid Arthritis

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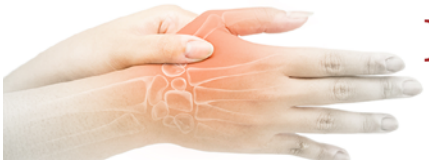

Research Developments in Rheumatoid Arthritis

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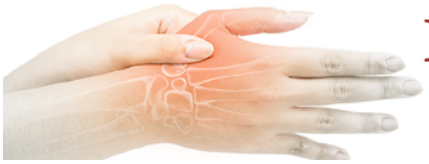


Research Developments in Rheumatoid Arthritis

Impact of targeting remission or low disease activity on 10-year severity in rheumatoid arthritis: Data from ESPOIR cohort

Lead Study Author: Dupont

Roy Fleischmann, MD: The study showed that achieving disease remission as assessed by the Simple Disease Activity Index, or SDAI, rather than low disease activity, leads to better radiographical and functional outcomes at 10 years in patients with early rheumatoid arthritis (RA). With use of the Disease Activity Score- 28 joints (DAS28), better results were also seen with DAS28 <2.6 for functional outcomes as assessed by the Health Assessment Questionnaire Disability Index (HAQ-DI), but there was no difference between those with a DAS28 <2.6 and those with a DAS28 2.6-3.2 for structural progression. SDAI is a superior endpoint for clinical practice.

Let's take a closer look at the details of the study. First, the goal of the study was to compare 10-year severity outcomes in patients with RA who achieved sustained remission vs those who achieved sustained low disease activity. Severity outcomes included structural progression, function, and orthopedic surgery.

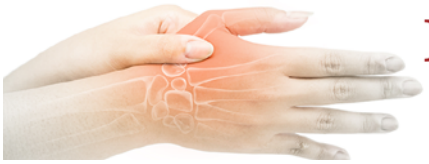
The study involved 813 patients with early RA who had not received disease-modifying anti-rheumatic drug (DMARD) therapy in the ESPOIR cohort. This cohort was established by the French Society of Rheumatology to facilitate investigations in early arthritis and RA. Data were analyzed over 10 years of follow up using SDAI and DAS28 scores available at 6 or more of 11 visits.

Disease remission was defined as an SDAI score ≤3.3 or DAS28 score <2.6. Low disease activity was defined as an SDAI score between 3.3 and 11 or DAS28 score between 2.6 and 3.2. Radiographs were evaluated centrally using the Total Sharp Score modified by Van der Heijde at baseline and at 10-year visits. At each visit, a HAQ-DI was completed and RA orthopedic procedures documented.

Patients were placed into 1 of 3 groups according to the SDAI at each visit. Group 1 was patients with sustained SDAI remission. Group 2 was patients with sustained SDAI low disease activity. Group 3 was patients with moderate or high sustained disease activity. Patients with unstable disease activity over time were not included in the analysis.

Now the results of the study. Group 1 patients, or those having sustained remission, included 9.2% as defined by SDAI and 14.9% as defined by DAS28. Group 2 patients, or those with low disease activity, included 25.8% as defined by SDAI and 10.1% as defined by DAS28.

The study results are important since they extend earlier findings showing that SDAI remission at 1 year compared with low disease activity at 1 year decreased the risk of 3-year structural progression in patients with rheumatoid arthritis. This was also true for function defined by the HAQ-DI. Although similar findings were observed with the DAS-28 for function, this was not observed for structural progression. These 10-year findings should encourage clinicians to make disease remission, as defined by the SDAI rather than the DAS28, their treatment focus. With the evolution in biologic and nonbiologic therapies, remission is increasingly possible.



The 10-year structural progression was significantly lower in the SDAI remission vs SDAI low disease activity group (*P*<0.02). Moreover, the mean 10-year HAQ score was significantly lower in patients with SDAI remission. As written in the abstract, but not included in the presentation, over the 10 years of follow-up, 3 of the 48 patients in SDAI remission underwent an orthopedic procedure compared with 14 of the 135 patients in the SDAI low disease activity group.

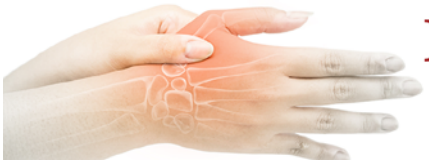
Using DAS28 scores, there was a significant difference in structural progression observed in the group with DAS28 <2.6 compared with the group with DAS28 2.6-3.2 although the mean 10-year HAQ score was significantly lower in the DAS28 <2.6 group compared with the DAS28 2.6-3.2. No difference was observed for the risk of orthopedic procedures, however.

Here are my thoughts and analysis of the study. First, the main points of the study are: (1) Remission is a better target for patients than low disease activity because of the improved 10-year outcomes with respect to function and structural preservation which seems to be substantiated by the lower risk for joint replacement in those patients in SDAI remission. (2) Use of the SDAI for patient management is superior to use of DAS28.

These study results impact the current state of patient management by: Many rheumatologists do not use validated metrics to assess whether a patient requires a change in therapy or not and those who do are more likely to use a DAS28 or RAPID3. This analysis points out the practical reason why the American College of Rheumatology and European League Against Rheumatism support a treat-to-target approach using the SDAI or Boolean remission rather than other metrics.

These study results impact the future state of patient management by: If the recommendations of this abstract are utilized in clinical practice, more patients will have much improved long-term outcomes.

Finally, there is a question which remains unanswered. Only a small group of patients was analyzed and whether these conclusions can be expanded to the larger general RA population is not known but is assumed.



Research Developments in Rheumatoid Arthritis

Long-term safety and efficacy of sarilumab over 5 years in patients with rheumatoid arthritis refractory to tumor necrosis factor inhibitors
Lead Study Author: Fleischmann

Roy Fleischmann, MD: The study showed that the safety profile of the IL-6 receptor inhibitor sarilumab over 5 years of follow-up was consistent with results of phase 3 trials with no new safety concerns. Similarly, clinical efficacy in patients who had responded in the initial double-blind portions of the study was sustained over the 5 years of follow-up.

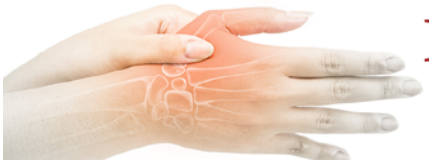
Let's take a closer look at the details of the study. First, here are the study methods. Patients were those who were initially randomized in the 24-week, prospective, controlled, double-blind TARGET trial. In the TARGET trial, patients were randomized to receive placebo, sarilumab 150 mg every 2 weeks, or sarilumab 200 mg every 2 weeks. Patients received concomitant conventional synthetic DMARD therapy. All randomized patients were eligible for the open-label extension phase in which all patients were treated with sarilumab 200 mg every 2 weeks. Dose reduction to 150 mg every 2 weeks was permitted to manage laboratory abnormalities or at the discretion of the investigator.

Key findings of the study include that 454 of the 546 patients randomized in TARGET entered the extension phase. This included 156 patients who had received placebo, 145 patients who had received sarilumab 150 mg, and 153 patients who had received sarilumab 200 mg. At the beginning of the extension phase, patient demographics were similar among the 3 randomized groups. At the beginning of the extension phase, the mean age was 53 years, 81% were women, and the mean duration of rheumatoid arthritis was 12 years.

There were 1655 patient-years of exposure to sarilumab over the 5 years of follow-up. Half of the patients had 4 or more years of treatment exposure. One hundred ninety-nine of the 546 patients initially randomized discontinued treatment over the 5 years of follow-up. One hundred patients (18%) discontinued treatment due to a treatment-emergent adverse event, 27 patients (5%) due to lack of efficacy, and 68 patients (13%) for other reasons. Overall, there were 160 treatment-emergent adverse events/100 patient-years. There were 10 serious treatment-emergent adverse events/100 patient-years, 8 treatment-emergent adverse events/100 patient-years that led to treatment discontinuation, and 0.3 treatment-emergent adverse events/100 patient-years that resulted in death. Causes of death were septic shock, acute pulmonary edema, myocardial infarction, pneumonia, and metastatic gallbladder cancer.

The most common adverse events were an infection, which occurred at a rate of 58 events/100 patient-years, injection site reaction, which occurred at a rate of 22 events/100 patient-years, leukopenia, which occurred at a rate of 18 events/100 patient-years, and neutropenia, which occurred at a rate of 15 events/100 patient-years. Grade 3/4 neutropenia occurred in 74 patients (14%) and normalized on treatment in 65%.

Efficacy was maintained over the 5 years. The mean change in the Clinical Disease Activity Index, or CDAI, score from TARGET baseline was -31.



The study results are important since they provide reassurance as to the sustained safety and efficacy of sarilumab over 5 years of treatment. This is especially important since there is a perception amongst rheumatologists that bDMARDs, such as sarilumab, will lose efficacy over time.

Here are my thoughts and analysis of the study. First, the main point of the study is: In a group of patients, patients who initially do well without significant toxicity with sarilumab, are likely to maintain benefit over years.

These study results impact the current state of patient management by: Understanding that if a patient is treated-to-target with sarilumab, a change to another medication may not be necessary over the long term. And, if a patient develops toxicity to sarilumab, lowering the dose may maintain efficacy and resolve the toxicity.

These study results impact the future state of patient management by helping us understand the long-term benefits and risks of sarilumab use.

Finally, some questions remain unanswered. These include: (1) Why do some patients lose efficacy or develop safety issues over time? How can we predict who will lose efficacy and who will develop toxicity?

Safety profile of baricitinib for the treatment of rheumatoid arthritis up to 8.4 years: An updated integrated safety analysis

Lead Study Author: Winthrop

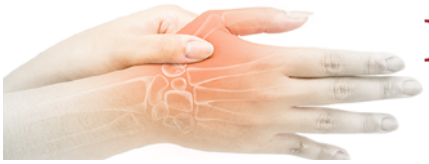
Roy Fleischmann, MD: The study showed that the safety profile of the Janus kinase inhibitor baricitinib over up to 8.4 years of follow-up was similar to previous reports.

The study results are important since they provide reassurance as to the sustained safety of baricitinib over up to 8 years of treatment. This is important as RA is a chronic disease and patients who benefit from a particular medication will require it for years.

Let's take a closer look at the details of the study. First, the long-term safety of baricitinib was assessed based on data from 9 completed randomized trials and 1 ongoing long-term extension trial. Five of the completed trials were phase 3 trials. Data were based on patients who received at least 1 dose of baricitinib.

Key findings of the study include a total of 3770 patients received baricitinib totaling 13,148 patient-years of exposure. The median time of exposure was 4.2 years and the maximum time of exposure was 8.4 years.

Overall, the incidence rates of individual adverse events were consistent with previous analyses. There were 25.8 treatment-emergent adverse events/100 patient-years of exposure and 7.2 serious adverse events including death/100 patient-years. Deep vein thrombosis or pulmonary embolism occurred at a rate of 0.5 events/100 patient-years in the baricitinib 2 mg group, as well as the baricitinib 4 mg group. There were 4.8 permanent treatment discontinuations due to an adverse event/100 patient-years. There were 3.0 herpes zoster events/100 patient-years. The rate of a serious infection was 2.1 events/100 patient-years for



patients age <65 years and 4.8 events/100 patient-years for patients age ≥65 years. The rates of a serious infection in patients who received baricitinib 4 mg were similar to or less than placebo in patients age <65 years, as well as patients age ≥65 years. The incidence rates for deep vein thrombosis or pulmonary embolism, a major adverse cardiovascular event, and nonmelanoma skin cancer generally remained stable over time.

Here are my thoughts and analysis of the study.

First, the main points of the study are: (1) The venous thromboembolic (VTE) results are interesting as the rates in the 2 mg and 4 mg groups were virtually identical over time. This raises an important question. If the FDA did not approve the 4 mg dose because of VTEs, why was the 2 mg dose approved? Alternately, if the 2 mg dose has an acceptable risk of VTE, similar to other drugs, why doesn't the 4 mg dose have the same acceptable risk? (2) More infections and serious infection episodes occur in patients age >65 years whether treated with placebo or baricitinib. We need to watch carefully for infections in this group. (3) After 8 years, there is no change in the incidence rate of significant adverse events and no new concerns have been observed.

These study results impact the current state of patient management by: Giving confidence in the overall safety of baricitinib over a prolonged period of time.

These study results impact the future state of patient management by: Suggesting that no new concerns with respect to safety will develop in the future.

Finally, sme questions remain unanswered. These inclue: The data is fairly clear about the similarity of baricitinib at doses of 2 mg and 4 mg for VTE, but we don't know if there is a difference in the incidence rates of other significant adverse events between the 2 mg and 4 mg doses. This is important because if the incidence rates are similar, and 4 mg is somewhat more effective, why don't we have approval of the 4 mg and why are we limited to the bDMARD failure population?