Promising New Treatments for Rheumatoid Arthritis
The Kinase Inhibitors

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Abstract

Three major advances over the last decade have impacted the way we treat rheumatoid arthritis: early and aggressive treatment, use of disease activity measures leading to treat to target, and availability of biologic agents. No oral biologic agents are available at this time but promising data is emerging for two drugs, tofacitinib and fostamatinib, inhibitors of JAK and Syk kinases, respectively. This paper will review some of the relevant published data for these agents and discuss where they may be placed in our treatment options for RA.

In the last decade, there have been major changes in the way rheumatoid arthritis (RA) is treated. These changes include the now accepted paradigm of an early and aggressive approach to treatment, the use of disease activity measures to guide this approach and to define targets at which to aim our medications, and finally the availability of biologic agents in addition to the traditional disease modifying antirheumatic drugs (DMARDS) and the use of these agents in combination with other DMARDs and also with biologic agents.1

Despite these advances, better long-term outcomes, and a larger proportion of RA patients in remission or with low disease activity, 30% to 40% of RA patients are still not adequately controlled with the available drugs and at least half of RA patients who were previously responding to a biologic or a biologic/DMARD combination lose the efficacy of this regimen over 5 years and need new agents for treatment.1

The nine current biologic agents approved in the USA are cytokine inhibitors of TNF alpha, IL-6, and IL-1, or cell modulators targeting T and B cells. These are all administered by either intravenous infusion or intramuscular injection. For the last decade, there has been a promise of biologic small molecules that can be administered orally, and we now have some candidate agents that have been shown to work in different groups of RA patients. The initial enthusiasm surrounding p38 mitogen activated protein kinase blockers was subdued following poor clinical trials results, and they are not actively pursued at this time. However, two other targets, Janus kinase (JAK) and spleen tyrosine kinase (Syk) are promising and have good data to possibly support their use.

In this review, we will present the data collected so far for these two agents in the treatment of RA.

Tofacitinib

The JAK family of kinases plays an important role in cytokine induced signal transduction. There are 4 JAK proteins (JAK 1, JAK 2, JAK 3, and tyrosine kinase 2) and 7 STAT (signal transducer and activator of transcription) molecules that work together to affect intracellular signals that originate when the cytokine binds a receptor.

Tofacitinib (initially called tasocitinib) is a selective JAK inhibitor with functional selectivity for JAK 1 and JAK 3 over JAK 2. Following proof of concept in animal models, it has been studied in clinical trials for patients with rheumatoid arthritis.2 In a 6-week phase IIA dose ranging trial, the drug exhibited robust ACR responses across a range of dosages up to 30 mg twice a day. At week 6, the ACR20 response rate was 70.5, 81.2, 76.8, and 29.2% for 5, 15, 30 mg, and placebo, respectively (p < 0.001 for all treatment groups). Patients receiving tofacitinib showed a rapid response, and an ACR20 improvement was observed from the first week across all groups receiving tofacitinib. The ACR50
and ACR70 responses were statistically significant at week 2 in the 30 mg group and from week 4 in all treatment groups (p < 0.05). All doses showed a significant improvement in pain and disability as measured by Health Assessment Questionnaire Disability Index (HAQ-DI) scores.3

This trial was followed by another dose ranging phase IIb, placebo and active comparator trial of 24 weeks duration in which tofacitinib (maximum dose 15 mg BID) was studied in methotrexate (MTX) failures in 509 RA patients. At 3 months, all doses above 3 mg showed clinical efficacy. However, doses 5 mg or greater showed more sustainable improvement in ACR20, 50, and 70 responses as compared to placebo.4

A similar IIb study in DMARD-failures had an active comparator arm, adalimumab 40 mg BID, in addition to a placebo arm.5 At 12 weeks, all doses greater than 3 mg showed significant improvement compared to placebo; when results were assessed at 6 months, doses greater than 5 mg twice day had better ACR20, 50, and 70 responses. The adalimumab arm did not do as well as previous studies of adalimumab in this population; however, the reasons for this are not clear.

Another published phase II study was conducted in Japanese patients who were MTX inadequate responders (IR). In this 12-week, double-blind study, 140 patients were randomized to receive tofacitinib, dosed at 1, 3, 5, or 10 mg twice daily, or placebo. The patients all remained on background MTX. At week 12, the primary efficacy endpoint was achieved with significant (p < 0.0001) ACR20 response rates for all groups treated with tofacitinib. A significant (p < 0.0001) dose-response relationship was observed. The ACR20 response rate was 64.3%, 77.8%, 96.3%, 80.8%, and 14.3% for 1, 3, 5, and 10 mg, and the placebo, respectively. Tofacitinib was rapidly effective with clinically significant change from baseline seen as early as week 1 in ACR20 response rates, DAS28-3 (CRP), and DAS28-4 (ESR) for the higher dosage groups. These improvements were sustained until week 12, by which time significant improvement from baseline was observed for all doses of tofacitinib as compared to the placebo in these categories as well as in HAQ-DI score, patient and physician global assessment, swollen joint counts, and pain. The most commonly reported adverse events were nasopharyngitis and increased aminotransferase levels. Tofacitinib was concluded to be efficacious and to have a manageable safety profile over 12 weeks in Japanese MTX IR with active RA.

Earlier this year, the initial results from a phase III study of tofacitinib in RA patients who had an inadequate response to traditional DMARDs was presented at the EULAR meeting.7 The objective of this study was to compare the efficacy and safety of tofacitinib as compared to a placebo over 12 months in patients with active RA who also had inadequate prior response to at least one DMARD. All patients remained on non-biologic background DMARDs. Patients were randomized to two doses of tofacitinib, 5 or 10 mg twice daily, or placebo. There were escape opportunities at months 3 and 6 for patients on placebo. The primary endpoint at month 3 was change in the HAQ-DI. The primary endpoints at month 6 were ACR20 and DAS28-4 (ESR) less than 2.6 responses. Seven hundred ninety-two patients were randomized (5 mg BID, n = 315; 10 mg BID, n = 318; placebo advancing to 5 mg, n = 79; placebo advancing to 10 mg, n = 80). Average disease duration was 8 years. Tofacitinib was statistically superior to placebo for the primary efficacy endpoints, HAQ-DI change (5 mg BID, -0.46; 10 mg BID, -0.56; placebo, -0.21; p < 0.0001 for both dosages versus placebo), ACR20 (5 mg BID, 52.7%; 10 mg BID 58.3%; placebo, 31.2%; p < 0.0001 for both dosages versus placebo), and DAS28-4 responses (5 mg BID, 11%; 10 mg BID, 14.8%; placebo, 2.7%; p < 0.001 for 5 mg BID and p < 0.0001 for 10 mg BID versus placebo); Tofacitinib was also statistically superior (p < 0.0001) for ACR50 (5 mg BID, 33.8%; 10 mg BID, 36.6%; placebo, 12.7%) and ACR70 (5 mg BID, 13.2%; 10 mg BID, 16.2%; placebo, 3.2%). Significant ACR20, ACR50, and HAQ-DI responses were seen as early as the second week. Most adverse events were mild, with the most frequently reported being infections and infestations. There were four deaths (acute heart failure, respiratory failure, traumatic brain injury, and RA) and four opportunistic infections. Also noted were decreases in neutrophils, increases in LDL and HDL, and small increases in serum creatinine.

This first phase III study where tofacitinib was used in combination with background DMARDs in patients with active RA provided results that are consistent with previous findings from phase II studies and a phase III monotherapy study. It was concluded that tofacitinib demonstrated reductions in signs and symptoms of RA that were rapid, significant, and clinically meaningful. Furthermore, no new safety signals were detected.

In addition to the efficacy studies described, we have some information about radiographic progression in a small number of patients from a retrospective cohort study that compared radiographic change in the hands.8 Twenty-one patients with RA were enrolled, all of whom had previously participated in a 6-month phase IIb tofacitinib monotherapy study and continued the medication for over 1 year in an extension study. MTX IR patients were included. The control group consisted of 43 patients who were treated only with conventional DMARDs at the same hospital during the same time period. When comparing the efficacy of tofacitinib and conventional DMARDs, the results indicated that the change of erosion score was significantly less and even reversed with tofacitinib treatment (control, 0.57 ± 0.27, versus tofacitinib treated, -0.60 ± 0.40; p = 0.029). The change of joint space narrowing (JSN) (1.19 ± 0.42 versus 0.095 ± 0.13; p = 0.042) and sum of joint space narrowing and erosion scores (1.76 ± 0.65 versus -0.50 ± 0.37; p = 0.0092) were also favorable in the tofacitinib group versus conventional DMARDs. When examining the rate of radiographic progression before and after administration of tofacitinib, the rate of erosion score
change per year was found to significantly decrease after administration of tofacitinib (0.62 ± 0.93 versus -0.14 ± 0.48; p = 0.0094). JSN score change per year tended to be flattened (0.28 ± 0.59 versus 0.16 ± 0.50; p = 0.30), and the sum score also became favorable (1.09 ± 1.27 versus -0.10 ± 0.63; p = 0.00090) after tofacitinib administration. From this small, pilot study, it was concluded that tofacitinib can prevent structural damage of RA in respect to joint erosion and JSN and that a large-scale randomized prospective study is warranted to confirm these results.

In conclusion, the efficacy of tofacitinib in all reported trials to date is significant when compared to a placebo group with ACR20, 50, and 70 responses after treatment intervals of 12 to 24 weeks and promise of improvements has been seen in other areas measuring disease activity, such as HAQ and DAS scores as well as radiographic progression. Most study-related adverse events were mild, with infections observed more commonly in the tofacitinib groups versus controls as well as elevations of transaminase enzymes and increases in LDL. Some studies also reported minor decreases in hemoglobin and neutrophils along with increases in serum creatinine measurement.

**Fostamatinib**

Syk is a cytoplasmic tyrosine kinase involved in signaling and the activation of Fc gamma receptors on macrophages, neutrophils, and mast cells; it leads to up regulation of TNF alpha, IL-6, and MMP synthesis. As such, inhibitors of Syk kinase may have a role in the treatment of RA. Fostamatinib is an oral inhibitor that is converted to an active drug, which may have a role in the treatment of RA. Fostamatinib and active Syk inhibitors prevent structural damage of RA in respect to joint erosion and JSN and that a large-scale randomized prospective study is warranted to confirm these results.

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The first study in MTX IR RA patients was a multicenter, randomized, double-blind, placebo-controlled trial conducted at 64 sites in six countries. Criteria for inclusion required that patients had active arthritis for at least 6 months and had been receiving a stable dose of methotrexate (between 7.5 and 25 mg per week) for a minimum of 3 months. Concurrent treatment with stable doses of sulfasalazine, chloroquine, hydroxychloroquine, NSAIDs, or oral corticosteroids was permitted. A total of 457 patients were randomized in a 2:2:1:1 ratio to receive fostamatinib at a dose of 100 mg twice daily, at a dose of 150 mg once daily, placebo twice daily, or placebo once daily. The primary outcome was the proportion of patients achieving the ACR20 response rate at 6 months.

The results indicated that significantly more patients in the fostamatinib groups than in the combined placebo group met the criteria for ACR20 response (100 mg BID, 67%, and 150 mg OD, 57%, versus placebo, 35%; p < 0.001 for both doses versus placebo). The percentage of patients achieving ACR20 response increased over time, but the predominant effect was seen quite early with the effects of fostamatinib being seen as early as 1 week after initiation of treatment. It was noted that ACR20 response rates in both the placebo and active drug groups were higher among patients in Latin America and in Eastern Europe than among patients in the USA, but the investigators offered no reasoning for this in the publication of their findings. Inhibition of Syk with fostamatinib also produced a significant effect in ACR50 (43% and 32% versus 19%; p < 0.001 for 100 mg twice daily versus placebo, p = 0.007 for 150 mg once daily versus placebo) and ACR70 (28% and 14% versus 10%; p < 0.001 for 100 mg twice daily versus placebo, p = 0.34 for 150 mg once daily versus placebo) response rates, and in rates of DAS28 remission (31% and 21% versus 7%; p < 0.001 for 100 mg twice daily versus placebo, p = 0.003 for 150 mg once daily versus placebo), with a higher response observed in the group that received fostamatinib at a dose of 100 mg twice a day than in the group that received the drug at a dose of 150 mg once a day.

Adverse events arising during the study included diarrhea, upper respiratory infections, and neutropenia. Fostamatinib was also associated with an increase in systolic blood pressure. It was concluded that, in this phase II study involving patients who had active RA despite treatment with methotrexate, the addition of a Syk inhibitor led to reduced disease activity.

One issue related to the difference in response in this study among sites from different geographic areas is that the mean or median dose of MTX before patients were considered “failures” was not reported. This factor alone may explain the differential response rates and may even change the conclusions of the study. The majority of recent clinical trials that involve new biologic agents, particularly from the USA, have involved MTX use at higher doses of 20 to 25 mg per week in most patients. If USA patients were enrolled in the discussed study after failing a higher dose than Eastern European or Latin American patients, as even trying a dose as low as 7.5 mg MTX for 3 months was enough to be considered a failure by the protocol, then the results seen would not be unexplainable but rather expected. Neglecting to report this information, as was also suggested in a letter, does not allow us to draw the conclusion that fostamatinib works in MTX IR but instead that fostamatinib maybe works in patients with milder disease: those who had been treated with lower doses of MTX before being called a “failure.”

A second study with fostamatinib studied the responses in biologic IR with RA. This study utilized magnetic resonance imaging (MRI) in addition to standard disease activity measurements in order to examine the effect of Syk inhibition on synovium and bone.

The phase II study was a multicenter, randomized, double-blind, placebo-controlled trial conducted at 49 sites in 7 countries. Inclusion criteria required that patients had active RA for at least 12 months and were currently not responding or had previously failed to respond to treatment.
with a biologic agent at an approved label dose for more than 3 months. DMARDs, including methotrexate, leflunomide, sulfasalazine, chloroquine, hydroxychloroquine, NSAIDs, and oral corticosteroids, were permitted if dosages were stable for 30 days prior to randomization.

A total of 219 patients were randomly assigned in a 2:1 ratio to either fostamatinib 100 mg twice a day or placebo. The primary endpoint was the percentage of patients meeting the ACR20 response at month 3. Secondary endpoints included the ACR50 and ACR70 responses, improvements in individual ACR components and the DAS28, and changes from baseline to month 3 in radiologic and structural responses as assessed by the OMERACT RA MRI Scoring method. Despite similar levels of clinical severity between the fostamatinib and placebo arms, it is noted that the baseline mean erosion, osteitis, and synovitis OMERACT RA MRI scores were all considerably higher in those receiving fostamatinib. Additionally, a higher proportion of patients in this active treatment group were receiving prednisone and had disease that failed to respond to three or more biologic therapies as compared to the placebo group.

The results showed no significant differences between the fostamatinib group and the placebo group in the ACR20 (38% in fostamatinib versus 37% in placebo), ACR50 (22% versus 12%), or ACR70 (9% versus 5%) response or change from baseline in DAS28 (-1.62 versus -1.27) at month 3. Significant changes were achieved, however, from baseline in CRP level (p = 0.003) and ESR (p = 0.004). Fostamatinib also improved disease progression on MRI as measured by the mean change in the synovitis score (-0.5 versus +0.4; p = 0.038) and osteitis score (-0.2 versus +1.2; p = 0.058). Both groups, however, showed continued progression of bone erosion, with no statistically significant difference between the groups (0.8 versus 0.9; p = 0.616). The results seem to present a contradiction where fostamatinib had a weak impact on signs and symptoms yet showed improvements on MRI scores.

Various reasons are offered in the study for this discrepancy seen in their results, starting with an exploratory analysis that revealed that although the proportion of patients who qualified for the study with an elevated CRP level was balanced between drug and placebo groups, the ACR responses of those patients who qualified by CRP level and those who qualified by ESR were notably different. For those patients who qualified via an elevated CRP level, a meaningful difference between those randomized to fostamatinib and placebo was suggested. Patients entering the study with a normal CRP level and an elevated ESR were found to have come from two sites and had a high negative impact on the overall efficacy.

Furthermore, despite randomization, patients in the fostamatinib arm appeared to have both more active disease and more refractory disease. These patients had failed treatment with a greater number of biologic agents, were taking greater amounts of prednisone, and received significantly higher scores for erosion, synovitis, and osteitis on baseline MRIs. Investigators suggest that these baseline differences may have played a role in the inability to distinguish a difference between the arms in the primary outcome, which is possible but still the primary outcome remains no different between the drug and placebo. These data are not that unexpected when the data from the MTX IR is also taken into consideration, where lack of a robust response was suggested when the dose of MTX used in different geographic areas is considered. It would have been desirable to provide this information, and it is not clear why this was not done.

**Conclusion**

Small oral molecules for the treatment of RA have viable candidates at this time. However, tofacitinib seems more effective than fostamatinib based on the data available so far. Further studies will be needed to better define the role of these agents in the treatment of RA in the future. Especially the question of using these drugs alone or in combination with MTX or even before MTX will need to be studied and will help physicians with their decision making.

**Disclosure Statement**

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