Latest developments in the treatment of rheumatoid arthritis: is there new hope for patients?

Katerina Chatzidionysiou*[1] & Ronald van Vollenhoven[1]

"A deeper understanding of the pathophysiological mechanisms of rheumatoid arthritis has led to an increasing interest in assessing the potential efficacy of novel agents."

Over the past decade, treatment of rheumatoid arthritis (RA) has been revolutionized with the introduction of biological disease-modifying antirheumatic drugs (DMARDs), such as TNF inhibitors (e.g., infliximab, etanercept, adalimumab, golimumab and certolizumab pegol), the IL-6 receptor inhibitor tocilizumab, the chimeric anti-CD20 monoclonal antibody rituximab and the T-cell costimulation inhibitor abatacept into everyday clinical practice [1]. Despite the dramatic improvement, there are still unmet needs, with patients refractory to currently available treatments and patients losing efficacy or not tolerating biologic agents. However, new small molecular compounds and biologics are in development, providing new hope.

Tofacitinib: the first JAK inhibitor approved for RA

Tofacitinib is a JAK inhibitor recently approved by the US FDA for the treatment of RA. It is the first oral kinase inhibitor to be approved for RA. JAKs are nonreceptor tyrosine kinases. In mammals this family of tyrosine kinases has four members: JAK1, JAK2, JAK3 and TyK2 [2]. Their name comes from the Roman God Janus, the two-faced god of beginnings and transitions who looks at the past and the future. Similarly, JAK kinases are 'two-faced' with respect to their two domains, the JH1 domain at the carboxyl end and the adjacent kinase-like domain JH2, which lacks catalytic activity but has an important regulatory role [2].

JAKs mediate signaling via surface receptors for several proinflammatory cytokines involved in the pathogenesis of RA. JAK inhibitors prevent signaling of JAK enzymes and thus interrupt signal transduction of cytokines. Tofacitinib is a selective inhibitor of JAK1 and JAK3. JAK1 is expressed in lymphoid cells and in the nervous system, while JAK3 is found in high levels in hematopoietic tissues, myeloid cells, NK cells, and activated B and T cells [3].

[1]Karolinska Institute, Department of Medicine, Unit for Clinical Research Therapy, Inflammatory Diseases (ClinTRID), Stockholm, Sweden
*Author for correspondence: aikaterini.chatzidionysiou@karolinska.se

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JAK1 binds to the β-subunit of several cytokine receptors such as IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21, while JAK3 binds to the common γ-chain of these receptors [4]. When one of these cytokines binds to its receptor JAK1 and JAK3 undergo autotransphosphorylation, which leads to the binding and activation of STAT proteins. These STAT proteins can be translocated afterwards to the nucleus where they regulate transcription of several genes critical for the immune response. The critical role of JAK3 in lymphoid development and the immune system in general has been clearly demonstrated in JAK3-deficient mice, which develop profound reductions in thymocytes and severe B cell and T cell lymphopenia similar to severe combined immunodeficiency, while the residual T cells and B cells are functionally deficient [5]. Over recent years, JAKs have emerged as attractive targets for the treatment of autoimmune diseases.

Efficacy of tofacitinib in clinical trials

Several Phase II clinical trials suggested that tofacitinib is a promising new drug for the treatment of active RA [6,7]. In a Phase III, double-blind, placebo-controlled, parallel-group, 6-month clinical trial the efficacy and safety of two different doses of tofacitinib were assessed [8]. A total of 611 patients who had previously failed at least one nonbiologic or biologic DMARD (inefficacy or intolerance) were randomly assigned, in a 4:4:1:1 ratio, to tofacitinib 5 mg twice daily (b.i.d.), tofacitinib 10 mg b.i.d., placebo for 3 months followed by tofacitinib 5 mg b.i.d., or placebo for 3 months followed by tofacitinib 10 mg b.i.d., respectively. Primary end points included at least a 20% improvement in the American College of Rheumatology scale (ACR20), Health Assessment Questionnaire Disability Index (HAQ-DI) improvement and remission rates (defined as DAS28 of <2.6) at 3 months after baseline. The ACR20 primary end point was met, with a total of 59.8% of the patients in the tofacitinib 5-mg group and 65.7% in the 10-mg group, as compared with 26.7% in the combined placebo groups, achieving an ACR20 response ($p < 0.001$ for both comparisons). Significant differences were also observed for ACR50 and ACR70 responses. Similar results with superiority of tofacitinib versus placebo were shown regarding physical function (HAQ-DI) but not regarding disease remission. Patients who switched from placebo at the 3-month mark had similar rates of response at month 6 as were seen in patients in the treatment arms at month 3. The results of this Phase III trial suggested that tofacitinib monotherapy was more efficacious than placebo in reducing inflammatory activity and in improving physical function in patients with active RA. This result has important clinical implications, since a significant number of patients do not tolerate methotrexate, and most biologic DMARDs available today are approved in combination with methotrexate.

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In another recently published Phase III randomized clinical trial [9], 717 biologic-naive RA patients with an inadequate response to methotrexate were assigned to one of five arms: tofacitinib 5 mg b.i.d., tofacitinib 10 mg b.i.d., adalimumab 40 mg administered by subcutaneous injection once every 2 weeks, placebo for 3 or 6 months followed by tofacitinib 5 mg b.i.d., and placebo for 3 or 6 months followed by tofacitinib 10 mg b.i.d.. This design, with the inclusion of an active comparator arm with a TNF inhibitor, allowed an estimate of the efficacy and safety of tofacitinib relative to an established biologic therapy. The three primary end points were, as in the previous trial, ACR20 response, HAQ-DI improvement and disease remission rate at 6 months. All three end points were met. ACR20 response at 6 months was achieved by 51.5% (tofacitinib 5 mg b.i.d.), 52.6% (tofacitinib 10 mg b.i.d.), 47.2% (adalimumab) and 28.3% (placebo groups), the difference being significant between the first three groups and placebo. The percentage of patients with a DAS28 <2.6 at month 6 was significantly greater with the active treatments than with placebo. Importantly, the efficacy outcomes for tofacitinib were numerically similar to those seen with adalimumab, suggesting that, at least as far as the clinical efficacy is concerned, these agents are comparable.

In a third Phase III trial, Burmester *et al.* addressed the efficacy and safety of tofacitinib in a population of RA patients who had previously failed TNF inhibition [10]. The results showed that tofacitinib had a good and rapid effect in managing disease activity in these patients, suggesting that it would be a treatment option in refractory patients who did not respond to traditional DMARDs or TNF inhibitors [10].

Safety issues

Information about the safety of tofacitinib in RA comes from Phase II and III trials, as well as

long-term extension studies [6–11]. Both when used as monotherapy or with background methotrexate, tofacitinib was associated with an increased rate of infections (upper respiratory tract infection, urinary tract infection, bronchitis and herpes zoster virus), increases in low-density lipoprotein levels and aminotransferase levels, cytopenias (neutropenia, anemia and thrombocytopenia), small increase in the creatinine levels and gastrointestinal adverse events. The effect on lipids is not yet fully understood. Few cases of tuberculosis have been reported. Longer follow-up and observational studies of real-life patients are needed in order to better examine the safety of tofacitinib.

New JAK inhibitors, SyK & PDE4 inhibitors

Tofacitinib was the first JAK inhibitor to be approved, heralding the 'transition' to a new era of RA treatment with small molecules. Several other JAK inhibitors are currently in development. Bariticinib is a selective blocker of JAK1 and JAK2 with promising efficacy in Phase II trials and, perhaps surprisingly, no major problems with cytopenias [12]. VX-509, a selective JAK3 inhibitor, showed a dose-dependent increase in ACR20 versus placebo in a Phase II monotherapy trial [13].

Fostamatinib is a novel inhibitor of Syk that has been shown to improve inflammation in RA. Syk is a spleen tyrosine kinase expressed on macrophages, neutrophils, mast cells and osteoclasts, and associates directly with the B cell- and Fcγ-receptor. In a Phase II clinical trial fostamatinib showed significantly better efficacy according to ACR20 response than placebo in patients with active RA despite treatment with methotrexate [14]. Adverse events include neutropenia, elevated liver enzymes, diarrhea and hypertension. In another Phase II study with RA patients who previously failed TNF inhibition therapy, no significant differences were shown between fostamatinib and placebo at month 3, with the ACR20 response rates being 38% in the fostamatinib 100 mg b.i.d. group versus 37% in the placebo group [15]. No significant differences were achieved in the ACR50 or ACR70 response levels either. A Phase III program is ongoing.

Apremilast is an oral PDE4 inhibitor. It has been shown to reduce production of TNF from synovial cells, thus suppressing inflammatory activity in experimental arthritis [16]. The efficacy and safety of apremilast in RA are currently being assessed in a randomized clinical trial setting.

New treatments in development

A deeper understanding of the pathophysiological mechanisms of RA has led to an increasing interest in assessing the potential efficacy of novel agents. IL-17 is a cytokine that has received a lot of interest during recent years, and several studies assessing the efficacy of antibodies blocking IL-17 are in Phase II. Secukinumab is a fully human anti-IL-17A antibody that has achieved greater ACR20 responses than placebo in a Phase II trial, although the differences were not significant and the primary end point was not achieved [17]. Ixekizumab, a humanized IgG4 mAb against IL-17 improved signs and symptoms of RA, with no strong adverse safety signal noted, when added to DMARDs [18]. In two randomized clinical trials tabalumab, a fully human IgG4 monoclonal antibody that neutralizes soluble and membrane-bound BAFF, showed significant efficacy both in biologic-naive RA patients and in those who have previously failed anti-TNF treatment [19,20]. Recently however, the sponsor of the tabalumab trials for

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Table 1. Possible future biologic and nonbiologic agents for the treatment of rheumatoid arthritis.

Type	Target	Agent
Biologics	IL-17	Brodalumab, secukinumab, ixekizumab
	IL-6	Sirukumab, BMS945429 (ALD518)
	BAFF	Tabalumab
Nonbiologics (small molecules)	JAK1/3	Tofacitinib
	JAK1/2	Baricitinib
	JAK1	GLPG0634
	JAK3	VX-509
	SYK	Fostamatinib
	PDE4	Apramilast

RA announced the decision to terminate the Phase III program due to disappointing interim results. GM-CSF is another future target for RA.

In conclusion, there is certainly new hope for RA patients, with numerous new targets arising and new treatments being under development **(Table 1)**. The rapidly growing number of available potent agents makes the need for a more personalized treatment even more obvious, and introduces a big challenge for clinical researchers.

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