Review

One year in review: novelties in the treatment of rheumatoid arthritis

G.M. Guidelli[1], T. Barskova[2], M.G. Brizi[1], G. Lepri[2], A. Parma[3], R. Talarico[3], L. Cantarini[1], B. Frediani[1]

[1]*Department of Rheumatology, Policlinico Le Scotte, University of Siena, Siena, Italy;*
[2]*Rheumatology Unit, Department of Experimental and Clinical Medicine, Azienda Ospedaliero-Universitaria Careggi, University of Florence, Florence, Italy;*
[3]*Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy.*

Giacomo M. Guidelli, MD
Tatiana Barskova, MD
M. Giuseppina Brizi, MD
Gemma Lepri, MD
Alice Parma, MD
Rosaria Talarico, MD, PhD
Luca Cantarini, MD, PhD
Bruno Frediani, Professor

Please address correspondence to:
Dr Luca Cantarini,
Research Centre of Systemic Autoimmune and Autoinflammatory Diseases,
Policlinico Le Scotte,
University of Siena,
Viale Bracci 1,
53100 Siena, Italy.
E-mail: cantariniluca@hotmail.com

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic disease characterised by inflammation of the synovial tissue in joints, which can lead to joint destruction. The primary aim of the treatment is to control pain and inflammation, reduce joint damage and disability, and maintain or improve physical function and quality of life. In this article, we provide a critical analysis of the recent literature on the novelties in the treatment of RA, with a particular focus on the most relevant studies published over the last two years.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by inflammation and deterioration of the joints, which can produce a loss of functionality, reduces quality of life and enhances morbidity and mortality. The objective of treatment is to achieve complete remission. Current treatment models promote intensively treating inflammation early in the disease course and it is recommended to start with disease-modifying anti-rheumatic drugs (DMARDs) as soon as the diagnostic has been established. In general, treatment begins with methotrexate (MTX). However, in patients with high RA activity, in which a rapid progression can be expected, a combination of MTX and a biologic agent is used. In this one year review we reviewed articles published during 2013 and 2014 and selected articles focusing on the novelties in the treatment of RA.

DMARDs

Since 1999, the introduction of the first biologic agents represents a "turning point" in the treatment of RA (1-5). On this basis, it is evident how the majority of the scientific effort was addressed to these new drugs. Nevertheless, the "old" DMARDs still represent a basic approach for RA patients, according to the 2010 EULAR recommendations (6). MTX is one of the DMARDs and is the most commonly used agent for treating RA. When MTX monotherapy provides inadequate disease control, combination therapies with other DMARDs, such as biological agents, is selected. Although the distinct efficacy of MTX with biological agents has been reported, some patients discontinue the biological agents because of adverse events, or inadequate or non-response. Therefore, the identification of other effective DMARDs for combination treatment with MTX is important. Although it is not a first-line DMARD, tacrolimus (TAC) is an effective alternative. TAC is an oral calcineurin inhibitor (CNI) that has been approved to prevent allograft rejection after liver and kidney transplantation. It suppresses the proliferation and activation of antigen-specific T cells. Because T cells play an important role in the pathogenesis of RA, TAC was applied as a treatment option for RA, especially in Japan and the USA. Recently, the efficacy of TAC in RA was assessed in three different studies; Kitahama *et al*. (7) demonstrated the efficacy of add-on therapy with TAC to MTX in a group of 175 RA patients, compared to 471 controls (MTX alone or plus another one DMARD), showing a significant decrease in the DAS28 score. Tanaka *et al*. (8) showed, in their multicentre RCT how adding TAC to MTX in 61 patients resulted in a significant suppression of disease activity and joint destruction, evaluated by the change in the total Sharp score. Simi-

larly, Kanzaki *et al*. (9) retrospectively analyzed the clinical course of 24 RA patients treated with a combination of MTX and TAC; after 3 years of treatment the DAS28 was decreased from 4.81 to 3.41, glucocorticoids doses decreased from 5.1 to 3.2 and 19/24 patients were still treated with the same combination-regimen. Other than the control of the clinical manifestations of the disease, in 2013 Kang *et al*. (10) showed the potential benefit of TAC on bone metabolism; indeed, 28 RA patients in three centres received TAC 3 mg once daily for 24 weeks and this treatment increased bone formation marker such as osteocalcin while C-telopeptide of type I collagen (sCTx-I) did not change its serum concentrations. Glucocorticoids (GC) are fast-acting anti-inflammatory drugs, now also considered as disease-modifying because of their ability to decelerate structural damage (11). Especially during the first weeks of DMARD treatment, GC are frequently used due to the rapid onset of their anti-inflammatory efficacy. In 2014 Den Uyl *et al*. (12) demonstrated how the COBRA-light therapy (prednisone 30 mg/daily, tapered to 7.5 mg /daily in 9 weeks, plus MTX 10 mg/weekly) is not inferior to COBRA strategy (with a 60 mg/daily of prednisone starting dose). Disease activity rapidly decreased in both groups, and not significant difference were found for functional ability and CRP levels. Among GCs, methylprednisolone (MP) is the standard steroid for the pulse therapy, but Sadra *et al*. (13) recently showed how dexamethasone (DEX) (longer half-life, higher anti-inflammatory activity and munch cheaper than MP) is safe and effective treatment for severe RA flares. The authors described the clinical improvement (by DAS28 score) of 14 RA patients, treated with 3 consecutive days of 120 mg DEX, compared to 16 patients treated with 1g of MP, for the same period. With regard to MTX, the tREACH trial conducted on 281 RA patients in order to compare efficacy of initial triple DMARD therapy with MTX as monotherapy, found that the DMARD combination group showed better results than the MTX alone group, regardless of corticosteroid administration (14). However, according to the Care-RA trial conducted on 290 DMARD naïve-patients with early RA at high risk of disease progression, MTX plus a moderate dose of prednisone (30 mg daily) proved to be as effective as DMARD combination therapies (MTX+Sulfasalazine or MTX+Leflunomide) associated with moderate or high prednisone dosages (up to 60 mg/daily) in inducing disease remission at 16-week follow-up (15). Recently, growing interest has been arisen on the evaluation of oral versus subcutaneous MTX administration. In particular, the retrospective MENTOR study conducted by Scott *et al*. on 196 RA patients, showed that subcutaneous MTX was more effective than oral formulation when used at the same dosage (16). In addition, a better bioavailability and a lower incidence of gastro-intestinal side effects were identified in patients administered with subcutaneous MTX. Iguratimod (T-614) is a novel anti-rheumatic drug that suppresses IL-6, IL-8 and monocyte chemoattractant protein 1 production induced by tumour necrosis factor-α via the inhibition of nuclear factor-kappa B activation (17). Also, Iguratimod reduces immunoglobulin production by acting directly on human B lymphocytes without affecting B lymphocyte proliferation and significantly decrease the production of rheumatoid factor, IgG, IgM and IgA. For this reason, given the peculiar mechanism of action, iguratimod has been suggested as a further DMARD for RA patients. A recent randomised, double-blind, placebo controlled trial conducted by Ishiguro *et al*. and a subsequent open-label extension study (18) disclosed that the combination Iguratimod/MTX therapy proved to be effective in achieving a low disease activity (ACR 20, 50, 70 and DAS28-CRP) and an improved quality of life. Moreover, the combination therapy was well tolerated and a good safety profile was highlighted. As a consequence, the authors suggested that Iguratimod+MTX may represent a good treatment option for patients with inadequate response to MTX alone or non eligible for other DMARDs or biological agents.

Anti-interleukin-6 (IL-6) family

Cytokines have a major role in causing joint damage. IL-6 is a pleiotropic cytokine with diverse activities and plays a central role in the pathogenesis of RA by contributing to T cell activation, B cell activation, synoviocyte stimulation, endothelial activation, osteoclast maturation and production of acute-phase proteins (19). Serum levels of IL-6 and soluble IL-6 receptor (IL-6R) are elevated and correlate with disease activity in RA patients and so blocking IL-6/IL-6R has been considered beneficial for the treatment of RA. In accordance with this, accumulated evidence has shown the clinical efficacy as well as the adequate safety of tocilizumab, a humanised anti-IL-6R monoclonal antibody (mAb), as monotherapy or in combination with synthetic disease-modifying anti-rheumatic drugs (sDMARDs) such as methotrexate (MTX) in patients who are sDMARD naive and have an inadequate response to tumour necrosis factor (TNF) inhibitors.(20) Also, in the 2013 EULAR recommendations for the management of RA, tocilizumab was listed as a first-line TNF inhibitor in patients with sDMARD-IR (21). The successful treatment of RA by tocilizumab has encouraged the development of novel biologic DMARDs (bDMARDs) targeting IL-6 or IL-6R. In addition to tocilizumab, the phase II clinical trials of olokizumab, sarilumab and sirukumab, three new bDMARDs targeting IL-6 are reported. All these drugs were studied in RA patients with moderate-to-severe disease activity despite TNF inhibitors.

Olokizumab

Olokizumab is a humanised anti-IL-6 mAb targets the IL-6 cytokine rather than the receptor. Genovese *et al*. (22) report the findings of a 12-week phase IIb study to assess the safety and efficacy of subcutaneous olokozumab in patients with rheumatoid arthritis (RA) with moderate-to -severe disease activity who had previously failed tumour necrosis factor (TNF) inhibitor therapy. Patients were randomised to one of nine treatment arms receiving placebo or olokizumab 60, 120 or 240 mg every 4 weeks (q4w) or every 2 weeks (q2w),

or 8 mg/kg tocilizumab q4w. Olokizumab at various doses across multiple endpoints demonstrated significantly greater reductions in DAS28 (CRP) and most higher ACR20 e ACR50 responses compared with placebo and similar efficacy to tocilizumab. Most adverse events were mild or moderate and comparable between olokizumab and tocilizumab treatment groups.

Sarilumab

Sarilumab is a fully human anti-interleukin 6 receptor α (anti-IL-6Rα) monoclonal antibody. Huizinga *et al*. (23) reported the results of a 12-week phase II study, aimed at assessing the safety and efficacy of subcutaneous sarilumab. All enrolled patients with active RA despite MTX were randomised to one of six treatment arms receiving placebo or sarilumab (100 mg q2w, 150 mg q2w, 100 mg qw, 200 mg q2w or 150 mg qw for 12 weeks) with background MTX. The proportion of patients achieving the primary endpoint, an ACR20 response at week 12, compared to placebo was significantly higher for sarilumab 150 mg qw e 150 mg q2w *versus* placebo. Sarilumab was generally well tolerated and infections were the most common adverse events, although no serious infections were reported. At week 12, mean total cholesterol was higher in the four highest dose groups compared to placebo group.

Sirukumab

Sirukumab is a human anti-IL-6 mAb. Smolen *et al*. (24) report the findings of two parts of a phase II study to assess the safety and efficacy of subcutaneous sirukumab in patients with active RA despite MTX. In Part A (proof-of-concept), 36 patients were randomised to placebo or sirukumab 100 mg q2w through week 10, with crossover treatment during weeks 12–22. In Part B (dose finding), 151 patients were randomised to sirukumab (100 mg q2w, 100 mg q4w, 50 mg q4w, or 25 mg q4w) through week 24, or placebo through week 10 with crossover to sirukumab 100 mg q2w (weeks 12–24). The primary endpoint (ACR50 response at week 12 in Part B) was achieved only with sirukumab 100 mg q2w *versus* placebo (26.7% *vs*. 3.3%). Greater improvements in mean DAS28-CRP at week 12 were observed with sirukumab 100 mg q2w *versus* placebo. The incidence of adverse events was similar for sirukumab-treated and placebo-treated patients. Infections were the most common type of adverse events; one death occurred (Part B, sirukumab 100 mg q2w, brain aneurysm). Safety results through 38 weeks were consistent with other IL-6 inhibitors.

Soon all these bDMARDs will be available for targeting IL-6, which will raise questions as to when and how these agents should be used. Indeed, all these studies demonstrated clinical efficacy as well as safety profiles appear similar among tocilizumab, olokizumab, sarilumab and sirukumab, making it difficult to differentiate between them compared to tocilizumab. Further studies are warranted to establish whether there are important differences among the five IL-6 inhibitors, and to determine which inhibitor should be chosen for a particular patient from a clinical standpoint as regards clinical response and/or structural damage, adverse events, and efficacy in patients with inadequate response to TNF.

Targeting interleukin-17 (IL-17) in active RA

Clinical and experimental evidence suggest that interleukin-17A (IL-17A; also known as IL-17) is an attractive therapeutic target in rheumatoid arthritis (RA). Rheumatoid synovial tissue produces IL-17A, which causes cartilage and bone degradation in synovial and bone explants. Serum IL-17A levels and, to a greater extent, synovial fluid IL-17A levels are elevated in many patients with RA. In some RA cohorts, higher IL-17A levels have been associated with a more severe clinical course. Several IL-17A blockers, including the anti- IL-17A monoclonal antibodies secukinumab and ixekizumab, and the anti-IL-17 receptor subunit A monoclonal antibody brodalumab have been evaluated in phase II clinical trials. Of these, secukinumab is the most advanced with respect to clinical evaluation in RA, with phase III trials ongoing in patients on background methotrexate who had inadequate responses to previous tumour necrosis factor blocker therapy.

Secukinumab

Secukinumab is a fully human immunoglobulin (Ig)-G1κ monoclonal antibody that binds with high affinity and selectivity to human IL-17A, resulting in the neutralisation of the cytokine activity

Recently, Genovese *et al*. (25) reported results of II phase long-term study (52-week) evaluation of safety and efficacy of secukinumab in RA patients with inadequate response to sDMARDs or bDMARDs. All patients received monthly subcutaneous injections of secukinumab (25, 75, 150, or 300 mg), or placebo. In patients taking 150 mg of secukinumab, responses were improved through Week 52 (ACR50: Week 16=45%, Week 52=55%; DAS28-CRP ≤2.6: Week 16=25%, Week 52=40%). The rate of adverse events (AE) from weeks 20 to 60 was 64.8%, with most AE being mild to moderate in severity. The overall rate of infections was 31.9%, most being mild (predominantly nasopharyngitis). Serious AE were reported in 21 patients (8.9%). There were 3 reports of malignancies (ovarian, lung, basal cell), and no deaths between weeks 20 and 60. Strand *et al*. (26) presented study of RA patients with incomplete responses to methotrexate were randomised equally to receive monthly subcutaneous injections of secukinumab 25 mg, 75 mg, 150 mg, 300 mg or placebo. Clinical endpoints used in this study included the ACR response criteria and its components and simplified disease activity score. Patients who achieved ACR20 responses on secukinumab had statistically significant and clinically meaningful improvements in Health related quality of life (HRQoL), which were seen across patient-reported outcomes (PRO) included Health Assessment Questionnaire-Disability Index (HAQ-DI), Medical Outcomes Study Short Form-36 [SF-36] Survey, and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue). Levels of ACR response were associated with incrementally greater HRQoL improvements. The REASSURE 1 trial (started

in 2011 and estimated study completion date at 2017) is comparing the safety and efficacy of secukinumab 75 and 150 mg *versus* placebo when added to background methotrexate therapy (7.5–25 mg/week) in patients with a TNF-IR and active RA. The primary efficacy outcome is ACR20 rate at week 24, and key secondary outcomes include changes from baseline in HAQ-DI, radiographic progression, and major clinical response rate (defined as 70% improvement in ACR response over 6 continuous months). Planned accrual is 630 patients.

The NURTURE 1 trial (started at 2011 end estimated study completion is 2015) is also comparing the safety and efficacy of secukinumab 75 and 150 mg *versus* placebo in patients with a TNF-IR and active RA [ClinicalTrials.gov identifier: NCT01350804]. However, this study also includes a fourth arm with the active comparator abatacept, and study treatments are being added to background therapy with stable doses of methotrexate (7.5–25 mg/week) or another single conventional DMARD. The ACR20 rate at week 24 is the primary efficacy outcome, and changes from baseline in HAQ-DI and major clinical response rate are key secondary outcome measures. Planned accrual is 548 patients.

Ixekizumab

Ixekizumab is a humanised IgG4 anti-IL-17A monoclonal antibody was evaluated in two studies.

Previously Genovese *et al*. (2010) reported results of phase I study active RA patients were intravenous ixekizumab added to DMARDs improved signs and symptoms of RA, with no strong adverse safety. This first evaluation of ixekizumab supports neutralization of IL-17 as a potential novel goal for the treatment of RA.

In more recent phase II trial (27), subcutaneous ixekizumab or placebo was added to background DMARD therapy in two group of RA patients: biologics-naive and patients with an inadequate response to tumour necrosis factor (TNF) inhibitors. For patients with an inadequate response to TNF inhibitors, ACR20 responses at week 12 were significantly better with ixekizumab than placebo. Ixekizumab improved RA signs and symptoms in patients of both groups. The safety profile was similar to that of other biologic agents, with no unexpected safety concerns. Adverse events occurred with similar frequencies overall in the ixekizumab and placebo groups. Infections were more frequent with ixekizumab than placebo (biologic-naive 25% *vs*. 19%; inadequate responders to TNF inhibitors 27% *vs*. 25%). No mycobacterial or invasive fungal infections were reported. Development of this agent is currently focused on psoriasis and psoriatic arthritis.

Brodalumab

Brodalumab is a fully human IgG2 anti-IL-17RA monoclonal antibody. Martin *et al*. (28) presented phase Ib study enrolled subjects with moderate to severe. Subjects were randomised 3:1 to receive brodalumab (50 mg, 140 mg, or 210 mg subcutaneously every two weeks for 6 doses per group; or 420 mg or 700 mg intravenously every 4 weeks for two doses per group or placebo. Multiple dose administration of brodalumab was tolerated in subjects with active RA. There was no evidence of a clinical response to brodalumab in subjects with RA. The study investigators concluded that there was no evidence of meaningful clinical efficacy, and therefore these preliminary results are not supportive of further evaluation of this agent in RA. As for ixekizumab, no trials in RA are ongoing and development is currently focused on psoriasis and psoriatic arthritis.

Therapies targeting B cells

In addition to therapies selectively acting on kay molecules in RA, also to target or to modulate circulating leukocyte subsets and/or within the target tissues has been tested. In this setting, some studies have suggested changes in B cell populations in patients with RA (29-30), these data indicate that the targeting of B cells may be important in the treatment of patients with RA. The treatment with rituximab a chimeric mouse-human monoclonal antibody anti-CD20 cells is approved for the treatment of RA patients, as it reduces the synthesis of autoreactive antibodies as rheumatoid factor and anti-citrullinated peptide antibody, and modifies the antigen presentation to T cells as well as cytokine production.

Ocrelizumab

Ocrelizumab is another B cell-depleting agent, it is a humanised anti-CD20 monoclonal antibody and it seemed to be effective in RA treatment. Large clinical trials have evaluated the OCR therapy in RA demonstrating a comparable efficacy than RTX, with comparable responder rates (31-33). These studies have evaluated the efficacy of OCR in patients with inadequate response to MTX, in patients with an inadequate response to TNFi and in those naïve to MTX and biological therapy. In February 2014 results from the Ocrelizumab (OCR) phase III programme have been published (34) showing a comparable safety profile of OCR 200 mg x 2+MTX and placebo+MTX. In this study 868 patients received placebo, 1064 OCR 400 mg (200 mg x 2 or 400 mg x 1) (OCR200) and 827 OCR 500 mg x 2 (OCR500) plus background MTX at baseline and 24 weeks. OCR500+MTX may be an effective therapeutic strategy in RA treatment, as demonstrated clinical benefit by improving RA signs and symptoms and radiographic outcomes (34-35). However, the study of Emery *et al*. demonstrated a difference in the safety profile regarding severe infectious events between OCR500+MTX and placebo+MTX. This difference in safety profile was not observed between placebo+MTX and OCR200+MTX, that, however, did not show superior efficacy compared with existing therapies. No differences in the rate of malignancies between treatment groups were reported by the OCR phase III programme.

Ofatumumab

Ofatumumab is another B cell-depleting agent that requires premedication with corticosteroids in order to avoid reactions during infusions. It is a humanised monoclonal antibody that targets extracellular domains of CD20 antigen. Two trials have reported a comparable

efficacy of ofatumumab and RTX in RA demonstrating similar ACR responder rates and relatively common infusion related adverse events (36-37).
In the review of Faurschou *et al*. it is reported that neither ocrelizumab nor ofatumumab are licensed for clinical use in patients with RA (38).
The B-cell activating factor (BAFF) exists as a soluble form and a membrane-bound form playing an important role in B cell generation and maintenance. It is a ligand in the TNF family requested for B-cell survival (39). An alteration in B cell activation, proliferation, survival and consequently immunoglobulin secretion may be caused by a BAFF dysregulation. For this reason acting on BAFF in order to neutralise may be an alternative therapeutic choice in RA; in addition studies have showed an abnormal high concentration of BAFF in RA patients (40).

Belimumab
Belimumab is a monoclonal humanised antibody targeting soluble BAFF and its use in RA was studied in a placebo-controlled trial with the enrolment of 283 patients with a active RA despite therapy with DMARDs (38). A review summarised pharmacological and clinical data on belimumab, a fully human monoclonal antibody that acts neutralising soluble BAFF, in RA patients. However, this trial suggested a relative low efficacy of belimumab in RA patients. Therapy with belimumab seems to lead to an increase of American College Rheumatology (ACR)20 responses at week 24. The efficacy was greater in patients that presented a high disease activity, positive rheumatoid factor and that did not have anti-TNF treatment and also in these patients in which MTX failed. However, no significantly improvement of ACR50 and ACR70n was demonstrated in patients treated with belimumab in the single Phase II clinical Trial (41).

Tabalumab
Tabalumab is a fully human IgG4 monoclonal antibody that neutralises the two forms of BAFF, the soluble and the membrane-bound one. A phase II, randomised, placebo-controlled trial indicated a significantly reduction of RA signs and symptoms with a good safety profile of the drug. In this trial the primary end point was the proportion of patients reaching an ACR20 response at week 16 and "Tabalumab (doses of 30, 60 and 160 mg) or placebo was administrated intravenously over 30 minutes at weeks o, 3 and 6" (29). MTX was continued during the study, but none received other DMARDs or biological drugs and no more of 10 mg corticosteroids daily. The primary end point was reached at week 16 and similar significant differences in response rates were noted in the secondary end points as ACR50, ACR70, DAS28 and EULAR response. In addition, no differences in the incidence of adverse events were noted between patients treated with tabalumab and those treated with placebo. The efficacy of tabalumab was also studied in patients with active RA and an inadequate response to TNF inhibitors (39). For this study patients with RA from 45 centres were enrolled, all patients had RA diagnosis defined by the American Rheumatism Association 1987 revised criteria and all had an history of inadequate response or intolerance to one or more TNFi. The primary end point was the percentage of patients reaching an ACR50 response at week 16 and it was not statistically different between the combined Tabalumab group and the placebo one. On the contrary the ACR20 and ACR50 response percentage was significantly greater in the tabalumab group than in the place one at weeks 6 and 9, but not at week 12. However patients treated with tabalumab showed a significant higher reduction of DAS28-CRP from baseline at week 6, 9, 12 and 16 when compared with patients receiving placebo. In this study was indicated that the reduction in efficacy after week 9 might be caused by a notable decline in tabalumab concentrations. The study suggested that the safety of tabalumab was similar to other biologic drugs in RA.

Tofacitinib and other Janus Kinase (JAK) inhibitors
Novel approaches have focused on the development of molecules that inhibit the JAK/STAT pathway.
This seems to modulate intracellular signalling transduction, resulting in differentiation and activation of lymphocytes as well as in the release of proinfiammatory cytochines (such as tumour necrosis factor-TNF-α), that lead to joint inflammation and damage.
Tofacitinib (Xeljanz – produced by Pfizer, development code CP-690,550, formerly named tasocitinib) is a small molecule that inhibits in order of potency JAK 3 over JAK1 and JAK 2 over Tyk2. It is an orally drug with a half life of about 3.5 hours. It is eliminated for 70% by hepatic metabolism and for the remaining by renal excretion. There are two doses of the drug: 5 mg twice daily and 10 mg twice daily.
In the last years, six Phase III studies have been developed to evaluate the efficacy and safety of this drug in adult patients with moderate to severe RA. All these studies are named under the acronym ORAL (Oral Rheumatoid Arthritis Phase III Trials):
ORAL Solo (30), Sync (31), Standard (32), Scan (33), Step (34) and Start (35). They were multicentre, double-blind, placebo controlled, parallel group study design trials. In these trials, patients were allowed to receive background therapies (NSAIDs – non-steroidal anti inflammatory drugs, opioids or corticosteroids). These trials showed significant improvement in RA as measured by ACR scores increase by 20-50-70%, disease remission scores, self-reported functional status measurements and radiographic changes (36). Particularly the ORAL Scan and Step, performed in the year 2013, evaluated the reduction of radiological progression and the efficacy of the compound, respectively, in a cohort of patients with failure to TNF inhibitor (TNFi). The study of Van der Heijde *et al*. is a 24-month, double-blind trial. This study evaluated the reduction of structural damage (as the mean change from baseline in modified Total Sharp Score – mTSS) in 797 patients with active RA non-responder to MTX. A statistically significant difference was observed only in the group who received the higher dosage of tofacitinib (10 mg bid) (33).
In the ORAL Step, Burmester *et al*. demonstrated the efficacy of tofaci-

tinib in 400 patients with moderate to severe RA and inadequate response or intolerance to TNFi. The study is a randomised, controlled, 6 months phase III study. At month 3 ACR20 response rates were 41.7% for Tofacitinib 5 mg bid and 48.1% for Tofacitinib 10 mg bid *versus* 24.4% for placebo (p=0.0001 and p<0.05, respectively). The same results were both for ACR50 (28% for tofacitinib 10 mg bid, 27% for tofacitinib 5 mg bid compared with 8% for placebo p<0.0001) and for DAS28-defined remission (7% for tofacitinib 10 mg bid, 11% for tofacitinib 5 mg bid compared with 2% for placebo; p<0.05) (34).

Finally, the ORAL Start Investigators published the last June the results of a 24 months phase III trial that compared tofacitinb in monotherapy to MTX in patients MTX naïve or treated with MTX at a non-therapeutic dose. These data demonstrated that Tofacitinib monotherapy (at dose of 5 or 10 mg twice daily) was superior to MTX in reduction of radiological damage progression, in clinical outcomes (*i.e*. ACR 20-ACR 50-ACR70 response; DAS 28) and patient-reported outcomes (*i.e*. HAQ-DI; FACIT-fatigue). Notably, Herpes zoster developed in 4% of patients who received tofacitinib *versus* about 1% of patients who received MTX; moreover, confirmed cases of cancer developed in 5 patients who received tofacitinib and only in one patient who received MTX. In conclusion, these results demonstrated that tofacitinib is effective in reducing signs and symptoms as well as disease activity and physical function in patients with moderate to severe rheumatoid arthritis, MTX-naive or after treatment failure to non-biologic and biologic DMARDs.

In November 2012 the Food and Drug Administration (FDA) approved Tofacitinib at the dosage of 5 mg bid for the treatment of moderate to severe RA in patients who have had intolerance or inadequate response to MTX. Tofacitinib can be used as monotherapy or in combination with MTX or other non-biologic DMARDs. It cannot be used with biological DMARDs or potent immunosuppressives such as azathioprine or cyclosporine. In the last 2013 EULAR recommendations for the management of RA Tofacitinib is recommended, where licensed, after the failure of at least one bDMARD. (40). To extend the use of this drug also after MTX or other cDMARD failure more safety data from registries, clinical experience and long term studies are needed. In fact, data currently available, underline more incidence of serious infections under treatment with tofacitinib (particularly TB and Herpes Zoster) and the presence of changes in laboratory parameters (neutropenia, anaemia, increase in serum levels of creatine phosphokinase, creatinine and dose-related increase in lipid levels – both LDL and HDL) (40). There are also other oral JAK inhibitor molecules: Baricitinib (LY3009104) with selectivity for JAK1 e JAK2 that is currently in Phase III clinical development; GLPG0634 that inhibits JAK1 and VX-509 with selectivity for JAK3 that are now investigated in Phase II. (www.clinicaltrials.gov)

Fostamatinib

Another promising drug for the treatment of patients with rheumatoid arthritis non-responding to conventional DMARDs or TNF is Fostamatinb. It is a small molecule, oral spleen Tyrosine Kinase (Syk) inhibitor. In a phase III study of Genovese MC *et al*. (OSKIRA-3) evaluated the efficacy of this drug in patients previous treated with MTX and a single TNF-α, was not achieved an improvement in ACR20 response at 24 weeks in the group of patients taking fostamatinib 100 mg bid for 4 weeks then 150 mg once daily compared to placebo (41).

In December 2014, Weinblatt *et al*. published the results of OSKIRA-1, a phase III clinical trial that compared fostamatinib at two different dosages (100 mg twice daily and 150 mg once daily, respectively) with placebo. It was demonstrated an improvement in the ACR20 response in patients MTX non-responders treated with Fostamatinib at 24 weeks compared to placebo but there was not reported a significant difference in the modified total Sharp/van der Heijde score of radiographic damage (38).

Mesenchimal stromal cells

In the last two years, two large studies evaluated the possible role of mesenchymal stromal cells (MSC) for RA patients refractory to conventional therapies. Wang *et al*. demonstrated that 136 patients with active RA receiving 40 million allogeneic umbilical cord derived MSC had a significant remission as ACR improvement, DAS28, HAQ and also a serum levels reduction of inflammatory cytokines such as TNF-alpha and IL6 compared to 36 patients treated with placebo (42). The second study, presented at the ACR congress in 2013, showed in 53 RA patients that the infusion with allogeneic adipose-derived MSC was safe in a dose of 3x1–4 million cells per kg when given at day 1, 8 and 15 with rescue therapy allowed at month 3 and 6. Only one patient had a serious adverse event (43).

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