Review

One year in review 2017: novelties in the treatment of rheumatoid arthritis

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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 goal of the treatment is to control pain and inflammation, reduce joint damage and disability, and maintain or improve physical function and quality of life. The present review is aimed at providing 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 year.

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 main goal of RA treatment is to stop inflammation, relieve symptoms, prevent joint and organ damage, improve physical function and reduce long-term complications. Current treatment models promote intensively treating inflammation early in the disease course; moreover, to meet these goals it is recommended following specific strategies: to start an early aggressive treatment, to target remission and to maintain a tight control

Efficacy

The treatment of RA has dramatically changed over the past decade, with the increased number of efficacious agents and the development of novel treatment strategies. In this scenario recommendations for the management of RA based on the latest evidence have become increasingly useful; indeed, in 2016, the largest International Task Force was created to further update the 2010 and 2013 EULAR sets of recommendations in line with the last 3 years' scientific insights

A new principle, deriving from recommendation 14 of the previous set of recommendations, has been added to the pre-existing overarching items. This "position" change further stressed the role of several disease-related and patient-related factors in the decision-making process: it is important to consider disease activity, radiologic damage and other patient factors, such as comorbidity and safety issues, in the treatment decision (1).

The Task Force confirmed Methotrexate (MTX) as "anchor" drug (rapid escalation to 25 mg/week) associated to short-term glucocorticoids (GC), while the combination therapy of csDMARDs was no more mentioned as an option for DMARD-naïve patients.

With respect to 2013, the role of GC therapy has been stressed as "bridging therapy", not only for those patients initiating DMARDs but also in the case of DMARDs changing. Thanks to their rapid onset of action, GC are now recommended in association with DMARDs to maximise their effects, but it is still unclear which regimen or route of administration would be more adequate. However, one of the key points remains that GC has to be tapered as rapidly as clinically feasible usually within 3–6 months from start of treatment, so as to possibly limit side effects (such as infections, diabetes, osteoporosis, and gastrointestinal and cardiovascular events) (2).

The effectiveness of MTX was further evaluated in the last three years; a recent Cochrane network meta-analysis tried to summarise and compare different regimens including this csDMARD. In patients MTX-naive and MTX-failure a statistically significant differ-

ence was observed in ACR50 response between the combination therapy with MTX plus biologic agents or MTX plus tofacitinib and oral MTX; among csDMARD combination therapies, only the triple therapy MTX+SZS+HCQ) showed similar results in both populations, while the other regimens demonstrated their superiority only in patients with inadequate response to MTX monotherapy. Moreover, csDMARD combinations other than the triple therapy seemed to be associated with a higher rate of withdrawals due to toxicity. Considering structural outcome (radiographic progression) methotrexate plus different bDMARDs were superior to MTX monotherapy in preventing joint damage only in MTX-naïve patients, but with (small effect over one year) (3). Regarding MTX formulation, additional real life data confirmed higher efficacy with SC over oral MTX, mainly justified by a significantly higher clinical efficacy together with a comparable safety profile; in line with previously published data, less gastro-intestinal discomfort seems to be associated with SC formulation (4). Furthermore, as demonstrated in a Spanish RA cohort study, this csDMARD appeared to significantly and independently impact on mortality, too; biologic agents did not show such a higher protective effect on death when compared with this reference drug (5).

Another substantial change in recommendations regards second line therapy after the failure of the first csDMARD: clinicians should be guided by unfavourable disease-related prognostic markers which have been specifically listed for the first time in the last set of EULAR recommendations, in line with existing scientific evidences. As suggested, when these are lacking, the best options are switching or adding another csDMARD (plus short-term GC). On the contrary, in patients with negative prognostic markers the Task Force suggested a bDMARD (current practice) or a JAK inhibitor as add-on therapy to background MTX/other equivalent csDMARD (6). In the 2013 update JAK inhibitors, considered targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs), were recommend-

ed only after a bDMARD failure; currently, due to growing positive results, they could be adopted, where approved, alternatively to bDMARDs

For the first time the recommendations introduce new IL-6 antagonists as therapeutic option for non-responder patients. Finally, the Task Force confirmed the higher effectiveness of bDMARDs in combination with a csDMARD (generally MTX) compared to bDMARD monotherapy, considering bDMARD monotherapy only in case of intolerance and/or absolute contraindications to all csDMARDs. Data from the DREAM registry supported this recommendation: patients treated with the association TNFi + any csDMARD have lower DAS28 and HAQ-DI values over time respect to patients receiving TNFi monotherapy; in particular the best clinical response has been observed with the combination TNFi + MTX (7). In a recent prospective two-year cohort study a longer drug survival for etanercept was demonstrated in patients on combination therapy with MTX respect to those on monotherapy (8). Similarly a recent Cochrane overview focused on the comparison between biologic monotherapy (including TNF-inhibitors, non-TNF inhibitors and tsDMARDs) to placebo or to an active comparator (MTX and other csDMARDs). Biologic monotherapy showed to significantly improve clinical and functional scores (ACR50 and HAQ) and to allow a higher rate of remission disease respect to placebo; when compared to MTX or other csDMARDs, bDMARD and tsDMARD monotherapy did not result in a significantly higher probability of clinical remission. Such results represent the most updated and comprehensive data on the topic: a similar effectiveness and safety profile came out for both biologic DMARDs (TNFi and non-TNFi) and tofacitinib monotherapy. Regarding structural damage, these data supported a lower radiographic progression in patients treated with biologic monotherapy *versus* MTX/other DMARDs groups, but the clinical significance of this result remains unclear. Safety issues about differences in withdrawals due to adverse events, serious

adverse events and risk of cancer have still been inconclusive (9).

Treat-to-target
The treat-to-target (T2T) principle has been still stressed in this last set of recommendations, too: to date this approach is widely accepted as the standard of care for RA patients, regardless of adopted drugs, since it has become clear as this strategy itself is successful to gain e the best outcomes (10). In this context the new concept of "windows of opportunity" for RA treatment is born and many studies have pointed the attention to the advantages of an early intensification therapy; the previous FIN-RACo and NEO-RACo trials had already demonstrated that an early treatment intensification could prevent bone erosions several years after initiation of treatment. More recently Levitsky *et al.* have further elaborated on these results and showed that an early introduction of anti-TNF therapy for 6 months was associated with additional radiographic benefit exclusively in RF-positive patients (11).

The use of an imaging T2T strategy with the goal of an ultrasound remission showed similar clinical and radiological outcomes, but with a more intensive treatment; all these data supported the choice of a clinical T2T strategy (12).

Steunebrink *et al.* compared the effectiveness of a T2T step-up approach starting with methotrexate (MTX) monotherapy to an initial DMARDs combination approach in a population of early RA patients. The results confirmed the efficacy of the T2T strategy with a more rapidly achieved remission in those treated with a combination therapy; however, at 12 months the study showed no significant differences in mean DAS28 scores and in the proportion of patients in remission 13. Lampropoulos confirmed such previous findings regarding clinical benefits of a T2T strategy, adding information on safety issues, too: the T2T arm experienced less serious AEs, especially infections, as an adjunctive result of active inflammation control (14). Considering the goal of a T2T strategy, an open question remains the role of anti-therapeutic antibodies (ATA) in

the management of RA patients, in particular of those taking TNF-inhibitor therapy. The prevalence of ATA varies in different studies according to the assay used; recent data on adalimumab indicate a potential correlation between ATA title and free circulating drug levels, speculating a significant influence on disease activity scores in RA and other articular inflammatory diseases. Therefore, these results would suggest to test both adalimumab levels and ATA title to improve the patient therapy in the optic of a personalised approach (15).

First line therapy after csDMARD failure

New recommendations confirm the role of T2T strategy,and introduce the important concept of prognostic stratification in the decision making process if a patient does not obtain remission or LDA with csDMARDs and presents poor prognostic factors (*e.g.* high disease activity, RF positivity and CCP antibodies, erosive disease), the Task Force suggests the addition of a biologic or tsDMARDs.

To date, all bDMARDs have demonstrated the same efficacy with few differences in safety profile; a recent head-to-head study on 915 patients failed to reveal the superiority of certolizumab pegol plus methotrexate *versus* adalimumab plus methotrexate. However, the study evaluate also the effects of switching to the other TNF inhibitor after a primary failure at week 12 without a washout period and showed good results in terms of efficacy and safety (16). New data of efficacy and safety are now available also for others TNF inhibitors; a recent retrospective study confirmed the efficacy of adalimumab most of all in patients with a shorter time lag between its introduction after MTX, while disease duration seems not to influence the response to the therapy (17). At the beginning of 2016 the results of the GO-FORWARD trial confirmed the efficacy of subcutaneous golimumab also after 5 years of treatment, despite MTX association; the data regarding the long-term safety was consistent with those reported in previous studies (18). All these treatment are

now indicated as first-line therapy after a DMARD failure in patients with poor prognostic factors; however, in this group of patients the response to anti-TNF has been reported to be less effective. For this reason it would be useful to identify some predictors of response; with this goal, Vastesaeger *et al.* developed a tool to predict the probability of remission and low disease activity in patients with RA treated with golimumab. They derived a matrix resulting by the combination of six baseline characteristics (low baseline TJC and ESR, male sex, absence of comorbidities, younger age, lower baseline HAQ) that could help the clinician in the selection of ideal candidates for a successful anti-TNF therapy (19); however, further studies are needed to validate this tool. As regards other biologic agents, new data are now available based on longer periods of observation. Abatacept confirmed its clinical and radiographic efficacy in routine care with a good safety profile even in elderly patients characterised by comorbidities (20). In particular the drug seemed more effective in seropositive patients as confirmed by the post hoc analysis of the 24 months AMPLE study that demonstrated better clinical and functional responses to abatacept and adalimumab between patients with a high titre of anti-CCP (>1000 UI/ml). However, only for abatacept was showed a significant direct correlation between the degree of response and the baseline antibody titres (21). The analysis of PANABA registry further support these data and presented the positivity for RF or ACPA as predictors not only of clinical response but also of a higher drug survival rate in patients on ABA therapy (22). Nowadays there is an increasing interest in the identification of factors influencing the drug retention rate; this has been the aim of the ACTION study which demonstrated an intravenous abatacept retention rate higher than 50% at 24 months (23). The same outcomes were investigated in patients in ABA monotherapy as almost one-third of patients in daily practice were described in biologic monotherapy. Based on ORA registry, ABA monotherapy demonstrated a lower retention rate compared with

the combination strategy, but without any significant differences in efficacy and safety. Further studies are needed but these data could provide ABA monotherapy as acceptable alternative when csDMARDs are contraindicated or not tolerated (24). Encouraging results have been observed also in long term studies with Tocilizumab (TCZ): in monotherapy this drug maintain its efficacy with a good safety profile and a stable rate of serious adverse events over time as demonstrated in the 5 years extension of AMBITION study (25). Similar data have been confirmed for the combination therapy TCZ plus MTX that after 5 years confirmed its efficacy both in controlling the disease activity that in preventing the progression of radiographic damage (26). So the efficacy and safety of TCZ have already been demonstrated both in monotherapy and combined therapy but, similarly to ABA, the TCZ drug retention rate appeared to be shorter under monotherapy than under combination with MTX (27). To date, few data are available regarding anti-IL6R as first bDMARD. Kihara *et al.* observed that, when used as first line, TCZ worked better than in second-line with clinical responses similar to that of patients starting TNFi (28). In contrast with these positive data, the CARD-ERA-2 failed to present Anakinra as a valid alternative therapeutic option in early RA patients: when added to MTX the anti-IL1 did not provide a further beneficial effect to the csDMARD monotherapy (29). In the current scenario of multiple therapeutic option available for RA patients, an important role is now assigned to biosimilars; to date we know that phase III studies did not show any significant differences between infliximab biosimilars (SB2 and CTP13) and the originator (Remicade) in terms of achievement of ACR20, reduction of radiographic progression, safety and immunogenicity (30, 31). The same conclusions came from trials on biosimilar Etanercept named SB4 which showed a comparable efficacy and safety profile with apparently a lower immunogenicity than the originator Enbrel (32).

Despite its indication as a second-line bDMARD, there is also growing evi-

dence on RTX use in biologic-naïve patients; this drug could be chosen as first bDMARD in some specific circumstancies as stated by current recommendations. In this regard, Porter *et al.* performed the first head-to-head, open-label, randomised-controlled trial to compare RTX and TNFi (adalimumab or etanercept) as a first line bDMARD in a group of RA seropositive patients, with active disease and inadequate response to synthetic DMARDs. Their hypothesis was that a treatment strategy that starts with RTX, and switches to a TNFi if needed, would be non-inferior to the opposite strategy. The authors found that initial treatment with RTX is non-inferior to initial TNFi treatment. Moreover, RTX resulted cost saving over 12 months. Finally, the two study groups showed a comparable safety profile, but these results are not generalisable to the long-term use of the drugs (33).

In the clinical practice setting, RTX is also used with different regimens. For example, Chatzidionysiou *et al.*, analysing data derived from twelve European registries participating in the CERERRA collaboration, found that on a cohort of 2.873 patients 91.4% received the approved regimen of 1g x2, while 8.6% received the low-dose regimen of 500 mg x2. Comparing the characteristics of the two groups, it seems that the low-dose regimen is preferred in older patients and/or in those with a milder phenotype of disease. At 6 months, the two doses showed a comparable clinical outcome (34).

First-line tailored biologic therapy
New recommendations introduced the option of an induction therapy with bDMARD and a subsequent continuation only of the csDMARD; to date there are few studies to support this approach and remains still unclear whether discontinuation of TNFi is possible after LDA or remission is achieved. As a result of a recent meta-analysis, it was found that an induction therapy with MTX+TNFi could be associated with a higher chance of retaining LDA and/or remission even after discontinuation of TNFi (35). Similar results came from two new different

studies with patients on therapy with certolizumab (C-OPERA study) or with Etanercept; the aim of both these trials was to evaluate the clinical and radiographic effects of bDMARD dose maintenance, reduction or withdrawal. The C-OPERA study was conducted in patients with early disease and poor prognostic factors and supported the effectiveness of an early aggressive combination therapy to induce remission (induction therapy); the second part of the study showed persistent beneficial effects up to 1 year after discontinuation of certolizumab (36). The Canadian Methotrexate and Etanercept Outcomes study demonstrated best outcomes in patients continuing combination therapy, but demonstrated the good results of a maintenance therapy with reduced dose etanercept. However, a higher risk of disease flare was observed in patients stopping the bDMARDs (37). In this optic, an Italian group guided by Cantini *et al.* critically reviewed literature data and tried to find out some guidelines for a first-line tailored biologic therapy by taking in account aspects regarding therapeutic agents (including costs), disease and patients characteristics. In absence of particular conditions any biologic could be used to treat a RA patient, reminding that the best cost-effectiveness profile is now represented by etanercept (ETN) and biosimilar infliximab (IFX).

As the authors stated, in line with evidences, there could be some specific clinical settings where clinician's choice should be oriented toward a specific agent over others; for example in patients with a potential higher infection risk or latent tuberculosis infection (LTBI) positivity it could be safer to employ abatacept (ABA), tocilizumab (TCZ), or ETN, while an increased CV risk should guide towards an anti-TNF agent, preferably etanercept. If there were controindications to csDMARDs or they were not tolerated, the first choice should be TCZ monotherapy (38).

Switching or swapping
One-third of patients with rheumatoid arthritis (RA) show inadequate re-

sponse to the first line biologic therapy with TNF-inhibitors (TNFi). In the last year, Singh *et al.* performed an update of the 2009 Cochrane overview comparing the benefits and harms of biologics and tofacitinib *versus* placebo or MTX (or other csDMARDs) in people with RA, previously unsuccessfully treated with biologics. The results of this systematic review and network meta-analysis still support the use of a second biologic in people with previous bDMARD-failure, showing that biologics (± MTX) improve signs and symptoms of RA, function, and remission rate. Only one study provided data on tofacitinib demonstrating its clinical efficacy when used in combination with MTX. Results of this meta-analysis were inconclusive for withdrawals due to adverse events, serious adverse events and cancer (39). However, head-to-head studies comparing biologics in patients with RA after failure of the first line bDMARD are few and rheumatologists have to face with the problem of how to choose the next biologic or tofacitinib. Moreover, actually there are no definitive different conclusions for subsequent therapy in primary failures compared with secondary failures to TNF-α-blockers (1). Therefore, several recent works focused on comparison between the two different possible strategies in anti-TNF-α failures: switching to another TNFi or changing mechanism of action/MoA (swap strategy). Overall, data coming from the most recent studies, comparing the efficacy of a second anti-TNF-α drug *versus* a non-TNF-α-targeted biologic, seem to support the choice of changing mode of action rather than switching to another TNFi (40). Fleischmann *et al.*, in particular, wanted to explore the efficacy and safety of sarilumab (an IL-6 receptor antagonist) as second line bDMARD. They evaluated the response to two different doses of sarilumab (150 mg or 200 mg every 2 weeks), plus background csDMARDs, *versus* placebo in patients with active RA, after an inadequate response or intolerance to TNFi. They found that both sarilumab doses improved clinical response and physical function in these patients. Moreover, the safety profile

of the drug is consistent with IL-6 receptor blockade (41). It is worth noting that currently no data could support a viceversa swap strategy, that is from a non-TNF MoA agent to an anti-TNF drug or from tociluzumab to another IL-6 pathway inhibitor agent (sarilumab). We only found a small retrospective study comparing the efficacy of TNFi *versus* abatacept (ABT) in RA patients after tocilizumab failure. This study seems to demonstrate that TNFi may be more effective to achieve clinical remission or low disease activity than ABT after insufficient response to TCZ. However, it has to be noted that more patients in the TNFi group took concomitant methotrexate (42). The 2016 EULAR recommendations (1) for RA state that, after failure of a first bDMARD, physicians may also consider treatment with targeted synthetic DMARDs (tsDMARD), that are Janus kinase inhibitors.

In this regard, Genovese *et al.* analysed safety and efficacy of open-label tofacitinib in an extension study, following a direct switch from blinded treatment with either adalimumab or tofacitinib in RA patients. The results demonstrate that treatment can be directly switched from adalimumab to tofacitinib. In fact, the safety and efficacy profile appeared similar in both treatment sequences. In particular, switching to open-label tofacitinib resulted in improvement of disease control and physical function, in both treatment groups (43).

Rituximab (RTX) is approved for use in RA patients after TNFi have failed. In the last year, Torrente-Segarra *et al.* assessed the short-term efficacy and safety of RTX and TNFi in RA patients with inadequate response (mainly a primary inefficacy) to a first TNFi, in a prospective observational clinical practice study. After a 6-months follow-up period, RTX and TNFi resulted comparable in terms of efficacy and safety, when used as a second line biologic therapy (44). In the already large scenario of biologic therapies for RA patients, an additional possibility is represented by biosilmilars (bsDMARDs). We have already mentioned the evidence coming from the use of anti-TNF-α biosimilars in the clinical practice, but now

new bsDMARDs are under study. We report here two recent trials on RTX-biosimilars: CT-P10 and PF-05280586. They both demonstrated a comparable clinical efficacy in RA patients with active disease and inadequate response to TNFi (45, 46). So, if RTX is a valid, efficacious and safe option after TNF-α blockers failure, what are our possibilities after RTX failure or intolerance? Walker *et al.* examined the effectiveness of TNFi, abatacept (ABT) or tocilizumab (TCZ) in patients previously treated with RTX, in a European observational longitudinal study. They enrolled 265 patients who had stopped RTX 6 months or less prior to the new biologic therapy and evaluated them after 6 months from the beginning of the new treatment. In this observational cohort, TCZ provided a better control of RA, than ABT or TNFi, after RTX discontinuation. Importantly, the reasons for discontinuation of RTX and the number of previous biologics had no influence on outcomes (47). Finally, The Italian board for the TAilored BIOlogic therapy (ITABIO) reviewed the most consistent literature to indicate the best strategy for the second-line biologic choice. The results suggest that a second anti-TNF-α may be indicated in cases of secondary loss of response and after an adverse event. In particular, better results are observed in patients who switch from a monoclonal antibody to another (golimumab having the highest level of evidence as second-line anti-TNF-α) or from anti-TNF-α monoclonal antibodies to etanercept (ETN). On the contrary, for patients who fail ETN, swapping to a different mode of action should be preferred. Moreover, patients who experience a serious or class-specific side effect should be managed with a second biologic agent other than anti-TNF-α. Among the non-anti-TNF-α bDMARDs, RTX and TCZ seem to have the strongest evidence of efficacy in the treatment of anti-TNF-α failures. Finally, the authors underline that some variables are still important to be considered: patients' preference, the indication for anti-TNF-α monotherapy in potential childbearing women and the intravenous route with dose titration in obese subjects (48). Patients usually

prefer subcutaneous (SC) injection of anti-TNF-α over the intravenous drug administration. However, injection site reactions (ISR) are not so uncommon, especially within the first month of treatment and they may influence patients' adherence to therapy. In order to improve understanding of the risk factors contributing to this side effect, Matsui *et al.* evaluated the relationship between aging and ISR for ETN and ADA, finding that younger patients are at higher risk of developing ISR. Moreover, they found that the association of MTX reduces the risk of ISR in comparison with anti-TNF-α monotherapy (49). A recent meta-analysis on adherence to anti-rheumatic therapy in RA patients revealed an overall adherence rate of 66%, without significant differences among the different methods used to measure adherence itself. The authors showed that adherence decreases during follow-up. Moreover, beliefs in the efficacy of treatment resulted a predictive factor for adherence (50).

Tapering
Thanks to all the new and effective treatment options for RA, an increasing number of patients reach and maintain clinical disease remission. Therefore, a new challenge for physicians is to understand whether continuation of DMARDs is always necessary.

The EULAR guidelines mention the possibility to taper bDMARDs (after having tapered GC), especially if they are associated with csDMARDs. Tapering means both reduction of the dose and "spacing" of drug administrations. Early disease, a major depth of improvement and a longer duration of remission are predictors of a successful tapering of bDMARDs (1).

However, some of the most significant recent studies, that take these aspects into consideration, show somewhat conflicting data. For example, Jiang *et al.* performed a meta-analysis of 5 RCTs including 771 participants with RA who achieved and maintained low disease activity or remission. They evaluated the efficacy and safety of down-titration (dose reduction or tapering) strategies compared with continuation of bDMARDs. They found that continua-

tion of a standard dose of bDMARDs does not result in a significant benefit, in comparison to down-titration strategy, in terms of rate of disease relapses, withdrawals due to inefficacy or toxicity and number of serious adverse events (51). Similarly, Tanaka *et al.* analysed a group of Japanese patients with early RA who achieved low disease activity with combined therapy with adalimumab + MTX and they demonstrated that almost 80% of patients who discontinued adalimumab for 3 years managed to maintain low disease activity, with a lower incidence of adverse events if compared with patients who continued adalimumab (52). However, some other studies conducted on large cohorts of patients with established RA seem to demonstrate that tapering TNFi may result in more disease flares if compared with maintaining a stable therapy, even if it seems that this does not determine a structural damage progression (53, 54). Haschka *et al.* performed a prospective RCT (RETRO study) to address the possibility of tapering or stopping conventional and/or biologic (TNFi or tocilizumab) DMARDs, in patients with RA and stable remission for at least 6 months. Patients were randomised into three different trial arms: 1) continuation of conventional and/or biologic DMARDs at full dose; 2) tapering of all conventional and/or biologic DMARDs by 50%; 3) initial reduction of the initial dose by 50% for the first 6 months and then stopping all DMARDs. More than half of the patients maintained remission after tapering or stopping DMARDs, even if the overall relapse rate was significantly higher in patients who tapered/ stopped DMARDs than in patients who continued stable therapy (44% *vs.* 15%). ACPA positivity resulted as a predicting factor of relapse, while longer disease duration and the use of bDMARDs, although suggestive of a more resistant phenotype of RA, did not predict a higher relapse rate in this study. It has to be underlined that, differently from what indicated in the EULAR recommendations, in this study DMARDs were tapered or stopped all together, without following a sequential order (55). As well as TNF-α

blockers, the "tapering strategy" also applies to other bDMARDs. We report here two studies that demonstrate that it is a feasible choice to reduce the intravenous dose of tocilizumab or abatacept for maintenance therapy of stable RA patients (56). Finally, Kuijper *et al.* particularly focused on de-escalation of csDMARDs in patients with early RA, after achieving sustained remission. Of patients tapering csDMARDs, 41% experienced a disease flare within 12 months (*vs.* 37% in patients tapering bDMARDs). After flare, 65% of patients re-achieved remission within 6 months after treatment intensification (57). However, it should be noted that data are from an early RA population with relatively mild disease, so results may not be generalisable to populations with established RA for which rates of remission and successful tapering of csDMARDs may be lower.

Safety
A major issue regarding RA therapy is, of course, its safety. Our knowledge about the long-term safety profile of biologic, conventional and targeted synthetic DMARDs is growing up.
Ramiro *et al.* published a systematic literature review including 26 observational studies addressing diverse safety outcomes of therapy with bDMARDs. Patients on bDMARDs, compared to patients on csDMARDs, exhibit a higher risk of serious infections and TB infection, but no increased risk of Herpes Zoster infection, neither an increased risk for malignancies, except for melanoma skin cancer; as for non-melanoma skin cancer, it may occur more frequently than in the general population, but compared with csDMARDs, it seems that there is no increased risk (58).
Cipriani *et al.* published data from an Italian multicenter prospective, observational study on infections among 731 rheumatic patients on biologic therapy. They found that the most common sites of not-serious infections are both urinary and respiratory tracts and they are mainly associated with disease duration, glucocorticoid therapy and comorbidities. Serious infections are mainly of the lower respiratory tract and they are associated with the

beginning of biologic therapy in older age. However, compared to previous papers, the authors observed, in daily practice, a lesser rate of serious and not-serious infections in rheumatic patients treated with biologics (59).
Surprisingly, Richter *et al.* found that RA patients exposed to biologic therapy at the time of a serious infection have a reduced risk of sepsis and mortality, if compared to patients exposed to csDMARDs. This apparently "protective" effect of biologic therapy may be explained by the evidence coming from studies on animal models that TNF-α plays a key role in triggering sepsis. So, an effective bDMARD-therapy could prevent this unregulated host response towards serious infection. Obviously, it cannot be concluded, from this single study, that bDMARDs should be continued in case of a serious infection (60).
A common situation is that of HBV infection in rheumatic patients candidate to biologic therapy.
Chen *et al.* analysed a group of 123 RA patients with chronic HBV infection (HBsAg positivity) without prophylactic therapy and under immunosuppressive treatment; 36/123 were receiving bDMARDs. 24.4% of patients developed HBV reactivation. They found that glucocorticoid significantly increase the risk of HBV reactivation. Moreover, among bDMARDs, RTX is the one associated with the highest risk of reactivation (61). In a small Taiwanese population of RA patients with previous HBV infection (HBsAg negative, HBcAb positive) treated with RTX, 9% of patients had HBV reactivation, after a mean period of 2 years after starting regular rituximab therapy, without fatal cases. In all the cases described, the discontinuation of rituximab and the administration of antiviral agents resulted in a good prognosis (62).
A recent Italian work found better results in a small group of patients with previous HBV infection (most of which with anti-HBsAg Ab positivity, receiving rituximab for RA without prophylactic therapy (with a median of three cycles of RTX). In fact, they found no cases of seroconversion to HBsAg positivity during RTX therapy.

Only one patient showed a positivisation of HBV DNA, after 6 months of RTX therapy, but he was effectively treated with lamivudine before active hepatitis occurred. However, in 21% of this cohort the authors observed a reduction, and in 2 cases a negativisation, of anti-HBsAg Ab titre. Finally, among 14 patients monitored for 18 months after drug discontinuation no cases of HBV reactivation occurred (63).

A major concern regarding biologic therapy in rheumatic patients is the potential increased risk of malignancies. Some recent publications on cancer risk associated with TNFi seem to indicate that patients without a history of pre-existing cancer have not an increased risk of cancer, although there have been reports of increases in melanoma. But what is the risk for patients who have a history of cancer prior to initiation of TNFi or other biologic therapies? It is usually recommended to avoid the use of the majority of bDMARDs in patients with a recent history of malignancy (less than 5 years), even if there is generally less concern about the use of RTX in these cases. Two previous analyses, one from the British Society for Rheumatology Biologics Register and the other one from the German register, showed that the rate of incident malignancy (IM) in patients with RA and a prior malignancy who receive a TNFi is not increased in comparison with patients receiving csDMARDs. However, these studies were small and only studied cancer risk over a short follow-up period (2–3 years) (64, 65). So, in the last year, Silva-Fernández *et al.* wanted to explore, in a larger cohort and a longer follow-up period, the influence of TNFi and RTX (when administered as the first biologic), compared to csDMARDs, on the incidence of cancer in patients with RA and a prior malignancy. They have shown that, after an average follow-up of 5 years, patients with RA and prior malignancy who receive treatment with either TNFi or RTX in the UK do not have an increased risk of recurrence or development of new IM. However, patients' baseline characteristics were unbalanced between groups, as for site and prognostic factors of previous can-

cer or time from malignancy and initiation of anti-rheumatic treatment. Moreover, it is presumed that patients treated with biologics underwent a more accurate cancer recurrence screening before they started therapy, while this may not be true for patients receiving csDMARDs. So, probably, this could explain in part why a higher rate of recurrence of the same cancer was seen in the csDMARD cohort compared with the TNFi cohort (66). Kim *et al.* focused on the risk of developing high-grade cervical dysplasia and cervical cancer for women with RA who were starting bDMARDs compared to non-biologic DMARDs. They found that initiation of therapy with a biologic DMARD was associated with a numerically although not statistically significant increase in the risk of high-grade cervical dysplasia or cervical cancer, as compared to initiation of a non-biologic DMARD (67).

Therefore, it is not yet possible to draw definitive conclusions on cancer risk related to bDMARDs use, especially in patients with a recent prior malignancy, but globally these latter data seem to be encouraging. New important data are emerging on the safety profile of oral JAK-inhibitors. In particular, we report here the results of two papers, published in the last year, on data derived from phase II, phase III and long-term extension studies on tofacitinib. The first one is on opportunistic infections: TB resulted the most common opportunistic infection in RA tofacitinib-treated patients, but 81% of cases occurred in countries with high background TB incidence rate. Importantly, among patients with latent TB who were treated with concomitant isoniazide, none developed the active infection (68). The second paper explores the malignancy risk under JAK-inhibitors. The overall rates and types of malignancies observed in tofacitinib-treated patients remained stable over time, with increasing tofacitinib exposure and the standardised incidence ratios for all malignancies and selected malignancies were within the expected range of patients with moderate-to-severe RA (69). Treatment with tocilizumab is associated with two peculiar issues

regarding its safety profile. One is the risk of developing lower intestinal perforations (LIPs). Strangfeld *et al.* confirmed, in a real world setting, that the incidence of this complication is higher in TCZ-treated patients than in all other DMARD treatments. In particular, it is thought that it is in patients with prior diverticulitis that the IL6-inhibition may interfere with locally accumulated fat tissue, that cover inflamed diverticula, thus favouring perforation. Moreover, the authors underline that, under TCZ, LIPs may occur with mild symptoms only and without CRP elevation (70). The second warning is the alteration of lipid metabolism, in particular with the increase of LDL cholesterol. So, Kim *et al.* compared cardiovascular (CV) risk among patients who newly started TCZ or TNFi, after a previous therapy with another TNFi, abatacept or tofacitinib. They included 9218 TCZ initiators and 18,810 TNFi initiators and they did not find any evidence of an increased CV risk among patients treated with TCZ *versus* TNFi (71). CV risk profile is an important aspect to consider in RA patients if we think that CV events are the leading cause of death in these patients, probably due to chronic inflammation. Therefore, it could be supposed that therapy with TNFi can improve CV risk through a better control of disease activity. Recent data coming from the British Register for RA show that patients who start therapy with TNFi, compared with biologic-naïve patients who receive csDMARDs only, have a decreased risk of myocardial infarction but no differences emerged as for the incidence of ischaemic stroke. Moreover, therapy with TNFi does not modify the risk of mortality both after MI and after ischaemic stroke (72). It is already known that therapy with Hydroxychloroquine (HCQ) has a positive influence on the CV risk profile of rheumatic patients because of its demonstrated antithrombotic properties and its association with a less atherogenic profile and a decreased risk of diabetes. So, confirming these acquired knowledge, in the last year a large retrospective study demonstrated that HCQ use is associated with a 72% decrease in the risk of incident CV disease in RA patients (73).

Pregnancy

It is not uncommon that RA patients are women of childbearing age that want to become pregnant. Nowadays we know that some therapies are allowed throughout pregnancy with a reasonable safety profile, such as antimalarial drugs and sulfasalazine, while other csDMARDs have to be stopped, like methotrexate and leflunomide. As for bDMARDs, TNFi can be continued during the first half of pregnancy and, if necessary, TNFi with a low rate of transplacental passage (etanercept or certolizumab) may also be used during the third trimester. As for the other bDMARDs, it is currently recommended to discontinue tocilizumab, rituximab, abatacept before pregnancy, due to lack of safety data (74). However, some evidences are emerging. For example, Kaneko *et al.* reported four cases of pregnancy in young women with exposure to TCZ. In these patients the drug was stopped as soon as possible when pregnancy was confirmed. Three patients delivered full-term infants without any adverse outcomes. One patient had a partial molar pregnancy and miscarried during gestational week 11. Two patients remained in clinical remission with low-dose prednisolone or no treatment for RA during pregnancy (75).

Few data are available on the use of tofacitinib too, during pregnancy. The ongoing recommendation is of course to stop this drug before pregnancy, because it is a small molecule and has the potential to cross the placenta. However, some data has been recently reported on the outcomes of pregnancy cases identified from tofacitinib-RCTs or non-interventional studies in patients affected by RA or psoriasis. 47 pregnant women were identified; the majority of them received tofacitinib monotherapy, while 13 received combination therapy with methotrexate. In this small cohort of RA and psoriasis patients, the pregnancy outcomes reported appeared similar to those observed in the general population and in patients treated with biologic therapies for inflammatory diseases. However, definitive conclusions cannot be drawn (76).

New therapies and perspective drugs

In last few years, new acquisitions on RA pathogenetic pathways gave the opportunity to synthesise new target therapies able to modify the natural history of the disease. Several clinical trials demonstrated their safety and efficacy with similar, and in some cases superior, results than the currently available drugs present in the therapeutic armour of the rheumatologist.

In the following paragraphs the most interesting work, published during the 2016 and 2017, on new RA therapies are summarised and grouped based on their specific features.

Anti-JAK

Janus Kinases (JAKs) are a family of four enzymes, non-receptor tyrosine kinases (JAK-1, JAK-2, JAK-3 and TYK-2) that are critical in cytokine intracellular signalling and strongly involved in many inflammatory disease. JAK activation phosphorylates the signal transducers and activators of transcription (STAT) inducing the expression of many genes that several studies have shown to be crucial in the pathogenesis of RA.

• *Tofacitinib*

Tofacitinib primarily inhibits JAK-1 and JAK-3 and it is the first oral targeted synthetic DMARD approved by FDA in 2012, in monotherapy or in association with other cDMARDs, for the treatment of moderate to severe RA in patients with inadequate response or intolerance to methotrexate (MTX). In the last few years, several studies have shown the efficacy and safety profile of tofacitinib in RA patients and it has been included in EULAR 2013 recommendation for the management of arthritis after the failure of at least one bDMARD; furthermore, recent studies tend to confirm RCT Phase II and III results highlighting the efficacy and safety profile of tofacitinib. Yamanaha *et al.* evaluated 308 Japanese RA patients, who had participated in a prior Phase 2 or Phase 3 study on tofacitinib with or without methotrexate, in a long-term extension study (median observation period of 3.2 yrs) administering tofacitinib 5 or 10 mg twice daily. Tofacitinib

confirmed a safety profile (primary endpoint) in term of adverse and serious adverse events (higher risk of herpes zoster infection) and a sustained efficacy (secondary + MTX and biologic + MTX compared to MTX (cDMARD) or placebo, Singh *et al.* performed a large network meta-analysis including 12 RCTs for a total of 3364 patients with RA previously unsuccessfully treated with biologics. Only one study analysed tofacitinib + MTX compared to MTX alone, showing a statistically significant improvement in ACR50 and functional indices measured by HAQ in paients treated with both therapies (39).

• *Baricitinib*

Baricitinib is a new promising therapy for RA, not yet available, but submitted to FDA in early 2016 for approval as an oral treatment for moderate-severe RA. Unlike tofacitinib, it selectively and reversibly inhibits JAK-1 and JAK-2. A recent review by Bindee Kuriya *et al.* summarises the major Phase II and III RCTs evaluating safety and efficacy of the drug: in the Greenwald and Keystone Phase II studies respectively, baricitinib in association with MTX has been statistically more effective in disease control (in terms of ACR20 and ACR50/70 and DAS28 respectively) *versus* MTX + placebo. Common side effects were lipid profile, creatinine and liver enzymes elevations, increased risk of herpes zoster reactivation and 3 cases of serious pulmonary infections. Three phase III RCTs studies evaluated the efficacy of baricitinib in patients with insufficient response to MTX (RA-BUILD study), inadequate response to one or more TNF (RA-BEACON) drugs and patients naive to cDMARDs respectively, comparing its effectiveness with MTX + placebo or MTX alone. All three studies showed statistically significant efficacy of baricitinib in achieving most of the primary and secondary endpoints (ACR20/50/70, reduction of DAS28, CDAI and SDAI and PROs); MTX in combination with baricitinib did not appear to increase the benefit observed with baricitinib monotherapy in terms of response rate. AEs were consistent with phase II studies in terms of severity and rates.

Interesting results came from the last two Phase III RCTs: in the RA-BEAM study, baricitinib + MTX was statistically more effective in disease control in MTX non-responder patients not only compared to MTX monotherapy but also compared to Adalimumab + MTX; furthermore, it is shown to be effective in inhibiting radiographic progression (mTTS <0.5).

Finally, all patients included in RA-BUILD, RA-BEGIN and RA-BEAM studies who had taken baricitinib for at least 15 months at a dosage of 4 mg/day were included in a large study (RA-BEYOND) to assess the efficacy of 4 mg *vs.* 2 mg/day regimen; the reduction to 2 mg/day evaluated at week 12 showed significant increases in disease activity indices (DAS28, CDAI and SDAI score), confirming that the effective dose of baricitinib appears to be not less than 4 mg/day (78). The most recent studies published in 2016 have substantially confirmed the results of previously mentioned RCTs in terms of safety, efficacy, effective dose and comparison with biological drugs.

Tanaka *et al.* demonstrated the efficacy of baricitinib at doses of 4 and 8 mg + MTX confirming statistically significant improvements in disease activity and physical function scores with initial response even at 2 weeks of treatment (79). Fleishmann *et al.* in a recent paper published in March 2017 evaluated the efficacy of baricitinib *versus* MTX monotherapy and baricitinib + MTX on 588 patients enrolled for a 52-week FU. Baricitinib monotherapy (and baricitinib + MTX) resulted not inferior than MTX at 24 weeks with a higher ACR20 response rate and an impressive significant response rate at first week of therapy; furthermore baricitinib seems to be effective also in reducing radiographic progression (80). Similar and encouraging results, in terms of efficacy, come from a new study conduced by Taylor *et al.* and published on NEJM on February 2017, evaluating 1307 moderate to severe RA patients in MTX therapy and randomly assigned to baricitinib, or adalimumab or placebo. Baricitinib reached the primary endpoint of ACR20 response at week 12 and the main 24-week endpoints (significant improve-

ments of DAS28, SDAI, HAQ and x-ray indices scores) compared to placebo; moreover baricitinib showed a statistically significant increased ACR20 response rate at week 12 (70% *vs.* 61%) and similar efficacy in radiographic progression compared to adalimumab (81).

• *Other anti-JAK*
In addition to the two drugs (tofacitinib and baricitinib) mentioned above, new JAK pathway inhibitors with different receptor selectivity are undergoing experimentation. ABT-494 is a selective JAK-1 inhibitor whose efficacy (depending on the daily dosage) and safety have recently been evaluated by a Phase IIb study conducted by Kremer *et al.* in 276 RA patients on MTX and previous inadequate response or intolerance to at least 1 anti-TNF. The efficacy of VX-509 (Decernotinib), a selective JAK-3 inhibitor, was evaluated by Genovese *et al.* in an other phase IIb trial including 358 patients with active RA despite MTX therapy. Both drugs added to MTX have been shown to be effective in satisfying 12 week primary endpoints, demonstrating statistically significant superiority *versus* placebo in terms of ACR20/50/70 and DAS28-CRP responses; furthermore ABT-494 showed (similar to baricitinib) a particular rapid dose-dependent action (in particular for 12 and 18 mg twice daily dosage) and Decernotinib has maintained efficacy up to 24 weeks with doses of 100 mg/day, 150 mg/day or 100 mg/twice daily (82, 83).

From a comprehensive analysis of the studies performed on anti-JAK drugs so far synthesised, we can conclude that small molecules are promising in controlling disease activity in patients who are not responsive to common DMARDs and/or anti-TNFs, in terms of major remission indices and disease activities with a safety profile that is consistent with approved immunosuppressive drugs. The most commonly reported side effects were generalised malaise (nausea, headache), increased levels of lipoprotein (iatrogenic dyslipidaemia), transaminases or creatinine, changes in leukocyte and erythrocytes count, herpes zoster reactivations and airway or urinary tract infection.

Rare cases of severe side effects and no statistically significant correlation with an increased number of malignancies have been reported.

New "old target" therapies
In recent years, scientific research has been used not only in the development of new therapeutic targets for RA treatment, but also in the synthesis of new molecules resulting from the evolution of existing and commercially available drugs. These novel drugs, monoclonal antibodies directed at proinflammatory cytokines and T ore B cell receptors, are distinguished by some features that modify the affinity, selectivity and target exclusivity.

Aletaha *et al.* recently published the results of phase 3 study SURROUND-T for assessing the efficacy and safety of Sirukumab, IL-6 inhibitor, which (unlike tocilizumab) inhibit the cytokine cytokine (not the receptor). In this multicentre, randomised, double-blind placebo-controlled study, 878 RA active patients non-responder to at least one biological drug (especially anti-TNF) were included and randomised to receive 1/3 50 mg of sirukumab every 4 weeks, 1/3 100 mg every 2 weeks and 1/3 placebo (in addition to cDMARDs). Sirukumab has been shown to be equally effective in controlling disease activity compared to placebo in both doses, in terms of ACR20 response rate at 16-week evaluation (primary endpoint); in addition, a good safety and tolerability profile was found for both the dosages (the most common AE was erythema on the injection site) at 52 week evaluation (84). A new similar anti IL-6 antibody is undergoing testing; olokizumab is a humanised antibody directed against cytokine (like sirukumab) which acts by blocking selectively the final assembly of the signalling complex responsible for mediating pro-inflammatory response. Takehuchi *et al.*, in a double-blind, placebo-controlled phase II trial, assessed drug efficacy and safety on a population of 119 active Asian RA patients who had previously failed anti-TNF therapy. 88.2% of patients completed the study after being randomised to receive olokizumab 60 or 120 or 240 mg every 4 weeks, or 60 or

120 mg every 2 weeks, or placebo. Primary endpoint (reduction of DAS28-CRP at week 12) was achieved in the three groups of patients undergoing therapy every 4 weeks and ACR20 and ACR 50 response for all drug portions were demonstrated. There was no significant differences in AEs rate between treated patients and placebo control group (85). Similarly to anti-IL6 drugs two new anti-CD20 biological drugs are being tested. Ocrelizumab, a humanised antibody recently approved by the FDA for the treatment of multiple sclerosis with apparent greater B-depleting effects than rituximab, has been the subject of recent clinical trials in rheumatoid arthritis. Abushouk et al. in a recent meta-analysis (4 RCTs for a total of 2230 active RA treated patients) showed that ocrelizumab + MTX was more effective than placebo + MTX at 24 weeks (ACR20/50/70 response rate, DAS28-ESR and Radiologic progression score improvements) (86). Ofatumumab is a new anti-CD20 biological drug that specifically targets a membrane-proximal epitope on the CD20 molecule distinct from other anti-CD20 antibodies including rituximab and ocrelizumab. Compared with other anti-CD20 antibody, it is associated with increased binding of C1q and more potent complement-dependent cytotoxicity. In a recent review by Pers et al., the authors confirmed the efficacy of the drug in disease control in patients with insufficient response and/or intolerance to cDMARDs and biological drugs therapies; the best results at 24 weeks were obtained in patients not previously treated with anti-TNF and anti-CCP positive (as expected) (87). Both drugs showed a good safety and tolerability profile in terms of AEs, counterbalanced by more infusional reactions than placebo. In the near future we will have the results about the potential efficacy of a new monoclonal antibody, ASP2409, which inhibits the co-stimulation of T cells (similar to abatacept), characterised by increased avidity and selectivity for CD86 binding. Phase I study results published by Zhang et al. are encouraging regarding safety and tolerability profile in patients with RA in remission with MTX (88). For

many authors, one of the most interesting frontiers in the field of rheumatoid arthritis biological therapies is the possibility to act on more than one target of the immune and inflammatory response at the same time. Of course, no clinical study to date has provided more than one biotechnology drug for the obvious and unpredictable risks for the patients. A new interesting molecule is undergoing animal testing on CIA mice; it is a recombinant IgG-like bispecific antibody acting as interleukin-1β and interleukin-17A inhibitor (FL-BsAb1/17). This molecule has been shown to be effective in clinical control of joint manifestations in CIA mice and also in reducing arthritic histopathological alterations at synovial, cartilage and bone levels compared to monovalent inhibitor (anti IL1 or anti IL17). In addition, FL-BsAb1/17 was more potent in inhibiting IL-1β, IL-17A, IL-6, TNF-α and anti-CCP antibody in the serum and in down-regulating the expression of IL-1β, IL-17A, IL-6, TNF-α, MMP-3 and RANKL in the spleen, furthermore it seems to decrease the production of IL-6 induced by IL-1β and/or IL-17A in fibroblast-like synoviocytes derived from RA patients (89).

New target therapy for RA
The role of IL-17 in the pathogenesis of RA inflammation has been documented by several studies, which also confirmed increased IL17 levels in joints and blood of affected patients correlated with the disease activity (90, 91). In a recent review conducted by Kunwar et al. and published in August 2016, the authors tried to evaluated efficacy and safety of anti-IL-17 agents in the management of RA analysing the results of the studies presented in literature. Meta-analysis included 7 studies for a total of 905 RA patients undergoing anti-17 and 321 placebo-treated patients; the analysis of the results showed a good efficacy in achieving ACR20 and ACR50 and a favourable trend for ACR70 responses with an excellent safety profile (no increase risk of any or serious side effects). However, separating the result for specific anti-IL17 drug, ixekizumab proved to be statistically more effective than placebo in reaching pri-

mary endpoints, whereas secukinumab showed only a tendency toward achieving ACR20 response and brodalumab showed no superiority *versus* placebo (92). These results have been substantially confirmed in two recent studies conducted on ixekimumab and secukinumab respectively. In the first study, Genovese et al, included 201 biologic-naive and 99 biologic non-responder RA patients who had completed the 16-week double-blind period of a phase II study for an additional 48 weeks of ixekizumab treatment. Ixekizumab was well tolerated and safety profile were consistent overall with those in the double-blind period of this study; clinical improvements (ACR 20/50/70 and DAS28-CRP) observed with ixekizumab were similar to the 16 week prior phase and maintained or improved in the next phase of 48 weeks treatment (93). In the second phase II randomised study, lead by Tlustochowicz et al., secukinumab administered with IV o subcutaneous loading regimen *versus* placebo in active RA patients did not achieve primary endpoints at 12 week (ACR 20); however, considering all patients undergoing both secukinumab therapeutic regimens, it proved to be statistically more effective than placebo in reducing DAS28, PGA and PhGA and CRP levels (secondary endpoints) (94).

New potential therapies:
mesenchymal stromal/stem cells
Over the last 30 years, immunosuppressive and immunomodulatory therapies have radically changed natural history and the prognosis of patients with rheumatoid arthritis; however, as claimed by many studies and clinical trial results, about 30 percent of the affected population does not respond to therapies (cDMARDs and biologics). One of the most fascinating future challenges in the panorama of rheumatoid arthritis therapy is to induce a profound modification of the immune system to restore naive immune tolerance and also avoid bone and subclinical cartilage damage. Important results were obtained on stromal mesenchymal stem cells *in vitro* studies, on RA animal models and on few phase I and II RCTs in RA

patients who were resistant to conventional therapy; as described by Ansboro *et al.* in a recent review on the state of the art, potential applications of cell therapy with stromal mesenchymal stem cells (MSCs) are multiple and act on various targets of rheumatoid arthritis (95). To date, many *in vitro* and animal models have been performed to demonstrate the ability of MSCs to act as immunomodulants and to restore a form of immune tolerance, with the final result of "extinguishing" one of the major aetiopathogenetic mechanisms that support the immune system activity and therefore RA damage. In fact, MSCs can regulate inflammation via both the adaptive and innate immune response, through inhibition of T-cell proliferation and function, induction of regulatory T cells (Tregs), suppression of B-cell proliferation, differentiation, and immunoglobulin production, suppression of dendritic cell maturation, promotion of macrophage polarisation towards an anti-inflammatory phenotype and suppression of natural killer cells. Immunomodulation by MSCs is mediated via both direct cell–cell contact and secretion of soluble factors such as prostaglandin E2, indoleamine 2,3-dioxygenase (IDO), nitric oxide, and interleukin-10 (IL-10), released in response to stimulation by interferon (IFN)-γ from activated immune cells. Other animal model studies have demonstrated the ability of MSCs to improve joint erosive damage by promoting cellular regeneration, but above all by acting on the above immunomodulation systems. Currently several studies are ongoing, providing infusion of MSCs to patients with refractory rheumatoid arthritis and/or intolerant to DMARDs and biological drugs to assess their safety profile and tolerability. In particular, a study of phase Ib/IIa by Alvaro Garcia *et al.* evaluated the safety and tolerability of the intravenous administration of Cx611, a preparation of allogeneic expanded adipose-derived Stem cells (eASCs), in patients with refractory rheumatoid arthritis (RA). The results obtained in 53 patients showed that the Cx611 infusion was substantially well tolerated in the absence of dose-dependent toxicity (at 1 million/

kg, 2 million/kg, 4 million/kg dosage) and it also seems to be a trend in terms of efficacy (ACR 20) at 1 month and 3 months evaluation (96).

New potential therapeutical approaches: nanoparticles and nanocarriers
Limits to current therapies used in the control of rheumatoid arthritis are multiple and depend on various mechanisms, justifying the percentage of patients still not responding. Among the major drug and patient-dependent factors: limited bioavailability and high clearance of the drug, requiring high dosages and frequency of administration able to induce side effects and unjustified iatrogenic damage. One of the most futuristic and promising novelties in the field of rheumatoid arthritis therapy is not based on new target molecules or antibodies that can immunomodulate or down regulate the inflammation system, but on the possibility of increasing the effectiveness of rheumatoid arthritis drugs already existing through particularly small carriers. Nanocarriers are small molecules (1-1000 nm diameter) consisting of micelles, polymers, carbon-based materials, liposomes, which confer particular biological properties to the molecule (hydrophilia, hydrophobia, resistance to liver or kidney clearance, selectivity for organs, tissues and cells). Therapeutic agents (properly loaded inside the carrier) can be selectively delivered to and accumulate in the inflamed sites *via* passive or active targeting of nanovehicles after systemic administration. For one thing, damages to other organs caused by off-target distribution are remarkably reduced and nanovehicles encapsulating the therapeutic agents protect them against biodegradation, leading to sustained drug release and prolonged circulation kinetics. Yang *et al.*, in an interesting review published in February 2017, describes the state of the art on nanocarriers in the treatment of rheumatoid arthritis *in vitro* and *in vivo* studies on cells and animal models of arthritis (CIA – collagen-induced arthritis mice) (97). Two examples of the interesting skills of nanocarriers are cited below. Heo *et al.* demonstrated

the ability of an anphiphilic polysaccharide molecule loaded with Methotrexate to be selectively incorporated into activated CIA mice macrophages 12 times more than macrophages of healthy mice (98). Similar results from a review conducted by Nogueira *et al.*, in which potential drug application in nanocarriers is described by receptors for folic acid (folate receptor beta -FR beta); these receptors seem to be particularly expressed on the membrane of the activated macrophages, allowing not only the drugs loaded to be selectively incorporated by the inflammatory macrophages, but also to avoid the clearance of the monocyte-macrophage system (99).

Conclusions
In the last two decades, advances in pathophysiology have allowed to develop new target therapies in order to modify the natural history of RA. Several clinical trials in this last year have shown how the available RA therapies are effective in the vast majority of patients, ensuring a significant reduction of symptoms, radiographic progression and thus improvement in quality and life expectation; furthermore, powerful clinical and laboratory efficacy of targeted therapies seem to be counterbalanced by good safety profiles, also for the new therapies in the rheumatologist's armor such as small molecules (anti-JAK therapies, JAK inhibitors) (100). Further studies will be needed to identify peculiar RA patient subsets deserving of specific target therapies in order to optimise and maximise the clinical response and prognosis.

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