Review

One year in review 2016: 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 (1-3). 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 to follow specific strategies: to start an early aggressive treatment, to target remission and to maintain a tight control (4-7).

DMARDs

In the last few years the treatment of RA experienced a meaningful shift towards biological response-modifiers, though the conventional disease-modifying anti-rheumatic drugs (DMARD), alone or in combination, still represent the first therapeutic approach (8-12). Among traditional DMARDs, methotrexate (MTX) is considered the anchor non-biological drug in RA treatment (13), because of its established long-term safety and clinical efficacy. Indeed, according to EULAR recommendations, MTX should be included in the first line treatment for active RA patients (14). Anyway the effectiveness of MTX seems to be influenced also by its way of administration, as recently demonstrated in a multicentre prospective cohort study on early RA patients (15). In this work, Hazlewood *et al*. observed that patients initially treated with subcutaneous (sc) MTX showed a longer adherence to treatment, an improved disease control and a lower rate of treatment failure compared with those obtained by oral MTX administration. Moreover, the cases of treatment failure were only due to its clinical inefficacy, since the toxicity profile was the same for the two ways of administration. Authors hypothesised that these findings may be related to the different bioavailability of the two ways rather than to a higher starting dose of sc MTX. Indeed, with a dose of MTX exceeding 15 mg/week its oral bioavailability tends to plateau, while the sc one continues to increase.
The success of RA therapy seems to be influenced by the treatment onset time and also by the intensity of the regimen adopted, even in early clinical settings. Thus, the "treat-to-target" strategy is widely considered the best practice in RA management. When MTX alone is not able to induce disease remission, current guidelines propose an early, intensive and to-treat combination strategy to improve clinical outcomes. In the CareRA trial (16) the clinical efficacy and the safety profile of different DMARDs with GCs bridging strategy were assessed in early RA patients after sixteen weeks from the baseline. Ver-

schueren *et al*. arranged the patients in high or low disease activity according to ordinary prognostic markers (bone erosions, rheumatoid factor and/or anticitrullinated protein antibody, and disease activity score based on C-reactive protein). Then the high-risk RA group was randomised into three arms: the COBRA Classic one which consisted of 15 mg MTX weekly, sulfasalazine daily and a weekly high step-down scheme of oral GCs; the COBRA Slim one with 15 mg MTX weekly with a moderate weekly step-down scheme of oral GCs; the COBRA Avant-Garde group, in which 15 mg MTX weekly, 10 mg leflunomide daily and a weekly step-down scheme of oral GCs were prescribed. After sixteen weeks of treatment, Authors found that rate of remission (defined as DAS28-CRP <2.6) was slightly higher in the Slim group (73.6%) rather than in the Classic (70.4 %) and Avant-garde (68.1%) ones. These results demonstrated that MTX combined with a moderate step-down dose of GCs was as clinically effective as DMARD combination therapies with moderate or high step-down GC doses in leading to remission. Furthermore, the numbers of adverse events observed in COBRA Slim patients were half as much as those registered in the Classic and Avant-garde ones. The same authors focused their researches on low-risk patients, who did not present the aforementioned poor prognostic markers (17). In this study 90 patients were randomised to 2 groups: the MTX tight step-up (MTX-TSU) group was administered only 15 mg weekly of MTX, while the COBRA slim one took 15 mg of MTX weekly with a step-down scheme of daily oral GCs. After 16 weeks, the rate of remission was higher in COBRA Slim patients rather than the one reached under MTX-TSU treatment (65.1% *vs*. 46.8% respectively) without notable differences in terms of side effects. Thus the study contributes to stress out the role of GCs in inducing remission, and in controlling inflammatory processes and radiographic progression in RA patients. Anyway safety concerns limit their long-term use, despite the lack of clear evidences.

The contribute of MTX to novel DMARDs is further highlighted in a recently published review (18), in which Buckley *et al*. found that the effectiveness of anti-tumour necrosis factor agents (anti-TNF) was strengthened by the combined use of MTX, as demonstrated by the greater ACR responses obtained with this scheme rather than with anti-TNF monotherapy.

Tacrolimus (TAC) is an another immunosuppressive drug that blocks T-cell activation by specifically inhibiting calcineurin pathway. It is approved in Japan for the treatment of RA since 2005 as an adding option of treatment in patients inadequately responsive to biological DMARDs. Recently, Ishida et.al carried out a post marketing surveillance of TAC in addition to biological DMARDs in 172 RA patients who previously did not achieve an adequate response to biological anti-rheumatic modifiers. With a mean dose at baseline of 1.1 mg/day, that was titrated up to 1.4 mg/day at week 24, remission or low disease activity was observed in 58.5% of the patients, while only the 10.5% of them presented at least one adverse event. Abdominal pain, stomatitis and malaise occurred at least twice, but none of them reached a significantly high incidence. (19).

Leflunomide (LEF) has been proposed as a pivotal drug in RA management, on a par with MTX alone in terms of clinical tolerability. Furthermore LEF has been showed to prevent and control radiological progression. It is now known that Leflunomide exerts its function when its blood concentration is above 13 mg/L, concentration that can be reached by a daily administration of 10 mg/day. Considering the long Leflunomide half-life (around 15 days) Ren *et al*. investigated its efficacy and safety on weekly administration (50 mg/week, LEF50) compared to the daily dose (10 mg/day, LEF10) in a group of 244 early RA patients with mild or moderate disease activity (20). After 24 weeks the EULAR response of LEF50 (good + moderate responses) was 59.5%, while the LEF10 one was 53.4%. As far as the adverse events, their rates were respectively 19% and 26,3 % in LEF50 and LEF10 treatment arms. Overall these results demonstrated similar clinical advantages for the weekly and daily administration.

However, since the use of many conventional DMARDs is increasingly burdened by side effects or clinical inefficacy, novel anti-rheumatic drugs have been developed in order to overcome these limitations (21). Among these, Iguratimod (IGU, also named T-614) represents a new synthetic DMARD recently developed in Japan and daily prescribed since 2012. IGU exerts its action by the inhibition of the inflammatory cytokines (TNF-α, interleukin (IL)-1 β, IL-6, IL-8 and IL-17), suppressing immunoglobulin production and TNF-α-induced nuclear factor-kappa B activation (22). IGU also produces anabolic effects on bone metabolism by means of osteoblasts stimulation and osteoclasts inhibition (23). This is confirmed in a recent *in-vitro* study (24) in which Wei *et al*. showed the IGU inhibitory effect on the IL-6-Induced RANKL/OPG, IL-17, and MMP-3 expression in RA synovial fibroblasts patients. All these mechanisms are clinically related to a reduction of bone erosions and joint degradation in RA.

Several recent trials were carried out to assess clinical efficacy of iguratimod, both taken alone or combined with the more traditional MTX (21-23, 25, 26). In a recent work (23) Duan *et al*. split 60 patients in two groups, who were treated with MTX+IGU and MTX alone respectively. The dosage orally administered to the patients was 50mg/day of IGU and 10mg/week of MTX for the first 4 weeks, increased up to 12.5mg/week for the remaining 20 weeks of treatment. The results showed a statistically significant higher reduction of various disease activity markers in the IGU+MTX group compared to that achieved in the MTX group. Additionally, the rate of adverse events was comparable among the two groups. Thus the MTX+IGU combined treatment was deemed to be more advantageous than MTX therapy alone.

The benefits of combined IGU and MTX treatment were further assessed in the following two works. In a retrospective observational study (26), Yoshioka

et al. registered notable improvements in disease activity since the eighth week relative to baseline of iguratimod with methotrexate treatment.

Xia *et al*. (21) demonstrated the greater efficacy of IGU+MTX therapy rather than MTX or IGU treatments alone. Their 24-weeks prospective trial involved 150 patients previously treated with traditional DMARDs who were randomised in three groups, treated with IGU+MTX, IGU alone or MTX alone respectively. The dosage of IGU was of 25mg twice a day, while that of MTX was of 10mg/week. The trial showed an increased rate of ACR20 and ACR50 after 24 weeks in the IGU+MTX patients compared with those of the other two groups. Also many other clinical and disease markers resulted to be significantly lower in the combined therapy (MTX+IGU) group than those observed in monotherapy (MTX or IGU) ones. Conversely, the risks of infections and liver damage were not increased in the double treatment patients. These results suggested that a combined therapy is more effective than the two drugs taken alone, but equally safe.

The use of IGU as a daily treatment of RA over 24 and 52 weeks has been assessed by Okamura *et al*. (22),(26) in a trial on 41 patients. The investigation has shown a remarkable decrease of DAS28-ESR, DAS28-CRP, SDAI, CDAI at 24 weeks and 52 weeks, but no significant reduction of CRP and ESR was observed. In the abovementioned research carried out by Yoshioka *et al*. (25) the efficacy of IGU treatment alone was observed from the twelfth week from the beginning of the therapy. In the same work the authors also proposed to evaluate effectiveness of IGU treatment after a time span of 12 weeks from the beginning of the therapy.

Taken together the presented results seem to show a higher clinical efficacy of combined iguratimod-methotrexate treatment compared to MTX alone both in untreated patients (23) and in those where MTX was ineffective (21). However, IGU alone still seems to be a promising alternative in case of MTX failure or related adverse events.

Biologic agents in RA

Short- and long-term outcomes have improved dramatically in RA since the introduction of biologic agents in 1998 with a significant reduction in disease activity, radiographic progression, health-related quality of life (HRQoL), and need for orthopedic procedures or mechanical aids/devices (27, 28, 29). With the approval of tumour necrosis factor(TNF)-α inhibitors (infliximab, etanercept, adalimumab, certolizumab, and golimumab), rituximab and other biologic agents (abatacept, tocilizumab, and anakinra), seminal advances in treatment options were made, and their efficacy was convincingly shown in randomised clinical trials. However, questions to be answered about the management of RA patients treated with biologic agents are still numerous. In this regard, the American College of Rheumatology has developed a new 2015 RA pharmacologic treatment guideline also addressing the use of biologics, clinical management of high-risk populations and the use of vaccines in patients receiving such therapies. Among other things, guidelines recommend that patients failing synthetic disease-modifying anti-rheumatic drugs (DMARDs) monotherapy and still showing moderate to high disease activity should be treated either with a combination of traditional DMARDs, or with a TNF inhibitor with or without methotrexate, or with a non-TNF-inhibitor with or without methotrexate, or with the janus kinase inhibitor tofacitinib plus methotrexate. Patients failing a first anti-TNF agent could receive another TNF inhibitor with or without methotrexate or a non-TNF-inhibitor with or without methotrexate. Conversely, those failing many TNF inhibitors should receive a non-TNF-inhibitor with or without methotrexate or tofacitinib with or without methotrexate. When both a TNF inhibitor and a non-TNF-inhibitor prove to be ineffective, another non-TNF-inhibitor with or without methotrexate or tofacitinib with or without methotrexate should be employed. Patients failing treatment with several non-TNF-inhibitor biologics should receive tofacitinib with or without methotrexate or a TNF inhibitor with or without methotrexate (30).

Anti-TNF agents

Efficacy

During the period covered by the present review, many studies have confirmed benefits resulting from long-term anti-TNF treatment. Among these, a retrospective study on 1754 RA patients from the British Society for Rheumatology Biologics Register compared subjects treated with synthetic DMARDs to patients using etanercept thus finding that patients undergoing TNF inhibition showed a significantly reduced disease activity and a better HRQoL after 6 months of therapy despite a significantly higher disease activity at the time of biologic initiation. Disease remission occurred more often in patients administered with etanercept and progression occurred more likely among subjects treated with DMARDs. Conversely, the group treated with etanercept showed a significantly higher incidence of serious infections and central nervous system events (31).

Another 52-week randomised study on 194 RA patients with mostly moderate disease activity at baseline randomised 1:1 to the anti-TNF agent certolizumab pegol or placebo showed that TNF inhibition was able to induced low-disease activity or remission in the majority of patients treated in combination to DMARDs. Specifically, at 24-week follow-up visit patients treated with certolizumab pegol met the primary endpoint consisting of a stable clinical disease activity index (CDAI) ≤2.8 and reached low disease activity more likely than subjects administered with placebo. Moreover, the disease activity score in 28 joints (DAS28) and the simple activity index (SDAI) remission rates as well as the assessment questionnaire disability index (HAQ-DI) were significantly higher with certolizumab pegol than placebo group. However, after certolizumab pegol withdrawal at week 24, only 3/17 patients maintained CDAI remission until week 52 among patients completing the study period, suggesting that this agent cannot be withdrawn in patients achieving remission (32).

As regards the issue of biologic dis-

continuation, an indirect index of drug effectiveness, a large meta-analysis on RA patients from world registries and health care databases observed that the overall discontinuation rates of anti-TNF agents at six months, 1, 2, 3 and 4 year follow-up were 21, 27, 37, 44 and 52%, respectively. Interestingly, etanercept was burdened by a significantly lower discontinuation rate at 3 and 4 years follow-up compared to infliximab and adalimumab (33). In line with these findings, a further study has recently observed that the drug retention rates at 6-month follow-up were similar for the different biologics (about 80%), with the exception of infliximab, which showed a significantly poorer drug adherence (34).

Another interesting study measuring the impact of combined etanercept and methotrexate therapy on work productivity in patients with early RA found a significant productivity gain during a 52-week follow-up. In particular, both absenteeism and presenteeism showed a declining trend, total costs of lost productivity decreased, patients gained paid and unpaid work productivity and the percentage of subjects stopping work because of their health became smaller (35).

Finally, according to an indirect pairwise meta-analysis aimed at evaluating the comparative efficacy of biologic agents, etanercept 50 mg weekly showed to be significantly favoured in achieving ACR20 response rate compared to adalimumab, golimumab 50 mg monthly and infliximab; regarding ACR50 response rate, etanercept tended to work better than other TNF blockers, while no differences were observed among different biologics for ACR70 and ACR90 response rates (36).

Safety

Infections and malignancies represent the most important factors taken into account for the evaluation of safety in patients treated with TNF inhibitors. Indeed, inhibiting TNF may impair the effectiveness of the host immune function leading to an increased risk of infections on a hand and to a reduced immunological surveillance against neoplastic cells on the other.

Regarding infections, beyond the use of immunosuppressive drugs the higher incidence of infectious events in RA patients may be related to the disease itself, to the presence of comorbidities, and to the administration of corticosteroids. Concerning this last point, corticosteroid use has been found to represent a risk factor for infections in patients treated with infliximab especially when steroids are administered at a dosage >5 mg/day. Consequently, the Authors concluded that corticosteroids should be used for the shortest period possible when administered concomitantly with anti-TNF agents (37).

A retrospective cohort study using Medicare data in order to determine differences in the risk of hospitalised infections between specific biologic agents in RA patients pointed out that 12-month risk was significantly higher for infliximab and etanercept compared to abatacept among patients treated with anti-TNF agents. However, significant differences were highlighted also for other TNF inhibitors when patients were treated for more than 12 months (38). According to another study with a similar aim, patients treated with adalimumab showed a somewhat higher risk of serious infectious events compared to etanercept and infliximab (39). Otherwise, an interesting study by Richter *et al*. aimed at evaluating sepsis outcome in RA patients affected by serious infections showed that the risk of sepsis and mortality was significantly reduced in patients exposed to TNF inhibition (or other biologics) compared to patients treated with synthetic DMARDs at the time of the infection (40).

Neoplastic risk represents the other crucial point in the evaluation of the safety profile of anti-TNF agents. Indeed, immunosuppression is an established risk factor for virus-associated cancers and can reduces immunological surveillance against neoplasms; nevertheless, whether the inhibition of TNF increases the incidence of malignancies is still matter of debate and current data are conflicting. Specifically, available data support the evidence of an increased risk of non-melanoma skin cancer in RA patients treated with anti-TNF agents compared to those administered with synthetic DMARDs (41). Accordingly, Scott et al have recently pinpointed that methotrexate use itself is associated with an increased risk of second non-melanoma skin cancer in RA patients, however the addition of TNF inhibition seems to further increase this risk (42).

According to the Australian Rheumatology Association Database no overall increased risk of malignancy was identified in RA patients undergoing anti-TNF treatment compared to both patients never treated with biologic agents and general population. Conversely, the relative risk of female breast cancer was reduced among patients administered with anti-TNF therapy compared to the group of patients never treated with biologics, while the risk of melanoma was increased for both groups compared to general population regardless TNF inhibition (43). Accordingly, data from British Society for Rheumatology Biologics Register also suggested no difference in the risk of solid cancer for patients administered with TNF inhibition compared to patients treated with synthetic DMARDs regardless the specific anti-TNF employed (44).

Concerning virus-induced cancers, a Sweden nationwide register-based cohort study examined the risk of cervical neoplasia in 9.629 women with RA undergoing a first TNF inhibitor compared to biologics-naive RA female patients and to general population. Study results showed that patients with anti-TNF therapy were not at increased risk of cervical intraepithelial neoplasia (CIN) grade 1, but were at increased risk of CIN 2-3 and of invasive cervical cancer compared with patients never administered with biologics. However, regardless of screening differences among groups, biologics-naive patients were at greater risk of CIN 1, 2 and 3, but not of invasive cervical cancer when compared to the general population, thus inducing the Authors to conclude that all women with RA are at elevated risk of cervical dysplasia beyond TNF inhibition and that the role of anti-TNF agents was not fully disentangled from bias factors and casuality in this study (45). Also head and

neck cancers (HNC) have been studied in AR patients undergoing anti-TNF treatment. In fact, HNC are strongly associated with human papilloma virus infection and immunosuppression could affect the natural history of the cancer. Nevertheless, a recent study on RA patients with HNC suggested that TNF inhibition could not be associated with an increased risk of recurrences or HNC-related death, suggesting that anti-TNF agents may be safe in patients with previous HNC especially when the time interval between HNC treatment and non-recurrence increases and with close monitoring. Advanced stage disease represented an adverse factor for recurrences and death, while radiation therapy and surgery were protective (41).

In the context of safety profile, the association between TNF inhibition and risk of ictus has been recently studied showing that TNF agents seem to not influence the occurrence of ischemic stroke in the medium term, while the impact on mortality appears inconclusive at both 30-days and 1-year evaluations (46).

Choosing anti-TNF agents in clinical practice

Several variables may influence the choice of biologic agents, including the efficacy and safety, the route of administration, the need for monotherapy, comorbidities, fertility status, and costs. In order to provide an evidence-based decisional tree for the selection of the first line biologic therapy, the Italian board for the TAilored BIOlogic therapy (ITABIO), a multidisciplinary expert task force, has recently published a systematic review aimed at analyse factors impacting with the biologic choice. Authors concluded that no driving biologic choice indicators could be identified in terms of clinical response, radiological progression and functional status. However, anti-TNF inhibitors should be employed in women at pregnancy risk; etanercept can be secondarily chosen in patients with latent tuberculosis after abatacept and tocilizumab. In addition, anti-TNF therapy should be preferred in patients with cardiovascular disease risk and when monotherapy is required in patients not eligible for abatacept and tocilizumab (47).

However, beyond evaluation of patient characteristics, disease activity, and local context, physician preference represents an important determinant in the decision of biologic drugs, as observed by Kalkan *et al*. on a cohort of 4010 RA patients (48).

Tapering anti-TNF agents

To date, establishing whether and when to taper biologic treatment in RA patients with complete disease control represents an important issue in routinely clinical practice. For this reason, recent research efforts have been geared to disclose this crucial point in order to reach a better patient's management. According to a systematic review of 41 publications, escalation of TNF inhibitors occurred more frequently with infliximab (ranging between 0% and 80%) and less frequently with etanercept (ranging between 0% to 22%), while tapering occurred in 7.5% to 36% of cases treated with adalimumab. However, the Authors noted that tapering doses induced an increase of RA-related and total costs (49). Another recent meta-analysis performed on 10 studies de-escalating TNF blockers identified an overall flare rate of 0.33 at 1-year follow-up in patients with low disease activity or in remission at the time of tapering. Radiological progression after de-escalation was low, but could increase slightly. However, on this last point the Authors specified that studies included were not powered to detect differences in radiological progression and adequate randomised controlled studies are required (50).

On the issue of treatment tapering, a prospective long-term follow-up study has recently evaluated the effects of half-dose etanercept (25 mg/week) in patients with clinical remission (DAS28<2.6) while on treatment with etanercept 25 mg bi-weekly. At last follow-up visit (18±11 months), 81.8% of 159 patients maintained remission for a mean period of 3.6±1.5 years, while radiographic progression was not statistically different when compared to patients administered with etanercept 25 mg twice weekly (51).

Another study investigating whether clinical and ultrasound assessment can select individuals suitable for anti-TNF tapering found that DAS28 and power Doppler ultrasound remission was maintained by 63% of 70 enrolled patients at 6 months follow-up, and by 34% at 18 months follow-up. Interestingly, the addition of power Doppler ultrasound evaluation allowed to recognise 8 patients with subclinical active disease not otherwise identified. Patients with negative rheumatoid factor and a low disease activity at initiation of anti-TNF therapy had lower probability of running into a flare (52). Concerning anti-TNF discontinuation, Kavanaugh *et al*. found that benefit after cessation of therapy therapy was maintained for more than 12 months in 73.4% out of 717 patients and in 42.2% through 24 months. Multivariate analysis highlighted that lower disease activity, less pain and better functional status at the time of anti-TNF therapy discontinuation represented predictive factors of maintaining clinical benefit. Conversely, RA disease duration did not have a role in preserving clinical benefit (53).

Switching practice

According to a retrospective cohort analysis of 9567 RA patients, switching to other TNF-α inhibitors is a common practice for rheumatologists. In particular, 36.7% of patients who had switched to a second anti-TNF-α agent switched again to a third-line TNF inhibitor during a 12-month follow-up; this percentage decreased to 27.6% among patients who had previously switched to non-TNF inhibitors. However, switching to non-TNF inhibitors was associated to higher all-cause costs especially related to outpatient biologic-administration visits (54). Accordingly, a study by Rashid *et al*. on 2171 RA patients found that switching to a different biologic agent had mean total RA related costs 25% higher compared to patients who did not switch. In this study, factors statistically associated with switching included female gender, obese weight, prior corticosteroid use, and etanercept as initial biologic agent (55).

A further study on 4700 patients evaluated the impact of previous biologic treatments on the effectiveness of therapy with adalimumab. The Authors observed that baseline disease activity correlated with the number of past biologic agents, while therapeutic response decreased. At the 12-month follow-up on adalimumab therapy, patients with no previous biologic agents showed the best outcomes and the group with at least two prior biologic agents had the worst response. Consequently, prior biologic therapy appeared as a significant negative predictor factor of response to therapy (56). Conversely, based on a cohort of 7052 RA patients treated with a first-ever TNF inhibitor, Chatzidionysiou *et al*. found that switching to a second anti-TNF agent after loss of efficacy or intolerance of the first TNF blocker can lead to significant clinical improvements, with almost 40% of patients achieving low disease activity or remission. In particular, best results were observed when patients switched from infliximab or adalimumab to etanercept after secondary inefficacy, while poorer results were obtained after primary efficacy (57).

Compliance to treatment

Good compliance to therapy is a crucial point to adequately obtain an optimal clinical response. On this issue, by using the 4-item Morisky Medication Adherence Scale questionnaire, Salaffi et al found that 20.6% of 209 patients administered with anti-TNF treatment were non-adherent to their medication at 12-month follow-up. In particular, low disease activity, higher patient-physician discordance, an older age, and a high number of comorbidities were significantly associated with poor compliance (58).

Non-TNF biologic agents

Tocilizumab

Tocilizumab (TCZ), a humanised monoclonal anti-interleukin-6 receptor antibody, has proven to be efficacious in patients who did not respond to methotrexate or other syntetic DMARDs as well as after failure to respond to anti-tumour necrosis factor (anti-TNF) (59, 60). These findings have led to the inclusion of TCZ in the algorithm of RA management as first-line biologic DMARDs after MTX failure similar to TNF antagonists or abatacept. Interleukin 6 (IL-6) plays a pivotal role in RA pathogenesis and has been implicated in the development of systemic symptoms and signs (as fatigue, pain, anemia) but also local inflammation, pannus formation and bone resorption leading to joint damage (61) Nowadays are available two formulations of TCZ and intravenous (IV) the first approved for RA treatment, and subcutaneous(SC); the long-term efficacy and safety of TCZ-SC was maintained and comparable to that TCZ-IV, except for injection site reactions which occurred more frequently in patients receiving TCZ-SC (62). Most international guidelines recommended the use of bDMARDs in combination of MTX or other sDMARDS based on the observation that MTX enhances the efficacy of TNF antagonists in both clinical trials and observational studies (63, 64). However, three trials have demonstrated the efficacy and safety of TCZ monotherapy in patients with RA (65-67). The results of these studies showed that, when considering some endpoints, the combination with MTX offered some advantage over TCZ as monotherapy in terms of archieving low disease activity at week 24 and in suppressing radiographic progression at week 52 even if both strategies were associated with meaningful clinical and radiographic response (66, 68, 69). The possibility to use a single therapy is a critical challenge for old patients with a lot of comorbidities or in case of MTX intolerance, therefore a question arises if addition of TCZ to MTX or switch from MTX to TCZ is comparable. In a recent phase III trial, has been evaluated the efficacy of inhibiting IL-6 signalling in a population consisting exclusively of MTX- and bDMARDs-naive patients with early RA (≤2 years' duration), demonstrating that TCZ is effective in combination with MTX and as monotherapy for the treatment of such patients (70), in accordance with the previous results. They included 1157 patients and randomly assigned TCZ+MTX, TCZ+placebo or MTX+placebo and found that significantly more patients receiving TCZ+MTX or TCZ alone archieved DAS 28-ESR remission at week 24. Interesting, the group TCZ+MTX showed the best outcomes across all efficacy measures at week 52, particularly concerning the radiographic progression. A 24-week large open-labelled study comparing the efficacy and safety of TCZ used as monotherapy or in combination with sDMARDs in 1681 patients with RA with inadequate response to sDMARDs or anti TNF inhibitors, confirmed that TCZ had comparable efficacy and safety when used as monotherapy or in combination with other sDMARDs (71). Kaneko *et al*. compared the efficacy and safety between TCZ added to MTX or switched from MTX in patients with active RA and the results suggest that TCZ added to MTX is clinically and radiographically superior than TCZ alone but the adverse events (not serious AEs) were higher with the add-on strategy (72). Gabay *et al*., analysed data from several European registries in a large observational study and found that TCZ with or without concomitant sDMARDs resulted in a comparable clinical response as assessed by CDAI change, but TCZ retention was shorter under monotherapy of TCZ (73). In an observational registry study from Japan, the odds to archieve DAS 28 remission were not different in patients treated with TCZ alone or in combination with MTX, however there was an increased probability for archieving remission for TCZ in combination in a subset of patients with high baseline DAS 28 >5 (61). Taken together, the results of these studies suggest that concomitant use of TCZ added to MTX rather than TCZ alone provides a slight advantage for some endpoints, while meaningful clinical and radiographic responses were achieved with both strategies. Given that clinical remission or at least very low disease activity manteinance is now a global aspiration goal for RA treatment, is an emerging need to stratify RA patient sub-populations who are likely to respond to the different treatment options identifying the predictors, in routine clinical practice, of early

clinical response to biologics. Given its biological actions, one could speculate that in those RA patients with a strong biochemical inflammatory response, defined by increased acute phase reactants with or without anemia, the disease could be preferentially mediated by IL-6. To this end, strong acute phase response (ESR >30 mm/h, CRP>10 mg/dl) the presence of extra-articular manifestations may help to identify patients who will have a rapid response to TCZ at three months; by contrast, higher baseline DAS-28-ESR values together with the number of previous DMARDs and biological therapies used, tended to decrease the likelihood for induction of remission (75). These results are supported by the data collected in the Swedish biologics register, in which a univariate analyses revealed that initial low level of CRP and/or ESR, initial higher HAQ value and having been exposed to an increasing number of biologics were predictor of drug discontinuation and indirectly of its response (76). In a study involving 87 patients it was found that improvement (evaluated throughout DAS28-ESR and CDAI) after tocilizumab treatment was more marked patients with high platelet count (≥400.000) (77). Drug-free remission remains a therapeutic goal in RA; in case of persistent remission, it has been hypothesised of tapering biological DMARDs; in this regard, Huizinga *et al*. reported the secondary objectives of the ACT-RAY study, a double-blind 3-year trial in which patients with active AR were randomised to add TCZ to ongoing MTX or switch to TCZ/placebo. Between weeks 52 and 104, patients with sustained clinical remission (DAS28-ESR<2.6 at two consecutive visits 12 weeks apart) discontinued TCZ and were assessed every 4 weeks for one year. Of patients entering year 2, 50.4% discontinued TCZ but most patients (84%) had a subsequent flare but responded well to TCZ reintroduction (78).

Abatacept

Abatacept (ABT) is a biologic disease modifying antirheumatic drug that selectively modulates T cell costimulation and has shown efficacy in several clinical trials involving RA patients; in the AGREE study, MTX-naïve patients with early RA who had been treated with abatacept plus MTX experienced clinical, functional and structural benefits and improvement in DAS 28 *versus* patients treated with MTX alone. (79) and in a post-hoc analyses, a high proportion of these patients archieved remission at months 6 and 12 according also to the stringent ACR-EULAR index-based SDAI and CDAI (80). Furthermore, for ABT plus MTX, the proportions of patients archieving stringent remission increased from month6 to month 12 regardless of the index used, suggesting that the efficacy of the two drugs may not peak at 6 months but appear to continue to increase after 6 months 9. It support the ACR-EULAR recommendations to report not only archievement but also maintenance of outcomes and sustainability of remission (81). Moreover, RA patients with prior anti-TNF exposures had similar outcomes if they switch to a new anti-TNF as compared with the initiation of ABT (82). In an international, prospective study to evaluate the prognostic factors for abatacept retention in a real-world setting in patients with RA who had received at least one prior biologic agent, anti-CCP positivity, failing <2 prior anti-TNF agents and cardiovascular comorbidity at initiation, were associated with higher retention (83). Concerning the withdrawal of ABT, in a substudy of the AGREE trial, the authors evaluated the impact on disease activity of reducing the dose of intravenous ABT from the approved monthly dose of 10 mg/kg to 5 mg/kg in patients who had archieved disease activity score ESR<2.6 at years 2 of treatment, and found that relapse was similar in both groups (84). In a prospective, multicentre observational study in Japan, of 51 patients in DAS-28 CRP remission after 2 years of abatacept treatment, 34 discontinued the treatement while 17 continued; after 52 weeks, 22 of the 34 patients remained biologic free (64,7%) although they had a significantly higher mean DAS-28 CPR score compared to the continuation group 12. Furthermore, Lower baseline HAQ-DI or CPR may predict maintenance of remission of low disease activity after discontinuation of abatacept (85). Abatacept dose reduction or cessation may be an option to ensure safety and health economic benefits in avoiding unnecessary drug exposure 10 which can provoke, in the real life, a higher risk of serious infections especially in older patients, with more comorbidities (like diabetes, history of previous serious or recurrent infections) (86).

Rituximab

Rituximab is a selective, B-cell depleting, biologic agent for treating refractory rheumatoid arthritis (RA). It is a chimeric monoclonal antibody targeted against CD 20 that is promoted as therapy for patients who fail to respond to other biologics. There is evidence to suggest that rituximab at licensed dose of two infusions of 1000 mg is effective and well tolerated when used in combination with methotrexate for RA and it inhibits structural damage and joint inflammation reducing erosion and cartilage loss (87).

However, 35% of patients do not archieve a European League Against Rheumatism moderate response and those who initially respond most relapse in the next 6-12 months (88). Patients seronegative for rheumatoid factor and anti-cyclic citrullinated protein (anti-CCP) have worse responses, suggesting that these patients have non-B-cell-mediated disease and require a different therapeutic approach (89, 90). The duration and quality of response appears to be related to the degree of B cell depletion; in a randomised double-blind placebo-controlled trial, patients with active rheumatoid arthritis despite methotrexate received a first infusion of rituximab 1000 mg and were tested for persistent B cells using highly sensitive flow cytometry on day 15. All received a second infusion of 1 g, but 25 patients with persistent B cells were subsequently randomised double-blind to receive, 2 weeks later, either a third infusion of 1000 mg rituximab or placebo. Treatment with 3×1000 mg rituximab resulted in significantly greater depletion (lower B cell and plasmablast numbers between 8 and 28

weeks) paralleled by significantly better EULAR and ACR20 response rates at 40 weeks and 52 week) compared with 2×1000 mg without an increased of adverse event (91).

Emery *et al*. compared the effectiveness of rituximab *versus* an alternative tumour necrosis factor (TNF) inhibitor (TNFi) in patients with rheumatoid arthritis (RA) with an inadequate response to one previous TNF due to inefficacy or intolerance to this drug. They found that after discontinuation of an initial TNFi, switching to rituximab is associated with significantly improved clinical effectiveness compared with switching to a second TNFi particularly in seropositive patients and in those switched because of inefficacy (92).

In summary, the emergence of new therapies for the treatment of RA, the paucity of head-to-head studies and the heterogeneous nature of responses to current biologics, highlight the need of identification of prognostic factors for treatment response and retention in clinical practice to individualise treatment strategies which still remain a critical challenge for the current rheumatology. However, a more accurate knowledge of long-term safety, the identification of response predictor biomarkers, the choice of monotherapy *versus* combination therapy, the employment of biologics in potentially childbearing women and in patients with severe comorbidities, represent important clinical issues requiring a definitive explanation.

Rheumatoid arthritis: new therapies

Nowadays remission is a realistic target for many patients with rheumatoid arthritis (RA), thanks to the numerous conventional and biological disease-modifying anti-rheumatic drugs (cDMARDs and bDMARDs) available.

Nevertheless, almost 20–50% of patients show an inadequate response to DMARDs or have to discontinue therapy due to intolerance or adverse events. So we still need new drugs and new drug targets for RA.

In the last year, several clinical trials have focused on a new class of drug: the Janus kinase (JAK) inhibitors.

JAKs are a family of non-receptor tyrosine kinases (JAK1, JAK2, JAK3 and TYK2) involved in the intracellular signal transduction of many cytokines. Once activated, JAKs phosphorylate the signal transducers and activators of transcription (STAT) that subsequently induce the expression of many genes. This pathway is involved in the pathogenesis of RA.

Tofacitinib is a pan-JAK inhibitor that primarily inhibits JAK1 and JAK3. It is the first oral targeted synthetic DMARD. In 2012, Tofacitinib was approved by FDA, in monotherapy or in association with other cDMARDs, for treatment of moderate to severe RA in patients with inadequate response or intolerance to Methotrexate (MTX). In the updated 2013 EULAR recommendations for the management of RA, Tofacitinib is recommended after the failure of at least one bDMARD because of the lack of long-term safety data.

In the last year, many studies have confirmed the efficacy and safety profile of Tofacitinib in RA patients.

Charles-Schoeman *et al*. (93) evaluated the efficacy and safety of Tofacitinib *versus* placebo in bDMARD-naïve patients and in patients with inadequate response to bDMARDs (bDMARD-IR), taking data from phase II and phase III studies. The limit of this work was that these studies had different designs and methodology and that they were not designed for comparison between bDMARD-naïve and bDMARD-IR patients. Anyway, this pooled analysis showed that Tofacitinib (5 mg or 10 mg twice a day), at month 3, was effective in reducing signs and symptoms of RA before or after bDMARDs. The proportion of patients achieving ACR20/50/70 was higher in the bDMARD-naïve subgroup than in the bDMARD-IR one, while the differences between the two subgroups were less prominent as for changes in DAS28 (ESR), CDAI and SDAI. Moreover, in the bDMARD-IR subgroup, patients with previous exposure to 2 or more TNF-inhibitors had poorer efficacy response in comparison with patients with only one previous anti-TNF-α.

The safety profile appeared similar among the various subpopulations. Noteworthy, patients receiving concomitant glucocorticoids had a higher incidence of serious adverse events (SAEs) and discontinuation due to adverse events (AEs). In particular, all serious Herpes Zoster infections occurred in patients treated with glucocorticoids.

Tanaka *et al*. (94) studied the efficacy and safety of multiple doses of Tofacitinib monotherapy in patients with active RA after failure of at least one previous synthetic or biological DMARD. The primary endpoint was the ACR20 response rate at week 12: dose-dependent and statistically significant ACR20 responses were observed in all Tofacitinib groups *versus* placebo from week 2 and maintained throughout the 12-week period. However, as for the ACR70 response rates, the DAS28(ESR)-defined remission and low disease activity, significant improvements *versus* placebo were reported only for Tofacitinib doses ≥5 mg twice daily. The study also showed a significant improvement in patient reported outcomes (PROs) (HAQ-DI, SF-36 and FACIT-F) with all doses. The incidence of AEs, although similar across all treatment groups, was higher for increasing tofacitinib doses. The most frequent AEs were nasopharyngitis and hyperlipidaemia. Among SAEs there were: increase in creatine kinase, ALT and AST levels leading to hospitalisation, gastric ulcer perforation, rheumatoid vasculitis, Herpes Zoster and post-herpetic nerve paralysis. A dose-dependent decrease in neutrophil and platelet counts and increase in haemoglobin levels were also observed in Tofacitinib-treated groups.

Strand *et al*. (95-96) demonstrated the efficacy of Tofacitinib, both in monotherapy and in association with MTX, on PROs in patients with active RA and failure of previous conventional or biological DMARDs. In particular, they analysed changes at month 3 from baseline in: patient global assessment of disease activity (PtGA), patient assessment of arthritis pain, HAQ-disability index (HAQ-DI), SF-36, FACIT-F, MOS sleep scale (MOS-SS). Statistically and clinically meaningful improvements *versus* placebo

were observed for all PROs, except for the MOS-SS, and for both Tofacitinib doses (5 mg or 10 mg twice a day), although numerically higher with 10 mg. Moreover, improvements were evident as early as the second week and were maintained to month 6.

Finally, in patients in Tofacitinib monotherapy, by analysing the various domains of the SF-36, we can observe that Tofacitinib improved not only physical functioning, pain and fatigue but also social and emotional functioning and wellbeing.

Cohen *et al*. (97) compared the efficacy and safety of Tofacitinib in US patients and patients from the rest of the world, through a post-hoc analysis of pooled Phase II and Phase III data. They found similar efficacy and safety profile of the drug worldwide. Moreover, Tofacitinib safety profile was similar to that of established DMARDs, but Herpes Zoster infection was higher for Tofacitinib both in US patients and in non-US ones.

Lee *et al*. (98) performed a network meta-analysis to compare the efficacy of Tofacitinib 5 mg or 10 mg twice daily, in monotherapy or in association with MTX in patients with active RA. They included ten randomised controlled trials (RCTs), for a total of 4867 patients. The best treatment for achieving the ACR20 response rate was Tofacitinib 10 mg + MTX, followed by: Tofacitinib 5 mg + MTX, Adalimumab 40 mg + MTX, Tofacitinib 10 mg, Tofacitinib 5 mg, MTX and placebo. As for the safety profile, no significant differences were detected. In conclusion, Tofacitinib in combination with MTX appeared to be the best treatment option for active RA, without a significant risk of adverse events.

The same group performed a network meta-analysis of RCTs, including 1796 patients with active RA and an inadequate response to TNF-α-inhibitors, to compare the efficacy and safety of Tocilizumab, Rituximab, Abatacept and Tofacitinib (99). The efficacy endpoint was evaluated as the number of patients who achieved the ACR20 response rate, while the safety outcome was the number of patients' withdrawals due to AEs.

It emerged that the most effective treatment as a second-line biologic was Tocilizumab 8 mg followed by: Rituximab, Abatacept, Tocilizumab 4 mg, Tofacitinib 10 mg, Tofacitinib 5 mg and placebo. As for the safety profile, no significant differences were observed among the seven treatment groups, even if the follow-up period was of short duration (6 months).

Boyle *et al*. (100) studied the effects of Tofacitinib on synovial pathobiology in a randomised, double-blind, phase II study. They enrolled patients with RA in therapy with MTX but with an inadequate response to this drug. Patients were randomised to receive Tofacitinib 10 mg twice a day or placebo for 28 days. A synovial biopsy was performed at day -7 and at day 28 and disease activity was evaluated by DAS28 and EULAR response. In the Tofacitinib group, they observed, besides a good clinical response, a reduction in metalloproteinase and interferon-regulated gene expression in rheumatoid synovium. Moreover they found that reduction in synovial phosphorylation of STAT1 and STAT3 correlated with clinical improvement.

In the last year, in addition to Tofacitinib, other JAK inhibitor molecules have also been studied in RCTs. These molecules show different degrees of specificity towards the four JAKs.

Among these new drugs, there is Baricitinib that is an oral, selective and reversible inhibitor of JAK1 and JAK2. Keystone *et al*. (101) studied the efficacy, dosing regimens and safety of Baricitinib in 301 patients with RA and inadequate response to MTX. Baricitinib, in patients taking background MTX, showed clinical efficacy *versus* placebo at all doses but significantly more patients achieved ACR20/50/70 response with the doses of 4 e 8 mg, compared to 2 mg daily. The administration of 2 mg twice daily or 4 mg once a day gave the same results.

The efficacy endpoints were achieved at week 12 and were maintained or continued to improve through week 24. Both at week 12 and 24, 4 mg and 8 mg had similar efficacy, but the higher dose was associated to an increased risk of AEs, in particular Baricitinib 8 mg determined a more pronounced decrease in haemoglobin levels. Other laboratory changes reported in the Baricitinib-treated group were increase in LDL, HDL, creatinine and creatinine phosphokinase (CPK) levels. Anyway, the drug was well tolerated at all doses. 3 SAEs were reported: 1 bronchitis, 1 pneumonia and 1 bacterial pneumonia. No tuberculosis, opportunistic infections or deaths were reported.

Peficitinib is a newly developed drug that inhibits JAK1, JAK2, JAK3 and TYK2 enzymes activity.

Takeuchi *et al*. (102) performed a phase IIb, dose-finding study to evaluate efficacy and safety of oral Peficitinib monotherapy in Japanese patients with moderate to severe RA. The primary efficacy endpoint was the ACR20 response rate at week 12. It was achieved by all the Peficitinib groups *versus* placebo. Anyway only the doses of 100 mg and 150 mg daily showed a statistically significant improvement also in the secondary efficacy endpoints (ACR50/70 and improvement of DAS28(CRP)). Peficitinib 100 mg and 150 mg efficacy was comparable to that of TNF-α-inhibitors monotherapy in Japan.

The drug showed a good safety profile at all doses. The most common AEs were nasopharyngitis, gastrointestinal events and increase of CPK. Herpes Zoster occurred in 4 patients in Peficitinib groups with no dose-dependence. At this moment, there are no clinical trials on combination therapy of Peficitinib and cDMARDs.

Decernotinib is an oral selective inhibitor of JAK3 that, differently form the other JAKs, is expressed only by haematopoietic cells. JAK3 seems to be involved in the pathogenesis of RA. In fact, it has been demonstrated that JAK3 expression is associated with the synovial inflammation in RA, the presence of JAK3-expressing cells correlates with higher serum levels of rheumatoid factor and successful treatment with DMARDs reduces JAK3-expression in synovial tissue.

A phase IIa, randomised, placebo-controlled, dose-ranging study (103) proved the efficacy and safety of Decernotinib monotherpay in patients with RA and an inadequate response

to at least one previous DMARD. Anyway, only the highest doses administered (50, 100 and 150 mg twice a day) demonstrated clinical efficacy (defined as the ACR20 response and change from baseline of DAS28(CRP)).

Infections were the most common AEs and they were more frequent in the 100 mg and 150 mg dose groups. 2 serious infections were described: 1 case of tuberculosis and 1 of fatal pneumonia. Moreover 3 cases of Herpes Zoster were reported. As for laboratory changes, Decernotinib therapy was associated with: neutropenia, lymphopenia, increase in serum creatinine and transaminase and hyperlipidaemia.

Decernotinib has also demonstrated to be efficacious in improving signs and symptoms of RA in combination with MTX in patients with RA and an inadequate response to MTX alone (104). Regarding safety profile, infections, headache and increase of transaminase and lipid levels were the most frequent adverse events.

Finally, Filgotinib is a selective JAK1 inhibitor which is currently in clinical development for the treatment of RA. Namour *et al*. (105) confirmed that this new drug does not need dose adjustments if co-administered with commonly used RA drugs.

Another new drug studied for the treatment of RA is Fosfamatinib that is an oral inhibitor of spleen tyrosin kinase enzyme (Syk).

Taylor *et al*. published the results of the OSKIRA-4, a phase IIb randomised, placebo-controlled study on the efficacy and safety of Fosfamatinib monotherapy *versus* placebo and *versus* Adalimumab monotherapy (106). 279 patients with RA, without other DMARDs therapy, were randomised to 5 arms: A. Fosfamatinib 100 mg twice a day for 24 weeks + placebo injection every 2 weeks; B. Fosfamatinib 100 mg twice a day for 4 weeks and then Fosfamatinib 150 mg daily up to week 24 + placebo injection every 2 weeks; C. Fosfamatinib 100 mg twice a day for 4 weeks and then Fosfamatinib 100 mg daily up to week 24 + placebo injection every 2 weeks; D. Adalimumab 40 mg every 2 weeks for 24 weeks + oral placebo twice daily; E. oral placebo twice daily + placebo injection every 2 weeks for 6 weeks and then switch to arm A or B.

Fosfamatinib showed clinical efficacy (evaluated by change at week 6 of DAS28(CRP) scores from baseline) as monotherapy *versus* placebo in the arms A and B, but not C. Anyway, at week 24 Fosfamatinib at all doses was inferior compared to Adalimumab. As for AEs, the most frequent were hypertension and diarrhoea.

IL-6 plays an important role in the pathogenesis of RA. It is involved in T-cell activation, B-cell proliferation, initiation of acute phase response and osteoclast differentiation. So IL-6 pathway represents an attractive therapeutic target for RA. Tocilizumab, a humanised monoclonal antibody targeting IL-6 receptor, has already been approved for treatment of RA in patients who failed to achieve remission with cDMARDs. New drugs targeting IL-6 or its receptor are being developed.

Takeuchi *et al*. (107) published data from a phase II, dose-ranging study on Olokizumab, a humanised IgG4 monoclonal antibody against IL-6. They studied efficacy and safety of Olokizumab in Asiatic patients with active RA despite therapy with MTX and with a previous inadequate response to an anti-TNF-α. At week 12, Olokizumab in all the 4-week cumulative dose groups (60, 120 or 240 mg) resulted more effective than placebo, in determining significant change in DAS28(CRP) from baseline. Significant differences were observed as early as the first week and were maintained throughout the 12-week period. Olokizumab also increased the ACR20 and ACR50 response rate compared with placebo at week 12. The AEs, similar across all the Olokizumab doses, were as expected for this class of drug, related to the blockade of the IL-6 pathway.

Sarilumab, a fully human anti-IL-6receptor monoclonal antibody, administered in association with MTX, appeared effective in improving signs and symptoms, physical function and radiographic progression of patients with moderate-to-severe RA. In a phase III study by Genovese *et al*. (108) patients with active RA, in therapy with MTX, were randomised to receive Sarilumab (150 mg or 200 mg sc every 2 weeks) or placebo. Co-primary endpoints of the study were: ACR20 response rate at week 24; change from baseline in HAQ-DI at week 16; change from baseline in the modified Sharp/van der Heijde score (SHS) at week 52. Both the 150 mg and the 200 mg Sarilumab group demonstrated significant improvements *versus* placebo for all the primary endpoints. Moreover, both Sarilumab groups also achieved the secondary endpoints of the study (ACR50/70 responses, DAS28(CRP) low-disease-activity or remission and reduction of CDAI scores). Infections were the most common AEs in the Sarilumab groups and the incidence was dose-dependent. The incidence of SAEs was similar to that observed for other biologic agents and JAK inhibitors. Herpes Zoster was the most common opportunistic infection. Finally, Sarilumab determined expected laboratory changes related to the IL-6 pathway inhibition.

Clazakizumab is a human monoclonal antibody against IL-6. A phase IIb study (109) evaluated efficacy and safety of Clazakizumab, in monotherapy or in association with MTX, *versus* MTX alone, in patients bDMARDs-naïve with moderate-to-severe RA and inadequate response to MTX. Clazakizumab, at all doses administered, both alone and with MTX, determined a rapid and significant improvement in disease activity (ACR20/50/70 response rates at week 12 and 24) compared with MTX alone. The combination treatment with Clazakizumab + MTX generally determined higher response rates compared to Clazakizumab monotherapy. The new drug was well tolerated and determined laboratory changes consistent with the pharmacologic effects of IL-6 inhibition.

In the last year, data from 3 phase III studies on Tabalumab have been published (110, 111, 112). Tabalumab is a fully human IgG4 monoclonal antibody that neutralises both soluble and membrane-bound B-cell activating factor (BAFF). In previous phase II studies, Tabalumab seemed to have clinical and biological efficacy in RA patients.

However, none of these phase III studies have confirmed these data. In particular, Tabalumab administered subcutaneously at the doses of 120 mg every 4 weeks or 90 mg every 2 weeks, despite the evidence of a biological activity (as shown by the reduction of CD20+ B-cells and immunoglobulin levels in patients treated), failed to demonstrate clinical efficacy in patients with active RA, both in monotherapy and in combination with MTX, both in patients with inadequate response to MTX and in patients with a previous anti-TNF-α drug failure.

On the basis of the evidence that not all patients with RA respond to Rituximab, van Vollenhoven *et al*. (113) performed an exploratory study to evaluate the safety of a combination therapy with Rituximab re-treatment + Atacicept, in patients with moderate-to-severe RA. Atacicept is a fully human recombinant fusion protein that neutralises the activity of BLyS (B lymphocyte stimulator) and APRIL (a proliferation-inducing ligand). The rationale of this combination therapy derives from the evidence that serum BLyS levels rise following B cell depletion by Rituximab, until B cells return to baseline levels. The results of this study showed that the association of Atacicept with Rituximab re-treatment did not present new safety concerns. The AEs profile was similar to that emerged for Atacicept monotherapy in previous studies. Anyway, the addition of Atacicept, administered 28 days after Rituximab at the dose of 150 mg sc once a week for 25 weeks, did not demonstrate clinical benefit.

Another cytokine that plays an important role in the pathogenesis of many autoimmune diseases, among which RA, is IL-17. So new agents targeting this cytokine are emerging.

In the last year, Genovese *et al*. (114) published data derived from the open-label extension of a previous 16-week, double-blind placebo controlled phase II study on Ixekizumab. This is a humanised IgG4 anti-IL17A monoclonal antibody and it was added to the background DMARD therapy to two subgroups of patients: bDMARD-naïve and patients with an inadequate response to TNF-α-inhibitors (TNF-IR). Data from the additional 48-week open label period confirmed the safety findings of the double-blind period. In particular, AEs in patients treated with Ixekizumab did not lead to study discontinuation. SAEs occurred in 7% of bDMARD-naïve patients and in 11% of TNF-IR ones. No mycobacterial or invasive fungal infections were observed. Moreover, clinical improvements observed at week 16 with Ixekizumab were maintained or improved through week 64.

Brodalumab is a human monoclonal antibody against IL-17 receptor. In a randomised placebo controlled trial, it did not demonstrate significant clinical efficacy *versus* placebo in patients with RA and inadequate response to MTX (115).

Finally, preclinical studies have shown that the combined inhibition of IL-17A and TNF-α may have an additive effect compared to the inhibition of the single cytokines. In this regard, Fisher *et al*. (116) have demonstrated that combined blockade of TNF-α and IL-17A was more effective than single blockade in inhibiting the cytokine responses from human mesenchymal cells in vitro. Moreover, bispecific anti-TNF-α/IL-17A antibodies were superior in inhibiting the development of inflammation and bone and cartilage destruction in arthritic mice.

A new possible therapeutic target for the treatment of RA is the GM-CSF (granulocyte macrophage colony stimulating factor) pathway. This cytokine promotes myeloid haematopoiesis but it also contributes to the activation of mature neutrophils, eosinophils and macrophages. The hypothesis that GM-CSF could be involved in the pathogenesis of RA and other autoimmune conditions derives from the evidence, in some case reports, that supportive therapy with GM-CSF can cause an exacerbation of inflammatory disorders and in particular arthritis flares. Greven *et al*. (117) studied the cellular expression of GM-CSF receptorα (GM-CSFRα) on macrophages in RA synovial tissue compared with disease controls and the effect of its inhibition. They found that there is an increased number of cells expressing GM-CSFRα in synovial tissue of patients with RA compared to non inflammatory controls. Moreover, cells that expressed GM-CSFRα were CD68+ and CD163+ macrophages whose number correlated with disease activity. They also found that, in a murine collagen induced arthritis model of RA, the anti-GM-CSFR antibody treatment determined a dose-dependent reduction of clinical signs of arthritis, with reduced synovial inflammation and joint destruction. This effect is probably due to the inhibition of migration and retention of inflammatory cells and secondary to a reduced survival of differentiated macrophages.

A phase II placebo controlled study (118) investigated the efficacy and safety of Mavrilimumab (an anti-GM-CSF receptor monoclonal antibody) in Japanese patients with moderate-to-severe RA. Mavrilimumab sc showed a rapid meaningful clinical response (DAS28(CRP) decrease >1.2 from baseline) *versus* placebo, in particular at the doses of 30 mg and 100 mg every other week. Patients who received 100 mg also demonstrated significant HAQ-DI and ACR20 responses. AEs were mild to moderate in intensity and only one SAE (pneumonia) was reported.

MOR103 is a human monoclonal antibody that targets directly the soluble GM-CSF. Behrens *et al*. reported data from the first in patient study with MOR103 in RA patients (119). 98 patients with RA, in stable therapy with cDMARDs and low doses of steroids, were randomised to receive placebo or intravenous MOR103 in different doses, once a week for 4 weeks. The primary endpoint of the study was to evaluate the safety profile of the new drug. The drug was generally well tolerated. Fatigue, cough and RA worsening (primarily occurring after the end of treatment) were more frequent in the MOR103 groups than in placebo. AEs were mild-moderate in intensity. Only one SAE was reported: a case of pleurisy requiring antibiotic therapy. In exploratory efficacy analysis, MOR103 determined significant clinical improvements compared to placebo, in particular with the dose of 1 mg/kg.

As shown in a phase IIa study (120), treatment with JNJ-40346527, an oral

colony-stimulating factor-1 receptor inhibitor, does not seem to be effective in DMARDs-refractory RA patients. In fact, it did not achieve the primary endpoint of the study that was a significant improvement from baseline of DAS28(CRP) at week 12 *versus* placebo.

Takeuchi *et al*. (121) evaluated the efficacy and safety of Denosumab (human monoclonal antibody against RANKL) in Japanese patients with RA. We know that an increased activation of osteoclasts contributes to bone erosions and bone loss in RA. So, the inhibition of RANKL, that is essential for osteoclast activation, can reduce joint destruction in RA patients. In this 12-month study, 350 patients were randomised to receive placebo or Denosumab at three different regimens (60 mg every 6 months, every 3 months or every 2 months). Patients were stratified for glucocorticoid use and for positivity of rheumatoid factor at baseline. They continued to assume background MTX, vitamin D and calcium support throughout the study, while bisphosphonate use and glucocorticoid >10 mg/day were prohibited.

Denosumab significantly inhibited the increase of the modified Sharp erosion score in all groups *versus* placebo, while it had no effect on the joint space narrowing. It seems that higher concentrations of Denosumab result in less progression of bone erosion but this study did not confirm significant differences among the three different Denosumab regimens.

Denosumab was able to increase bone mineral density (BMD) at all sites, regardless of glucocorticoid use.

On the contrary, Denosumab did not influence disease activity in RA patients. Treatment with Denosumab was well tolerated and no significant differences were observed among the three groups as for the safety profile. So, we can infer that the addition of Denosumab to background MTX can represent a new therapeutic option for patients with risk factors for joint destruction and that cannot move to biologic therapies for a variety of reasons.

Šenolt *et al*. (122) reported data from a phase IIa clinical trial on the use of a recombinant human *anti-IL20 monoclonal antibody* (NNC0109-0012, 3 mg/kg/week sc) in combination with MTX in patients with RA. Patients treated showed a significant clinical improvement, defined as change from baseline in DAS28(CRP) score, at week 12 *versus* placebo. Improvements were evident as early as the first week of therapy. Improvements in disease activity were more pronounced and were sustained for 13 weeks of follow-up after stopping drug administration in seropositive patients. Moreover, a greater proportion of seropositive patients achieved also ACR20/50/70 responses and significant improvements in HAQ-DI at week 12. The incidence of AEs was similar between placebo and treated patients, although injection site reactions and infections were reported with a higher frequency in the treated group.

Chopra *et al*. (123) evaluated the safety and efficacy of Itolizumab + MTX in patients with RA. Itolizumab is a humanised anti-CD6 monoclonal antibody. CD6 is a co-stimulatory molecule necessary for optimal T-cell stimulation by the antigen presenting cells. 70 patients with RA, in an open label phase II trial, were randomised to receive Itolizumab + MTX or MTX alone for 12 weeks. Itolizumab, at all doses, in combination with MTX, showed clinical efficacy, evaluated as ACR20 and DAS28 response rates and efficacy was sustained also for the following 12 weeks of follow-up. Itolizumab was also well tolerated. AEs were generally mild or moderate and infusion-related reactions mainly occurred after the first infusion.

Based on the positive findings in psoriatic arthritis, Genovese *et al*. (124) investigated the efficacy and safety of Apremilast in RA patients with active disease and inadequate response to MTX. Apremilast is an oral inhibitor of phosphodiesterase 4. In this phase II study, patients receiving a stable dose of MTX, were randomised to receive placebo or Apremilast (20 mg or 30 mg twice a day). Data emerged from the study did not demonstrate a significant clinical efficacy of the drug as measured by the ACR20 response rate at week 16. In any case, Apremilast demonstrated an acceptable safety profile.

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