
Recommendations for the use of biologic therapy in rheumatoid arthritis: update from the Italian Society for Rheumatology

I. Efficacy

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ABSTRACT

Given the availability of novel biologic agents for the treatment of rheumatoid arthritis (RA), various national scientific societies have developed specific recommendations in order to assist rheumatologists in prescribing these drugs. The Italian Society for Rheumatology (Società Italiana di Reumatologia, SIR) decided to update its recommendations and, to this end, a systematic literature review was carried out and the evidence derived from it was discussed and summarised as expert opinions. Levels of evidence, strength of recommendations and levels of agreement were reported. The recommendations reported are intended to help prescribing rheumatologists to optimise the use of biologic agents in patients with RA seen in everyday practice; they are not to be considered as a regulatory rule.

Background

Because of significant cost and particular safety profile implications, most scientific rheumatological societies developed specific recommendations for the use of biologic agents in the treatment of rheumatoid arthritis (RA). The Italian Society for Rheumatology (Società Italiana di Reumatologia, SIR) has previously published a set of recommendations for the use of anti-TNF therapies in RA (1) and now presents a broader update on the recommendations for the use of biologic drugs in RA.

Introduction

The treatment of RA includes non-pharmacological measures, non-steroidal anti-inflammatory drugs and/or glucocorticoids (2), but the mainstay is the use of disease-modifying anti-

rheumatic drug (DMARD) treatment to achieve disease control. In the last few years, treatment strategies have changed, with early referral and early DMARD use being the most important strategy to optimise the response and the reduction of long-term disability (3, 4). Moreover, it has been clearly demonstrated that tight control, using composite measures of disease activity and appropriate combination and switching of drug treatment is highly effective (5-8).

Biologic drugs, particularly the inhibitors of the key pro-inflammatory cytokine TNF- α , have represented a significant progress in the therapy of RA, resulting in dramatic changes in the therapeutic approach and treatment paradigms (9, 10). These drugs have proven to be more effective than traditional DMARDs and to work faster; however, they are much more expensive and represent a major concern for payers because 1 month of treatment may cost 100 times more than a year's supply of an older DMARD such as methotrexate (MTX) or hydroxychloroquine (11). In addition, although these drugs have a satisfactory safety profile, relevant adverse events such as severe infections, even opportunistic infections, or tuberculosis reactivation can occasionally occur. Since complete disease control is the main goal in treating RA today (12), and this may need biologic treatment as well, it was the objective of this committee to update the recommendations for the treatment of RA with biologic drugs in clinical practice.

At time of completion of the literature analysis done for these recommendations, six biological products were licensed in Italy for the treatment of RA.

Three are TNF antagonists (infliximab, etanercept and adalimumab), one is an inhibitor of IL-1 (anakinra), one is a B-cell depleting drug (rituximab) and one is an inhibitor of T-cell co-stimulation (abatacept). With respect to the present indication of regulatory agencies, anakinra and TNF-antagonists are indicated for treatment of active RA after DMARD failure, while rituximab and abatacept should be used after failure of first-line biologic drugs. The rather modest efficacy profile of anakinra, which is still on the market in Italy, seems to limit its use in RA, while it has been successfully used in the treatment of different inflammatory conditions (*i.e.* autoinflammatory diseases) (13).

At the time of submission for publication, other biological agents were marketed. In particular, they included an inhibitor of IL-6 receptor (tocilizumab) which was licenced for treatment of RA after DMARD failure or after failure with biologics (14, 15), and 2 other TNF-antagonists (golimumab and certolizumab) (16, 17). In the meantime, the European regulatory agency (EMA) and the Italian Regulatory Agency also approved the use of abatacept as a first-line drug, after DMARD failure.

Recommendations

Who should be treated

A definite diagnosis of RA is a prerequisite for considering TNF antagonist therapy. The patient must meet classification criteria for RA, and a diagnosis of RA must be made by a physician with extensive experience in the management of RA.

- 1- Patients candidate for treatment with TNF antagonists should be those with insufficient response to MTX taken for at least 3 months at the highest tolerated dosage (up to 20 mg/week) (Ia, A).
- 2- In patients with contraindications or intolerance to MTX, treatment with TNF antagonists should be started after failure of another drug with structural efficacy taken for at least 3 months at the optimal tolerated dosage (*e.g.* leflunomide 20 mg/day, sulfasalazine 2 g/day, cyclosporine 3-5 mg/kg/day) (Ia, A).

3- In case of failure of MTX (or other DMARDs as stated above), the following scenarios should represent indications for the use of TNF antagonists:

- 3.1. High disease activity for at least one month, as defined by the 28-joint count disease activity score (DAS28) >5.1 (Ia, A).
- 3.2. Moderate disease activity (DAS28 >3.2 and ≤5.1) in the presence of unfavourable prognostic factors:
 - 3.2.1. immunological and serological markers: a positive test for anti-citrullinated protein antibodies (ACPA) or IgM rheumatoid factor (RF); elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) (Ib, B);
 - 3.2.2. clinical markers: persistence of at least 1 swollen joint (Ib, B);
 - 3.2.3. imaging markers: early occurrence of bone erosions on x-rays (III, C); ultrasonography detection of active synovitis with power Doppler signal (III, C).
- 3.3. Joint damage progression (new erosions) regardless of disease activity (III, C).
- 3.4. For patients with moderate disease activity (DAS28 >3.2 and ≤5.1) without unfavourable prognostic factors, a DMARD combination therapy or the substitution of the first DMARD with another synthetic DMARD might be considered before TNF antagonists (Ia, A).

RA therapy has undergone a major transformation over the past years: the early introduction of DMARDs to take advantage of the window of opportunity, the use of combinations of synthetic and biological DMARDs, and the availability of biologic agents in patients who fail to respond to DMARDs have allowed to significantly ameliorate the long-term outcome of the disease (18). Nevertheless, some patients, even those treated with biologic agents, show a suboptimal response or develop adverse events that lead to the discontinuation of therapy (19). Furthermore, remission rates remain low and patients with RA suffer from a decreased overall quality of life and still miss a significant number of working days (20).

It has been widely recognised that the timing of instituting an appropriate therapy appears crucial to avoid an unfavourable RA phenotype and to yield a positive impact on long-term outcome. Indeed, erosions, a marker of disability in late disease, develop within 3 months of disease onset in 10–26% of RA patients, and in 75% they are appreciable within 2 years (21–24). However, the decision of when to introduce biologic agents, which have proven to minimise structural damage, is really challenging in that the disease course of RA varies considerably among patients and, while some patients may experience a severe, acute onset of the disease, others show chronic and intermittent symptoms (20). In addition, in patients treated with TNF antagonists, an apparent dissociation between inflammation and radiologic outcome has been observed: in fact, joint damage can be retarded or stopped even in cases with persistent active disease (25, 26). On the other hand, several reports have shown that joint damage may occur even in patients who have satisfied the criteria for clinical remission, suggesting ongoing disease activity (27–30). This feature is particularly relevant in that evidence has been provided that both radiographic damage and disease activity are independent contributors to impaired physical function in RA, both early on and late in the disease process (31). Thus, complete remission remains a challenge for a significant number of patients with evidence of residual disease activity by imaging techniques in spite of clinical improvement, and it still has to be defined what is the best way to treat RA optimising the wide array of therapeutic options available nowadays.

MTX is a highly effective drug in RA and it is considered the anchor drug in combination with both other DMARDs and biologics (32). The task force agreed that patients candidate for starting TNF antagonists should be those failing MTX taken for at least 3 months at the highest tolerated dosage (up to 20 mg/week). The statement about the minimal duration of MTX treatment takes into account data recently obtained by the post-hoc analysis of the ASPIRE trial, where patients with

Table I. Category of evidence, strength of recommendation and level of agreement of different items.

Item	Category of evidence	Strength of recommendation	Level of agreement
a1	Ia	A	9.67 (± 1.15)
a2	Ia	A	9.08 (± 1.5)
a3.1	Ia	A	9.41 (± 1.5)
a3.2	Ib*, Ib**, III***	B*, B**, C***	8.67 (± 1.61)
a3.3	III	C	9.08 (± 1.08)
a3.4	Ia	A	9.58 (± 1.16)
b1	Ib	A	9.83 (± 0.58)
b2	Ib	A	9.42 (± 1.24)
c	IV	C	9.33 (± 1.23)
d1	Ia	A	9.58 (± 0.79)
d2	Ia	A	9.58 (± 1.16)
e	Ia	A	9.17 (± 1.59)
f1.1	IV	C	8.92 (± 1.38)
f1.2	IIIb	D	8.83 (± 1.11)
f1.3	Ia	A	9.17 (± 1.27)
f2.1	IV	C	9.67 (± 0.78)
f2.2	Ia	A	9.83 (± 0.39)
f3	Ib	A	9.75 (± 0.45)
g1	IIIb	B	9.58 (± 0.79)
g2	IIIb	B	8.92 (± 1.44)

*Immunological and serological markers: a positive test for ACPA or IgM RF; elevated ESR or CRP;

Clinical markers: persistence of at least 1 swollen joint; *Imaging markers: early occurrence of bone erosions by x-ray (III, C); ultrasonography detection of active synovitis with power Doppler signal.

active RA for ≤ 3 years and no prior MTX treatment were randomised to receive MTX plus placebo or MTX plus infliximab. At weeks 14 and 54, more patients in the latter group were in remission, but MTX plus placebo halted radiographic progression only if patients achieved remission within 3 months, while MTX plus infliximab also halted or minimised progression in patients with low or moderate disease activity, respectively (33). On the other hand, the results of the COMET study, in which the combination of MTX and etanercept was compared to MTX alone in patients with early active RA, showed that the proportion of patients treated with MTX alone reaching DAS28 remission increasingly rose up to week 24 of treatment (34).

In patients with contraindications or intolerance to MTX, the task force stated that TNF antagonists should be considered after failure of another drug with structural efficacy taken for at least 3 months at the optimal tolerated dosage. The drugs considered as valid options were leflunomide 20 mg/day, sulfasalazine 2 g/day, cyclosporine 3-5 mg/kg/day. These three DMARDs demonstrated a slowing down of the radiographic

progression (35-39); however, considering the great amount of data on efficacy and safety of MTX, they should be used in patients with contraindications or intolerance to MTX.

In case of failure of MTX (or the other DMARDs as stated above), the task force hypothesized the following four scenarios as possible indications for the use of TNF antagonists.

1. Patients with high disease activity lasting at least one month, as defined by DAS28 > 5.1 (Ia, A) (6, 34, 40, 41).

2. Patients with moderate disease activity (DAS28 > 3.2 and ≤ 5.1) in the presence of unfavourable prognostic factors, including immunological and serological markers: ACPA, IgM RF, and elevated ESR, CRP (Ib, B); clinical markers: presence of at least 1 swollen joint (Ib, B); imaging markers: early occurrence of bone erosions on plain x-rays (III, C), ultrasonography (US) detection of active synovitis with power Doppler signal (III, C). With this statement the committee emphasises the importance of taking into account all possible factors predictive of joint damage progression to decide treatment strategy. In the ASPIRE trial, patients with early active RA, not previously treated

with MTX, were randomly assigned to receive escalating doses of MTX up to 20 mg/week plus placebo or infliximab plus MTX to identify disease characteristics leading to progression of joint damage. CRP and ESR levels, and swollen joint count were associated with greater joint damage progression in the MTX-only group, while none of these parameters was associated with progression in the infliximab plus MTX group. Patients receiving MTX alone who had persistently active disease showed greater radiographic progression of joint damage than those taking MTX plus infliximab (42). Recently, positivity for ACPA also appeared to be the strongest independent predictor of radiographic progression in a cohort of RA patients followed longitudinally for 10 years (43).

Serial power Doppler ultrasonography (PDUS)-assessed synovitis appeared to be a valid predictor of erosions when comparing patients with early RA who did or did not develop erosive disease.

The results of different studies showed that PDUS findings at baseline may have a predictive value in disease activity and radiographic outcome (44, 45). It should be underlined that no randomised controlled trials (RCTs) have tested this approach based on prognostic factors; however, it is supported by various indirect evidence from the existing literature.

3. Patients with joint damage progression (new erosions), regardless of disease activity, documented by plain radiographs.

4. For patients with moderate disease activity (DAS28 > 3.2 and ≤ 5.1) without unfavourable prognostic factors, DMARD combination therapy or sequential administration of another synthetic DMARD should be considered (Ia, A) before TNF antagonists. MTX combination therapy was superior to MTX monotherapy in patients with a previous inadequate response to MTX (taken for at least 3-6 months), resulting in significantly more American College of Rheumatology (ACR)20, ACR50 and ACR70 responses (46-50). TNF antagonists should be used in the case of failure of these additional treatment strategies.

Monotherapy or combination therapy

- 1- In the treatment of RA, the combination therapy [TNF antagonists + MTX] has a higher efficacy (in terms of ACR, EULAR responses and DAS remission rates) compared to MTX monotherapy (Ib, A).
- 2- In case of intolerance, toxicity or refusal to take MTX, patients may be treated with a combination of a biologic drug and another DMARD (leflunomide, cyclosporine) (Ib, A) or with a biologic monotherapy (adalimumab, etanercept) (Ib, A)

Biologic agents should be used in combination with MTX (or other DMARDs if MTX is contraindicated or not tolerated), since the combination has greater efficacy and better structural protection than monotherapy, with no increase in adverse events. This has been clearly demonstrated in phase III trials for TNF antagonists (51, 52) and for rituximab as well (53). It is noteworthy that the TNF antagonist adalimumab and etanercept are licensed as monotherapy on the basis of their efficacy in clinical trials, while infliximab should only be used in combination with MTX; rituximab and abatacept should also be used in combination with MTX (54).

As for treatment with TNF antagonists, in case of intolerance, toxicity or refusal to take MTX, patients may be treated with a combination of biologic TNF antagonist and another DMARD such as leflunomide, azathioprine, sulfasalazine and cyclosporine (55-60).

Which biologic drug should be tried first¹

The choice of which drug should be tried first is largely based on physician's opinion and should be shared with the patient; it may be based on the different way of administration (subcutaneously vs. intravenously) or frequency of administration (every 8 weeks for infliximab, every 2 weeks

for adalimumab, weekly or twice a week for etanercept) and patients' characteristics (4, C).

At the time of completion of these recommendations, the only biological agents licensed in Italy for treating RA patients with active disease despite classical DMARDs were TNF antagonists. RCTs directly comparing the efficacy of different TNF antagonists are lacking, even if differences exist among the three compounds actually on the market; the safety profile seems roughly similar among the 3 agents as well. The choice of which drugs should be tried first is largely based on physician's opinion and should be shared with the patient; it may be based on the different way of administration (subcutaneously vs. intravenously) or frequency of administration (every 8 weeks for infliximab, every 2 weeks for adalimumab, weekly or twice a week for etanercept).

It should also be mentioned that anakinra (IL1 receptor antagonist), while effective in individual patients with RA, did not show high level of clinical efficacy in clinical trials (61, 62) and so it has not been recommended as a major biologic for RA treatment.

Recommended regimens for the three TNF antagonists are as follows:

- infliximab: at a starting dose of 3 mg/kg intravenously at week 0, 2, 6, and then every 8 weeks;
- etanercept: at a dosage of 25 mg subcutaneously twice a week or 50 mg once a week;
- adalimumab: at a dosage of 40 mg subcutaneously every 2 weeks.

How and when disease activity should be evaluated

1. In daily practice EULAR response and DAS low disease activity or remission evaluation with swollen joint count, tender joint count and Health Assessment Questionnaire (HAQ) are necessary to evaluate patients' clinical response during biologic treatment (Ia, A).
2. In daily practice the efficacy evaluation of RA patients treated with biologics should be performed at least every 3 months using DAS28. Functional outcome using HAQ score should also be evaluated every

3 months, while radiologic progression should be evaluated at least every 12 months by plan radiographs of hands, feet, and symptomatic joints (Ia, A).

Different trials have shown that aiming at low disease activity or remission by adjusting treatment every 1-3 months in conjunction with strict monitoring is associated with better clinical, radiographic and functional outcome than with classical follow-up (33, 63, 64). Thus, the treatment target should be reached ideally within 3 months. In line with these data, monitoring should be regularly performed. Valid measures for this purpose are represented by composite scoring systems including joint counts such as DAS, DAS28, simplified disease activity index (SDAI) and clinical disease activity index (CDAI) (65). As the majority of trials evaluating the efficacy of biologic therapies as well as the published guidelines consider DAS28 as the method of choice for evaluating disease activity and response to treatment, the expert panel suggests the use of DAS28 to evaluate response in biologic-treated patients in everyday practice.

Definition of treatment failure

- 1- Patients not achieving EULAR response (using DAS28) after 12 weeks of biologic treatment should be considered non-responders and a change in the treatment strategy is recommended (Ia, A).

Nowadays it is clear that attaining a state of remission or low disease activity leads to better structural and functional outcomes (5, 66, 67). Thus, remission is the primary therapeutic aim, in particular in patients with early RA, even if low disease activity may be an appropriate alternative, especially for patients with longstanding RA. However, achieving clinical remission cannot be used in clinical practice as the main criterion for deciding whether to change the treatment regimen. So patient response to treatment should be defined based on the EULAR response criteria using the DAS28. At least 12 weeks of treatment are required before concluding that a patient fails to respond.

¹After the completion of the bibliographic research and before manuscript submission, other three drugs came on the market in Italy with the indication for RA showing insufficient response to MTX (or other DMARDs): tocilizumab (IL-6 receptor antagonist), golimumab and certolizumab (both anti-TNF). Moreover, abatacept received the approval for RA patients with MTX insufficient response.

Strategies after biologic failure

1- First failure:

- 1.1. If the TNF antagonist is used alone, a reintroduction of conventional DMARD, in general MTX (up to 20 mg/week, if tolerated), is suggested (IV, C).
- 1.2. If the TNF antagonist used is infliximab, decreasing the dose interval (every 4 instead of 8 weeks) or increasing progressively by 1.5 mg/kg the dosage (3 to 7.5 mg/kg) may be effective (IIIb, D).
- 1.3. In patients with inefficacy or adverse events to the first TNF antagonist agent, either a treatment with a second TNF antagonist or with another biologic with a different mechanism of action is recommended (Ia, A).

2- Second failure:

- 2.1. Switching from a second to a third TNF antagonist is not recommended, as the rate of response to the third drug appears significantly lower (IV, C).
- 2.2. In patients failing to respond to a second TNF antagonist, other biologics with different mechanisms of action should be considered (Ia, A).

3- Three or more failures:

Even in patients failing to respond to 3 (or more) drugs, an attempt with another biologic drug might be helpful (Ib, A).

At the end of the literature search for the present paper, 3 TNF antagonists (infliximab, etanercept and adalimumab) were on the market in Italy for RA; in the real world up to 50% of patients fail to respond to these drugs or develop adverse events leading to treatment discontinuation (68-73). Patients who fail TNF antagonists have different treatment options, including the addition of conventional DMARDs, increasing dosage or decreasing administration intervals, switching to an alternative TNF antagonist, or changing to an agent with a different mechanism of action.

The better efficacy of the combination of biologics plus MTX or a different conventional DMARD has been clearly demonstrated in various clinical trials (54-57).

Several studies suggest that decreasing

the dosing interval or increasing the dosage may be helpful in patients not responding to infliximab therapy at the classical dosage of 3 mg/kg every 8 weeks (74-76).

Increasing the dosage of the other 2 TNF antagonists (etanercept and adalimumab) is only seldom reported and it does not seem to be helpful on clinical ground (76).

Data on switching TNF antagonists come from small case series and on the analyses of country-based large registries of patients treated with TNF antagonists. These studies are limited by their short duration, small sample sizes, and the lack of randomisation or controls (77-85).

The sequence and type of TNF antagonist switch may affect the effectiveness of subsequent anti-TNF therapies. Greater benefits with switching between a soluble receptor (etanercept) and a monoclonal antibody (infliximab or adalimumab or golimumab or certolizumab), compared with switches between monoclonal antibodies have been reported (78-81). The reason for stopping the first TNF antagonist may affect the rate of response to a second. It has been reported that a patient is more likely to stop taking a second TNF antagonist because of inefficacy if the first was also stopped because of inefficacy and, similarly, that a patient is more likely to develop an adverse event due to a second agent if the first was stopped because of an adverse event (80). The ReAct study, which included 899 patients who switched to adalimumab, demonstrated a better response rate in patients who replaced previous treatments because of loss of efficacy and adverse events than in those who presented primary failure (86). On the other hand, a third switch does not seem to be useful as the rate of response to the third TNF antagonist is significantly lower (87). It is fair to say that after two TNF antagonist failures even the other biologics with a different MOA (mode of action) do less well.

Several RCTs demonstrated that patients who fail a first course of a TNF antagonist may respond to rituximab or to abatacept (84, 88). Observational studies suggest that switching from a

TNF antagonist to another as well as switching from a TNF antagonist to abatacept or rituximab is beneficial. There are no controlled trials comparing switching between TNF antagonist and drugs with a different mechanism of action: at the moment there are no robust data to recommend the use of a second TNF antagonist with respect to change mechanism of action. At the moment the choice is largely based on the physician's experience as well as the patient's preferences and characteristics (89).

Management of patients achieving remission

1- In patients who achieve clinical remission, glucocorticoids and drugs that are mainly symptomatic (*i.e.* pain killers and non-steroidal anti-inflammatory drugs) should be decreased and stopped if possible (IIIb, B).

2- When a prolonged remission without glucocorticoids is obtained (over 12 months), a dose reduction in DMARDs and biotherapies may be considered (IIIb, B).

There are many definitions of remission, such as those by the ACR or based on composite disease activity measures (*i.e.* DAS, DAS28, CDAI, SDAI), and it is well established that some criteria allow for more residual disease activity than other (63). Furthermore, even when swelling cannot be discerned clinically, it may continue to exist at a subclinical level. If possible, this subclinical level should be evaluated with US and/or magnetic resonance imaging (MRI), which are more sensitive than physician's evaluation for detecting a low disease activity. Imaging demonstrates that synovitis can progress despite normalisation of laboratory parameters and clinical examination.

US is an important tool to monitor disease activity and progression and even remission. The Doppler technique enables evaluation of blood flow in different tissues (*i.e.* synovium, tendon and muscle). Despite a few limits (operator-related imaging technique, with few standardised protocols), it can detect and monitor soft tissue and joint inflammation (88, 89).

If available, MRI may be a useful and complete tool to evaluate erosive damage, bone oedema and (with contrast-enhanced MRI) synovial inflammation. In particular, bone oedema is seen as the most important predictor of radiographic progression (90).

Conclusion

These recommendations by the Italian Society for Rheumatology summarise the latest evidence pertaining to RA treatment, focusing on the use of biologic agents marketed in Italy. While MTX is still considered the primary option for most RA patients, the biologic agents currently available represent an effective treatment modality, in particular for patients showing a sub-optimal response to MTX. These recommendations will be reviewed periodically, in light of new published evidence.

Competing interests

C. Montecucco has received grants and research support from Abbott, Merck Sharp and Dohme, Pfizer, Schering-Plough, and Roche; R. Caporali has received honoraria as a speaker from Abbott, BMS and Roche; the other co-authors have declared no competing interests.

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