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# Biologic Treatment in Rheumatoid Arthritis

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## 1. Introduction

Rheumatoid arthritis (RA) is a common, chronic, inflammatory disease. It affects around 1% of the adult population in all age groups, although the incidence peaks during the fifth decade of life. The aetiology of RA is unknown, but it is considered to be autoimmune in nature. Inflammation in the synovial tissues of the joints is the hallmark of RA, causing pain, stiffness, loss of function and progressive destruction of the cartilage and bone in the inflamed joints in the majority of patients. Early diagnosis and appropriate treatment is crucial for the amelioration of symptoms, improvement of function and prevention of structural damage.

Traditionally, treatment of RA has been based on the use of a group of disease-modifying antirheumatic drugs (DMARDs), of which methotrexate (MTX) is the most widely used, often in combination with corticosteroids and/or NSAIDs (non-steroid anti-inflammatory drugs). Leflunomide, sulphasalazine, azathioprine, are examples of other synthetic DMARDs. The landscape of RA treatment has changed dramatically during the last decade due to the introduction of biologic DMARDs, small molecules that target small molecules (like cytokines) and cells of the immune system, important mediators of the immunological mechanisms in RA. To date, nine biologic agents have been approved for the treatment of RA and more molecules with distinct mechanisms of action are currently being tested in laboratories and in clinical trials. The good efficacy and general safety of these agents is well established from both clinical and epidemiological trials, but there are still several issues that remain unclear or need further study, such as long-term safety, more individualized treatment by finding predictors of response, cost-effectiveness, when to introduce biologic treatment and the feasibility of discontinuation after achieving low disease activity or remission.

Biologic (generic name)	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab
<b>Brand name</b>	Humira	Cimzia	Enbrel	Simponi	<b>Remicade</b>
<b>Structure</b>	monoclonal antibody, fully humanized	PEGylated Fab' fragment of humanized anti-TNF monoclonal antibody	Dimerized soluble TNF receptor	monoclonal antibody, fully humanized	Chimeric anti-TNF monoclonal antibody
<b>Mechanism of action</b>	TNF inhibition				
<b>Approved dosage</b>	40 mg	200 mg	50 mg	50 mg	<b>3 mg/kg</b>
<b>Approved interval</b>	every 2 weeks	every 2 weeks	once weekly	once monthly	<b>every 8 weeks</b>
<b>Route of administration</b>	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	<b>Intravenous</b>
Biologic (generic name)	Abatacept	Anakinra	Rituximab	Tocilizumab	
<b>Brand name</b>	Orencia	Kineret	MabThera (Rituxan)	RoActemra (Actemra)	
<b>Structure</b>	Dimerized CTLA4 molecule	Recombinant IL-1 receptor antagonist	Chimeric anti-CD20 monoclonal antibody	Humanized anti-IL-6 receptor antibody	
<b>Mechanism of action</b>	Inhibits T-cell activation	Binds IL-1 receptor	Binds and eliminates B cells	Binds IL-6 receptor	
<b>Approved dosage</b>	500–1000 mg	100 mg	1000 mg x 2 (with 2 weeks interval)	8 mg/kg	
<b>Approved interval</b>	once monthly	once daily	every 6–12 months	once monthly	
<b>Route of administration</b>	Intravenous	Subcutaneous	Intravenous	Intravenous	

**Table 1.** Biologic agents approved for the treatment of rheumatoid arthritis (RA).

## 2. Biologic agents

TNF (tumor necrosis factor) is a key cytokine of the immune response. Analysis of cytokine mRNA and protein in rheumatoid arthritis tissue revealed that many proinflammatory cytokines such as TNF alpha, IL-1 and IL-6 are abundant in all patients regardless of therapy<sup>1</sup>. These cytokines are of major importance in rheumatoid arthritis and are therapeutic targets. Five TNF inhibitors have been approved for the treatment of RA: the monoclonal antibodies infliximab (chimeric), adalimumab and golimumab (fully human), the TNF receptor etanercept, and the PEGylated Fab fragment of a fully human anti-TNF monoclonal antibody certolizumab pegol. There are several differences in pharmacodynamics and pharmacokinetics between these agents (table 1). Apart from the TNF inhibitors, biologics with different mechanism of action have been increasingly used in the clinical practice. Rituximab targets CD20 on the surface of B-cells and have been widely used in hematology for lymphoma treatment; Tocilizumab is an IL-6 (interleukin 6) inhibitor while anakinra blocks IL-1. Finally, abatacept inhibits costimulation of T-cell by binding B7 (table 1).

## 3. Efficacy of biological DMARDs

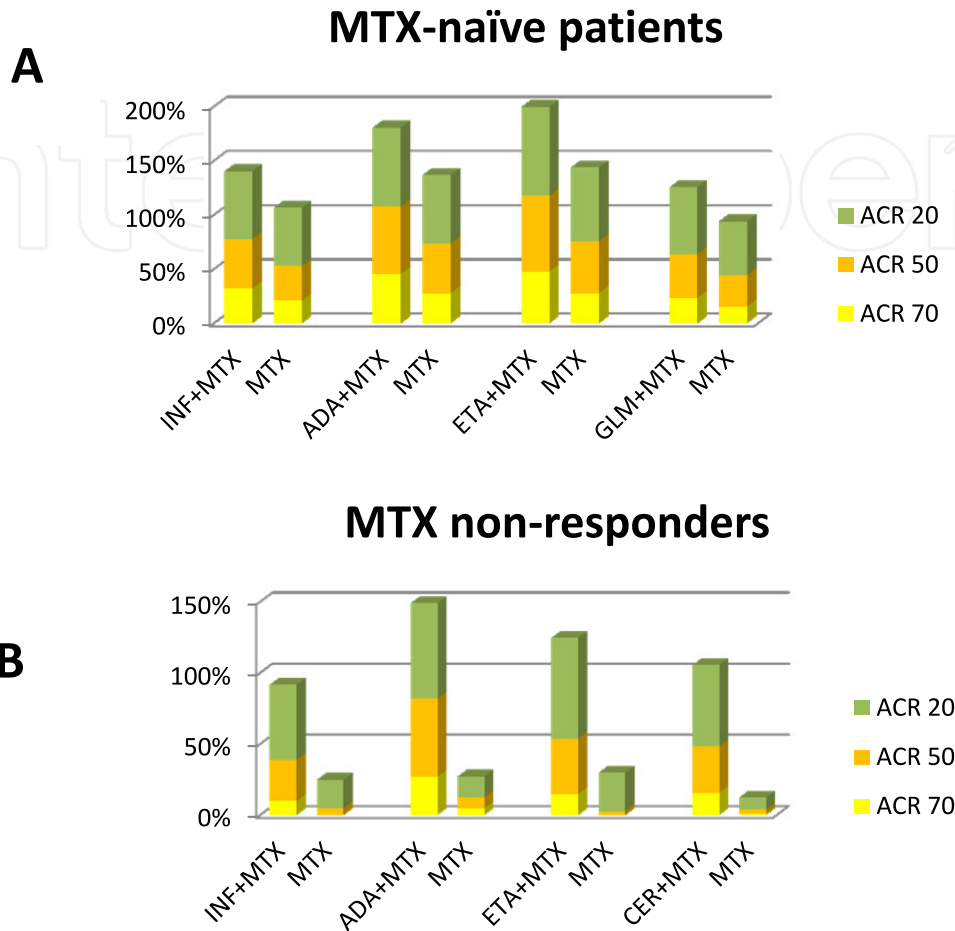
Numerous randomized clinical trials provide clear evidence on the efficacy of biologic agents in RA, both in early disease (short disease duration) in biologic-naïve population and in late RA (longer disease duration) after failure of traditional DMARDs. These trials show the superiority of combination treatment of a biologic agent with methotrexate versus methotrexate monotherapy in both early and late disease<sup>2-18</sup>. In figure 1 and 2 the ACR 20, 50 and 70 responses\* of TNF inhibitors and other biologics from the largest clinical trials in methotrexate naïve patients and after inadequate response to methotrexate, are shown. The data demonstrate also clearly, especially in the MTX-naïve population, that a considerable proportion of patients respond to the simpler and less expensive monotherapy with methotrexate (MTX). Thus, one should keep in mind that in the combination groups, there are patients who would have responded to MTX monotherapy as well.

In figure 2, the clinical responses of other biologic agents plus MTX versus placebo plus MTX are summarized. Again efficacy in early and in late disease is evident. Superiority of rituximab over placebo was observed in the IMAGE and SERENE trials<sup>9,10</sup>. Abatacept demonstrated acceptable safety and clinically meaningful efficacy in methotrexate naïve patients and methotrexate non responders<sup>7,11</sup>. Additionally, in the TOWARD trial<sup>17</sup>, tocilizumab-treated patients achieved significantly better results than those who received placebo during the first 6 months of therapy, after inadequate response to traditional

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\* ACR responses is a validate tool for the evaluation of efficacy of treatment in RA. ACR 20/50/70 response is defined as at least 20, 50 or 70%, respectively, improvement in both swollen joint count (SJC) and tender joint count (TJC), and at least 20, 50 and 70% improvement in 3 of the 5 following measures: pain VAS (visual analogue scale), Patient global assessment, Physician global assessment, ESR (erythrocyte sedimentation rate) or CRP (C-reactive protein) and functional questionnaire.

DMARDs. A large trial on the efficacy of tocilizumab in early RA is currently conducted. All these biologic agents seem to have comparable efficacy and significantly greater efficacy than placebo.

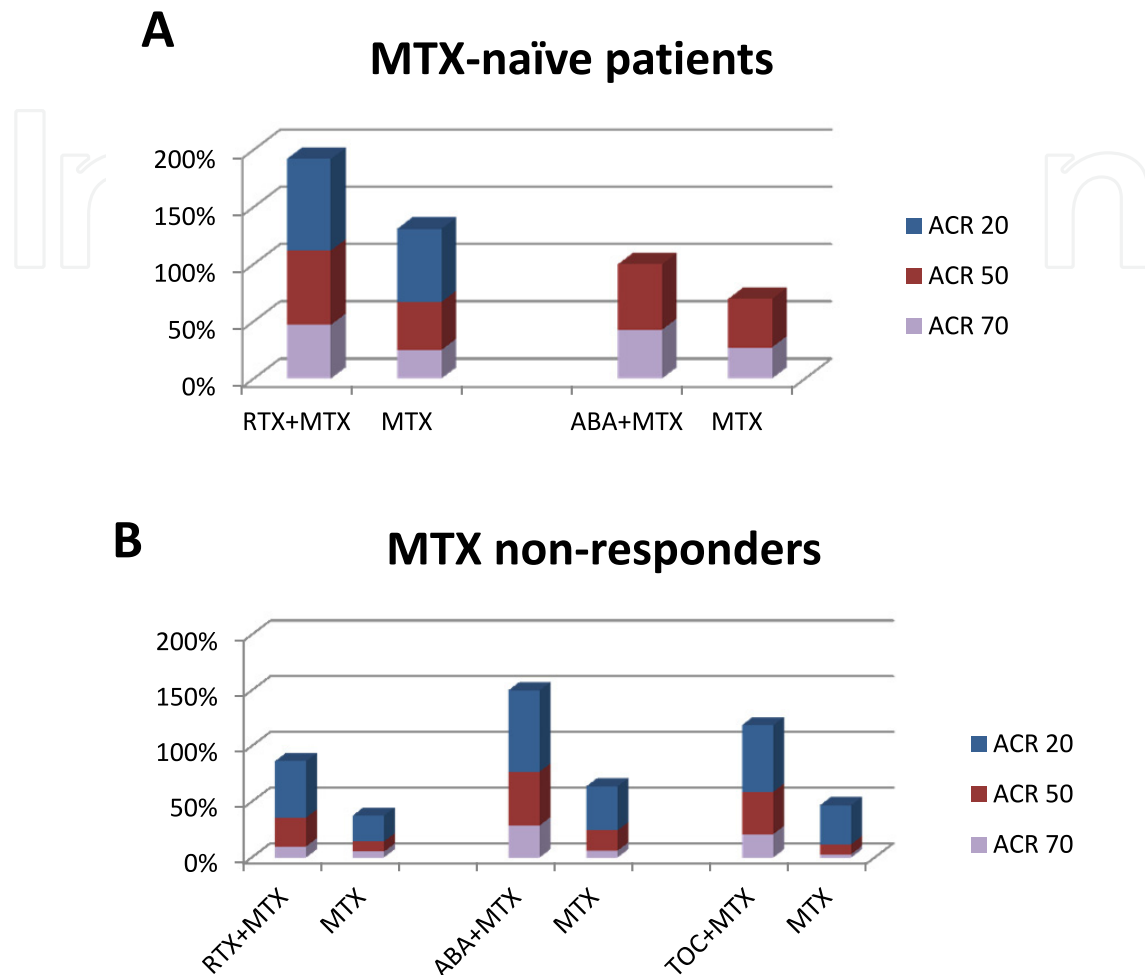


**Figure 1. A and B.** Efficacy of TNF inhibitors (infliximab INF, etanercept ETA, adalimumab ADA, golimumab GLM, certolizumab pegol (CER) in combination with methotrexate (MTX) versus MTX monotherapy in MTX-naïve RA patients (1A) and RA patients with an inadequate response to MTX (1B). Efficacy is assessed by ACR 20, 50 and 70 responses.

#### 4. Safety of biological DMARDs

Extension phase of clinical trials as well as data from registry studies provide us with important information about the safety of biologic DMARDs. The safety profile is generally acceptable, with a small increase risk for infections being the most common adverse event<sup>22</sup>. Reactivation of latent tuberculosis is a well known risk during treatment with TNF inhibitors, therefore screening for tuberculosis is recommended before initiation of a TNF inhibitor. Infusion reaction is a common adverse event for rituximab and infliximab. Anti-TNF induced SLE and demyelinating disease are rare complications of TNF inhibitors. Regarding risk for malignancies, data so far have not shown any clear increase in risk for malignancies. A meta-analysis of clinical registries and prospective observational studies showed no increase in malignancies other than skin cancers, including lymphoma,

associated with the use of TNF inhibitors<sup>23</sup>. However, longer follow up especially from large cohorts of patients, is needed.



**Figure 2. A and B.** Efficacy of rituximab (RTX), abatacept (ABA) and tocilizumab (TOC) in combination with methotrexate (MTX) versus MTX monotherapy in MTX-naïve RA patients (2A) and RA patients with an inadequate response to MTX (2B). Efficacy is assessed by ACR 20, 50 and 70 responses.

## 5. When to start biologic agents

The effectiveness of biologic agents is well established in the above large, randomized clinical trials. These results do not, however, answer the question of when a biologic DMARD should be initiated. Traditional DMARDs, and most often methotrexate, unless contraindicated) is the first line treatment. However, about two third of patients who start treatment with methotrexate will discontinue treatment for reasons of either inefficacy or intolerance. The next step is either a combination of synthetic DMARDs (e.g. sulphasalazine and hydroxychloroquine) or introduction of a biologic agent. So far, only a few clinical trials have made a direct comparison of these two treatment options. In the SWEFOT trial, patients with early RA with an inadequate response to MTX after 3 months, defined as lack of achievement of low disease activity, were randomly allocated to addition of either sulphasalazine and

hydroxychloroquine or infliximab. The latter group had significantly greater responses after 12 months of therapy, with 39% of patients achieving the primary endpoint (European League Against Rheumatism (EULAR) good response<sup>†</sup>, which is a widely used validated outcome) compared to 25% in the former group (p=0.016)<sup>24</sup>. However, at the 2-year follow-up assessment, the clinical difference was no longer present (EULAR Good response was 38% in infliximab group vs. 31% in the conventional DMARDs group (p=0.2), but radiological disease progression was significantly greater in the latter group than the former<sup>25</sup>.

Similar results were established in the BeSt trial<sup>26,27</sup>. In the BeSt trial three treatment groups were formed: sequential DMARD monotherapy (group 1), step-up combination therapy (group 2), initial combination therapy with tapered high-dose prednisolone (group 3) and infliximab (group 4). It was shown that a more aggressive treatment strategy as in group 3 and 4 provided earlier clinical improvement than a less aggressive strategy as in groups 1 and 2. Low disease activity (defined by DAS<sub>44</sub> ≤ 2.4) was reached by 53%, 64%, 71% and 74% of patients in group 1, 2, 3 and 4, respectively (p=0.0004 for group 1 vs. 3, p=0.001 for group 1 vs. 4). After 2 years, patients in all four treatment groups had approximately the same improvement in disease activity and functional status irrespective of initial treatment, probably because of tight control and frequent treatment adjustments. However, the more aggressively treated patients had less radiological progression of joint damage, and during the second year more of them could be treated successfully with monotherapy, suggesting that the initial aggressive therapy did result in some long-term gains.

## 6. When to stop biologic agents

A significant number of patients who receive biological treatment achieve low disease activity or remission. It is often difficult to define these terms, and there are today several definitions of both low disease activity and remission. According to the 2011 ACR (American College of Rheumatology) / EULAR (EUropean League Against Rheumatism) criteria, remission of rheumatoid arthritis is defined as tender joint count ≤ 1 AND swollen joint count ≤ 1 AND C-reactive protein ≤ 1 mg/dl AND patient global assessment ≤ 1 (on a 0-10 scale) (boolean-based definition) or a Simplified Disease Activity Index score of ≤ 3.3 (Index-based definition)<sup>28</sup>. Other definitions of low disease activity and remission are also frequently used, as for example DAS28 score ≤ 3.2 (low disease activity) and DAS28 ≤ 2.6 (remission).

When a patient is in state of low disease activity or remission for a sufficiently long period of time (usually at least 6 months) the next step is to assess the feasibility of discontinuation of the biologic agent with the aim of maintaining the good clinical response. This is a

<sup>†</sup> Definition of EULAR responses:

DAS28 at endpoint	Improvement in DAS28 from baseline		
	≥1.2	>0.6 and <1.2	≤0.6
≤3.2	GOOD	MODERATE	NO
>3.2 and ≤5.1	MODERATE	MODERATE	NO
>5.1	MODERATE	NO	NO

DAS28=Disease Activity Score (based on 28 joint status)

$$DAS28 = 0.56 * \sqrt{TJC28} + 0.28 * \sqrt{SJC28} + 0.70 * \ln(ESR) + 0.014 * (\text{General Health})$$



question of importance for reasons of safety and health economics. In various settings, the possibility has been investigated of discontinuing the biologic agent while maintaining the patient in remission on a conventional DMARD.

In the ATTRACT study 17 patients in a single centre in the UK received infliximab and all 17 experienced flare-ups after discontinuation of the biologic therapy after 2 years, with a mean time of 13.5–15.0 weeks after the end of therapy<sup>29</sup>. Of importance, re-introduction of infliximab after disease flare was associated with comparable responses without any safety issues. In another study Quinn et al. addressed the same question in a randomized, double-blind, placebo-controlled trial in a population of patients with early RA, with symptom duration of <12 months<sup>2</sup>. Induction of remission with infliximab plus MTX in early, poor prognosis RA provided not only significant reduction in synovitis and erosions at 1 year (shown by magnetic resonance imaging), but also sustained functional and quality-of-life benefits for 70% of the patients at 2 years despite infliximab withdrawal. These two studies tested the same question in different populations of RA patients; the former one in patients with longstanding disease (mean disease duration, 11 years), and the latter in patients with early RA. More recently, Tanaka et al. determined the possibility of discontinuing infliximab after attaining DAS-guided low disease activity in patients with RA in the remission induction by Remicade in RA (RRR) study<sup>30</sup>. Of 102 patients, 56 (55%) maintained DAS28<3.2 and 44 (43%) reached remission (DAS28<2.6) 1 year after the discontinuation of infliximab. The mean disease duration in this study was 5.9 years which suggests that discontinuation of infliximab would be possible not only in patients with early RA but also in patients with more established disease. In a post hoc analysis from the BeSt study, it was shown that significantly more patients who received initial combination therapy with infliximab and MTX achieved sustained DAS<sub>44</sub>≤2.4 and were able to discontinue infliximab, compared with those with delayed introduction of the biologic agent (56% vs. 29%, p=0.008)<sup>31,32</sup>. It was also shown in the BeSt study that the shorter the symptom duration, the higher the likelihood of a biologic-free, and even a drug-free, remission. A systematic review and meta-analysis showed that patients with established RA who stopped treatment with traditional DMARDs had a significantly higher risk of disease flare or deterioration than those who continued treatment<sup>33</sup>. In this analysis, however, patients had RA of more than 2 years duration. Larger randomized, controlled, double-blind trials are needed in order to better approach this important issue.

Several conclusions can be drawn from the information that exists today about discontinuation of biologic DMARDs:

- Discontinuation of biologic treatment and sustained remission or low disease activity is the long-term therapeutic goal, important for matters of long-term safety and health economics.
- Biologic-free remission may be possible after achieving remission or low disease activity in a considerable proportion of patients.
- The duration of disease until the introduction of the biologic treatment may be negatively associated with the risk of deterioration after discontinuation of treatment, thus suggesting that earlier initiation of biologic treatment leads not only to better results, but also increases the possibility of withdrawal of biologic agents with maintenance of remission.



- More data about the feasibility of dose reduction or discontinuation of biological DMARDs are needed.

## 7. Principles for use of biologic treatment in rheumatoid arthritis

The rapid progress and advances in the field of biologic treatment in RA, combined with the high cost of these drugs and the potential long-term safety issues, makes it necessary to define clear rules that will guide the use of these agents in clinical practice.

The rheumatologist should always keep in mind that the goal of RA treatment today is remission or low disease activity, if remission cannot be achieved. Treatment efficacy should be assessed in tight time intervals and changes in treatment should be considered if the goal has not been reached<sup>34</sup>.

As soon as the diagnosis of RA is established a synthetic DMARD (most often Methotrexate) is started with or without concomitant corticosteroids. If the goal of treatment is not achieved after 3 months, an additional DMARD can be added or a biologic agent can be introduced. As it was analyzed above, data have shown superiority of the latter choice. Especially for patients with multiple negative prognostic factors, such as seropositivity, radiographic progression and high disease activity, early aggressive treatment is strongly indicated. In the absence of these unfavorable factors one could consider testing switching of synthetic DMARD or combination of synthetic DMARD +/- corticosteroids before biologics. In patients with active RA who have not yet been treated with DMARDs there is strong evidence that biologics provide better results at the group level, but not widely used in practice based on various considerations (safety, high cost, possibility of very good effect of methotrexate).

The first biologic agent is most often a TNF inhibitor, unless contraindicated. If possible, TNF inhibitors should be combined with MTX; the clinical efficacy particularly the radiological efficacy of the combination is clearly superior to TNF inhibitor monotherapy. In case of a contraindication to TNF inhibitor therapy, a biologic agent with a different mechanism of action (rituximab, abatacept or tocilizumab) can be chosen.

About one third of patients will discontinue the first TNF inhibitor for reasons of either intolerance or inefficacy (lack of efficacy or loss of efficacy). Since the goal is still remission, even patients with moderate responses ('partial responders') should eventually be candidates for an alternative treatment.

After the failure of one biologic agent for the reasons described above, and after having perhaps tried to modify the dose of the concomitant DMARDs and/or corticosteroids with no effect, three main treatment options are available: a) optimize the dose of biologic drug; b) switch between TNF inhibitors; or c) switch to a biologic agent with a different mechanism of action.

### 7.1. Optimize dose of biologic

As it is shown in table 1, the TNF inhibitors have different dose intervals, ranging from once weekly (etanercept) to once every 8 weeks (infliximab). Concerning optimization of the

infliximab dose, controversial data are available. In the ATTRACT trial, four different treatment regimens of infliximab were studied: infliximab 3 mg kg<sup>-1</sup> every 4 and 8 weeks and 10 mg kg<sup>-1</sup> every 4 and 8 weeks. At 24 weeks similar American College of Rheumatology (ACR) responses were observed. At 48 weeks, however, there was a tendency for the lowest dosage of infliximab to be less effective than the higher ones, but this difference was only significant with respect to the ACR50 responses<sup>29</sup>.

An important question is whether dose increase or change of treatment interval can yield better results in patients with secondary loss of efficacy to infliximab. Results from uncontrolled observational studies have suggested that this might be true<sup>35</sup>. On the other hand, in a double-blind randomized trial, Pavelka *et al.* showed no significant difference in efficacy of two dosages of infliximab (3 and 5 mg/kg) after initial failure of the lower dosage to lead to remission<sup>36</sup>. Moreover, the higher dosage had a poorer safety profile. In an observational study conducted in our centre, patients in whom the dose of infliximab was increased in clinical practice appeared to have a benefit, as defined by reduction in the disease activity score (DAS28)<sup>37</sup>. However, patients in the control groups (i.e. patients with no change in infliximab dose and those receiving a stable dose of etanercept) also showed an improvement in DAS28. This observation suggests that the improvements were most probably attributable to regression to the mean and that no important benefit is gained from dose increases of infliximab. Finally, van den Bemt *et al.* found that 17 of 18 patients who were in clinical practice treated with infliximab at dosages higher than 3 mg/kg showed no deterioration of their RA if the dosage was reduced to 3 mg/kg<sup>38</sup>. In conclusion, the evidence suggests that increasing the dose of infliximab might result in loss of time, higher cost and potentially more side effects with no significant efficacy gain in most patients. Therefore, it would clearly be useful to be able to identify, using relevant biomarkers, a smaller subset of patients who might truly benefit from dose increases. Studies to investigate this possibility are currently underway.

## 7.2. Switching to an alternative TNF inhibitor

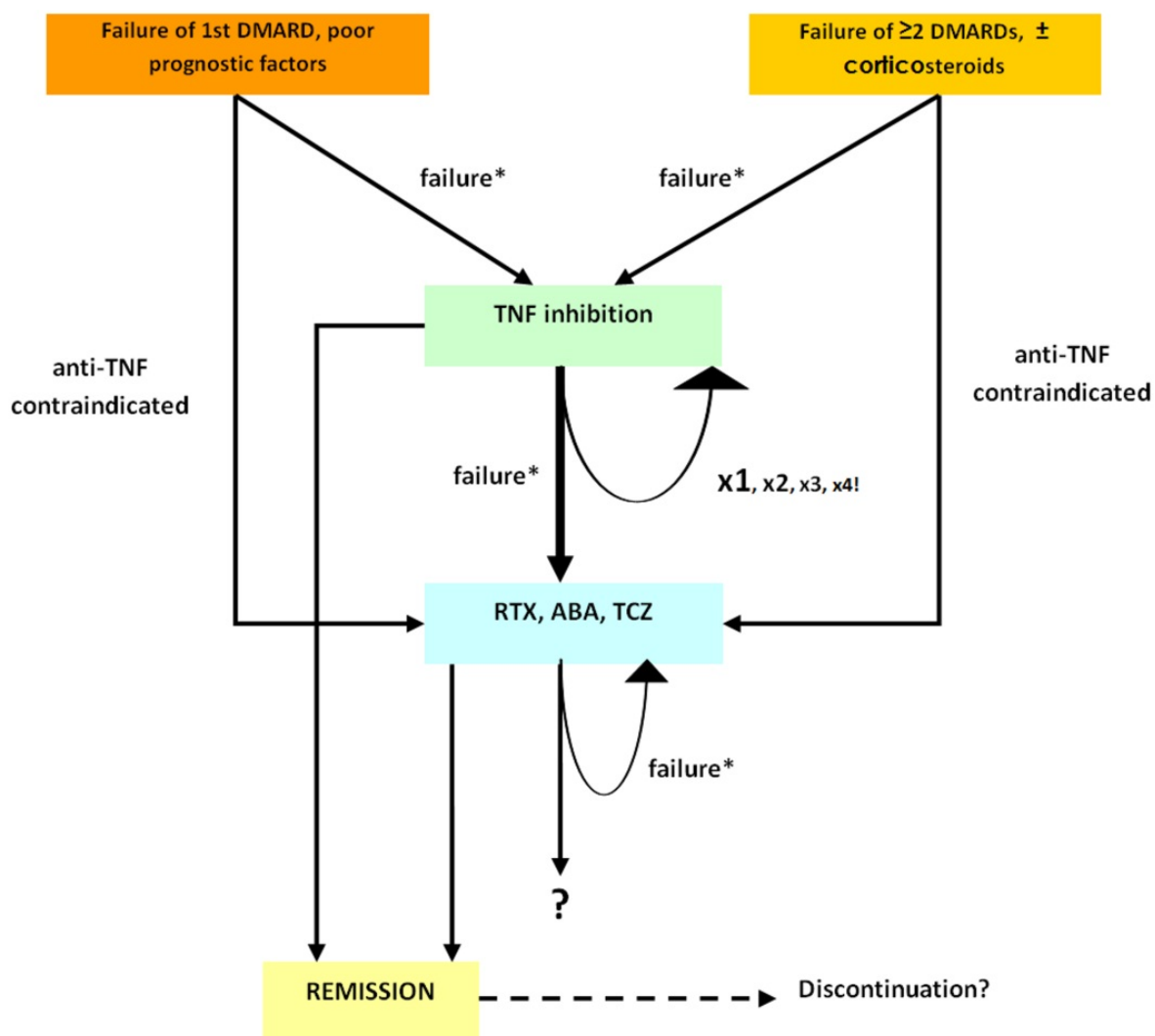
As it is shown in table 1, there are substantial differences between the five TNF inhibitors available today (in molecular structure, immunological actions and in pharmacokinetics). This is the reason why switching from one TNF inhibitor to another does make sense and is often used in the clinical practice, although these agents target the same cytokine. Observational studies support this argument, as a significant proportion of patients benefit from this switching. In the randomized double-blinded GO-AFTER study, patients who received golimumab after failure of a prior TNF inhibitor, showed significantly greater responses than those who received placebo<sup>39</sup>. However, cohort study data have shown a gradual loss of efficacy after a greater number of switches<sup>40-44</sup>. Thus, a first switch might provide significant improvement, whereas the effect is much less profound at the second or third switch.

## 7.3. Switch to a biologic with different mechanism of action

It might sound more reasonable, after the failure of TNF inhibition the next step to be change of mechanism, rather than switching between agents of the same drug class. There is

strong evidence about the efficacy of rituximab, abatacept and tocilizumab after TNF treatment (figure 2). However, there is no randomized clinical trial comparing head to head these two treatment options, but there are some observational studies from national registries. In the Swiss Clinical Quality Management program for RA (SCQM-RA) registry, patients with inadequate response to TNF inhibitor treatment achieved greater reductions in DAS28 when switching to rituximab than to an alternative TNF blocker<sup>45</sup>. This was especially obvious when the reason for discontinuation of the previous TNF inhibitor was secondary inefficacy<sup>46</sup>. A small observational study by Venkatachalam *et al.* provided similar results, whilst a study reported by Buch *et al.* also demonstrated comparable results of rituximab and alternative TNF inhibitors<sup>47,48</sup>. Our data have shown slightly better overall results for patients who had failed TNF inhibitor therapy when treated with rituximab than with another TNF blocker, but both options provided clinical benefits<sup>49</sup>.

In figure 3 an algorithm of biologic treatment in RA is presented<sup>50</sup>.



**Failure\*:** primary or secondary loss of efficacy, intolerance or a partial, inadequate response. (After optimizing DMARD dose and/or trying combination of DMARDs).

**Figure 3.** Algorithm of biologic treatment in RA.

## 8. Conclusions

The field of RA treatment has changed dramatically after the introduction of biologic DMARDs. Despite the advances though, several issues remain to be further studied and clarified. On the one hand treatment algorithms are needed of the choice and time of introduction of biologics. On the other hand a more individualized treatment might be possible in the future. Such an approach is crucial, taking into consideration the increasing number of biologic agents, their high cost and the importance of choosing the right treatment from the beginning. These are some of the important challenges of clinical, epidemiological and basic rheumatologic research.

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