



Review

Strategies after the failure of the first anti-tumor necrosis factor α agent in rheumatoid arthritis

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ABSTRACT

During the last two decades fundamental changes have taken place in the treatment of patients with rheumatoid arthritis (RA). The effective establishment of methotrexate as the anchor drug and the introduction of new drugs, in particular anti-tumor necrosis factor (TNF) α blockers and the novel biologics have made the goal of remission feasible for plenty of RA patients. However, almost 14–38% of patients do not respond to first-line anti-TNF- α treatment at all and as many as 40% discontinue these drugs within a year and 50% within 2 years. Currently, no recommendations exist as regards the treatment of RA patients after TNF- α -antagonist failure. In this review the issue of anti-TNF- α therapy failure is discussed. Further, the various options for overcoming the apparent failure are explored according to evidence from the published literature.

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1. Introduction

Rheumatoid arthritis (RA) is a chronic disease affecting almost 0.5–1% of the population [1]. Through chronic synovial inflammation, it causes destructive changes to articular cartilage and bone leading to

various deformities, while it is often accompanied by extra-articular features, such as rheumatoid nodules, pleuritis, ocular inflammation, generalized osteoporosis, cardiovascular disease and amyloidosis. The patients experience pain, distress, loss of function in daily living, permanent disability and an increase in overall morbidity and mortality compared to the general population [2,3]. Given the considerable burden of the disease, both on the individual and the community level, a great deal of scientific work during the past 30 years has fundamentally changed the way the disease is regarded and treated. One should distinguish three crossroads in this pursuit, each often being the starting

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point for the other: the advances in basic research have deciphered to a significant depth the pathogenesis of the disease, putting various players (genes, environment, cells, cytokines, receptors etc) and their sophisticated interactions down on a complex pathogenetic map. Once the suspects had been identified and with the aid of advances in pharmacology, new treatment options rose leading to the era of targeted therapies, like anti-tumor necrosis factor (TNF) α , anti-B-cell therapies etc. Finally, clinical trials and long-term observations on thousands of patients have helped forge treatment strategies in RA.

Indeed, based on the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) recent recommendations [4,5], in every patient with inflammatory polyarthritis treatment should be initiated as early as possible, even if the ACR criteria for RA classification are not fulfilled. Treatment should aim for remission and should always include a disease-modifying anti-rheumatic drug (DMARD), with methotrexate (MTX) as the anchor drug. If the patient does not respond adequately to DMARD monotherapy, then a modification of the DMARD dose should be made or another drug should be added in combination, the latter drug being another DMARD or a biologic agent. So far, it is the TNF- α blockers that have almost universally been used as the first biologic agent in RA. Although abatacept has also been approved in the United States for treating RA as the first biologic drug and tocilizumab has recently been approved in the European Union for use after first DMARD failure, the largest experience with a biological agent in this setting still concerns the three TNF- α blockers, infliximab, etanercept and adalimumab. However, there are no recommendations regarding how to treat patients after the first anti-TNF- α drug has failed.

2. Rephrasing the question

Even if no formal guidelines exist for RA treatment after failure of the first TNF- α inhibitor, all agree that the patients should be treated to the point of remission. The rationale behind this is that even smoldering disease activity may produce accumulating structural damage which through time leads to progressive and irreversible disability [6]. To this, plenty composite disease activity measures have been proposed and validated, so as to measure disease activity (e.g. disease activity score [DAS], DAS for 28 joints, [DAS28], clinical disease activity index [CDAI], simplified disease activity index [SDAI]), or response to treatment (e.g. ACR or EULAR response criteria). Nevertheless, defining remission still remains elusive, given that almost 10% of RA patients judged to be in remission according to ACR or EULAR criteria keep on progressing radiographically. In a cohort of RA patients in remission, a significant predictor of structural progression was found to be an increased power Doppler signal in musculoskeletal ultrasound [6]. Thus, independently of the drugs used for treating RA, one should previously define the tools to use and the goals to set, e.g. remission according to a composite index and/or inhibition of structural progression and/or suppression of power Doppler signal.

Defining treatment goals allows defining treatment failures as well. In the case of anti-TNF- α therapy, it would be prudent to distinguish the following cases: (1) a patient has received anti-TNF- α treatment with no subsequent improvement at all; alternatively the drug has produced some benefit, but has never adequately suppressed disease activity; (2) a patient experiences a relapse of disease activity, despite continuing an anti-TNF- α treatment which had initially been successful (i.e. had produced a major response/remission); and (3) a patient discontinues anti-TNF- α treatment as a result of adverse events. These adverse events could further be classified as drug-specific (e.g. infusion-related reaction, injection site reaction) or class-specific (e.g. reactivation of latent tuberculosis, demyelinating nervous system disease, emergence of autoimmunity, deterioration of congestive heart failure, lymphoproliferative disorder etc).

3. Response to anti-TNF- α therapy

Due to channeling bias, RA patients who have failed at least one DMARD and subsequently are added an anti-TNF- α blocker are less likely to achieve disease remission compared to patients who have received no treatment at all, because drug-naïve patients comprise also those who will respond to MTX monotherapy. Thus, the highest efficacy of TNF- α antagonists is expected to occur in randomized controlled trials (RCT) comparing MTX monotherapy to combination treatment with MTX plus anti-TNF- α blockers in drug-naïve patients. In such trials, the percentage of patients who did not achieve an ACR20 response at 12 months were 37.6% for the combination of MTX plus infliximab 3 mg/kg [7], 14% for MTX plus etanercept [8], and 27% for MTX plus adalimumab [9] while the respective value (at 6 months) for the combination of MTX plus golimumab 50 mg monthly was 38.4% [10]. Further, ACR70 responses were achieved by 32.5% with MTX plus infliximab, 48% with MTX plus etanercept, 46% with MTX plus adalimumab and 23.9% with MTX plus golimumab 50 mg. This means that 52.0–67.5% of patients receiving a combination of MTX with one of the currently licensed TNF- α inhibitors (golimumab had not been licensed when these lines were being written) fail to achieve a major response.

Besides measures of efficacy, the overall success of TNF- α inhibitors can be assessed by means of survival of the drug over time. Such data are available for various countries, indicating at the same time some peculiarities of each of the three available anti-TNF- α agents. In the Netherlands, the one-year survival for infliximab, adalimumab and etanercept were 59%, 76% and 80% respectively, while the two-year values were 49%, 66% and 74% respectively, with infliximab having a significantly shorter survival than the two other drugs. The anti-TNF- α agent was discontinued due to inefficacy in 35% and adverse events in 42% of patients with no difference observed between the individual TNF- α antagonists [11]. In a report from the Spanish registry of biologics in chronic arthritides (in which 68% patients were treated for RA), 83% of patients remained on anti-TNF- α therapy after one year. The main reasons for discontinuation were adverse events (48%) and inefficacy (38%) [12]. Similarly, 84.5% of our own RA patients treated with infliximab remained on therapy after 1 year, 73% after 2 years and 59% after the third year. Over 3 years 19% of treated patients discontinued infliximab due to adverse events and 11% due to inefficacy [13]. Data from France show that 78% of RA patients remain on anti-TNF- α therapy after one year and 62% after 2 years. As in the aforementioned Spanish registry infliximab survival was less than that of adalimumab or etanercept [14]. Additionally, after eight years of follow-up in the context of the Danish registry, etanercept had the best survival rates compared to infliximab and adalimumab [15]. Conversely, observational data from Switzerland did not reveal a difference in survival rates between the three TNF- α blockers, although intensification of concomitant DMARDs or increases in the dose of the anti-TNF- α agent were more common with infliximab compared to adalimumab and etanercept [16].

The reasons for treatment inefficacy are not clearly understood. A possible mechanism is the development of antibodies that target infliximab and adalimumab. As shown recently, patients treated with infliximab or adalimumab who had anti-anti-TNF- α antibodies had lower serum trough levels of the drug and poorer response to treatment [17]. On the contrary, etanercept use has been associated with anti-etanercept antibody formation in a low proportion of RA patients. Furthermore, these antibodies do not seem to neutralize etanercept and do not affect clinical response [18].

4. Strategies after first anti-TNF- α failure

Since no formal studies have been conducted regarding which is/are the best option(s) after a RA patient has failed the first TNF- α blocker, it is on the physician's discretion to choose. Reasonably, the

optimal treatment should be swiftly effective, safe in the long term and at an acceptable cost, given the already high costs of the anti-TNF- α therapy (Table 1).

4.1. Optimize DMARDs

The DMARD most extensively studied in conjunction with the anti-TNF- α agents is MTX. In the initial combination therapy with infliximab and MTX group of the BeSt trial, where remission was the goal, MTX was started at a dose of 25–30 mg weekly before any modification of the infliximab dosage could be made according to disease activity [19]. Moreover, a recent systematic literature review of MTX use in RA showed that MTX should be started at 15 mg weekly and in case of inadequate response should be raised by 5 mg/week monthly up to 25–30 mg/week, or as tolerated [20]. In case of intolerance of MTX per os, a switch may be attempted to parenteral MTX. Hence, in patients who have not achieved remission on anti-TNF- α therapy adding MTX or, more likely, increasing MTX to the best tolerated dosage (up to 25 mg weekly) or finally switching to parenteral MTX is a reasonable option for patients to gain some extra benefit towards remission.

All three anti-TNF- α agents have been formally tested in RCT either in monotherapy or in combination with MTX. However, in the real world they are used in combination with other DMARDs as well, although there are no relevant clinical trials. In a study from our department, infliximab was added to 18 patients with active RA despite treatment with a combination of cyclosporin A (CsA) plus prednisone. These patients had been prescribed CsA due to MTX intolerance. After one year, the patients showed a satisfactory response with 80% of them achieving an ACR20 improvement and 39% achieving ACR50. Moreover, no unusual adverse events emerged during the use of the combination of infliximab with CsA [21]. Recently, data have been published concerning the use of leflunomide in combination with anti-TNF- α agents in patients with RA in the German registry. The data showed that the combination of each TNF- α blocker with leflunomide was comparable to the combination with MTX in terms of efficacy and anti-TNF- α agent survival. The survival of leflunomide within each combination though was slightly less than that of MTX. According to these results, patients on anti-TNF- α therapy not tolerating MTX could be switched to a combination with leflunomide [22].

4.2. Optimize TNF- α inhibitors

Before discontinuing an anti-TNF- α agent due to inefficacy, a rational approach would be to use it up to its dose limits. This approach is more applicable for infliximab that can be given at doses starting from 3 mg/kg up to 7.5 mg/kg and at intervals ranging from 8–4 weeks. Which approach is more efficacious, if at all, is still debated. In one of the oldest infliximab studies, the ATTRACT trial, pharmacokinetic models predicted that shortening the dose intervals from 8 to 6 weeks could achieve higher trough serum levels than increasing the dose by 100 mg [23].

However, in the RISING clinical trial patients who had started infliximab at 3 mg/kg at weeks 0, 2, 6 were subsequently randomized

to receive 3 mg/kg, 6 mg/kg or 10 mg/kg every 8 weeks. One year later, patients who had received 10 mg/kg had showed a better response than those who had received 3 mg/kg, although neither radiographic progression nor the occurrence of adverse events were statistically different between groups. At week 54 the trough serum levels of infliximab were positively correlated with clinical response and radiographic inhibition. Interestingly, in a subanalysis, patients who had not initially responded to 3 mg/kg and later received 6 mg/kg or 10 mg/kg had a better outcome than those who had not responded to 3 mg/kg but remained at the same dose. However, this trial was not specifically designed to assess if raising infliximab dose may produce additional benefit in patients not responding to 3 mg/kg. The subanalysis mentioned above included few patients (10, 16, 11 in the groups receiving 3, 6, 10 mg/kg respectively). Finally, the main comparison was made between the groups receiving 3 and 10 mg/kg, although infliximab is not currently licensed at so high a dose [24].

On the contrary, in another double blind RCT patients who had responded to infliximab 3 mg/kg, but had not achieved remission were randomized to receive either 3 mg/kg or 5 mg/kg for another 12 months. At the end of the 12 months, patients receiving both doses had similar disease activity scores, while the occurrence of adverse events was slightly higher in the group that had received the 5-mg/kg dose. This was a well-designed study aimed precisely to the issue in question, although it did not comprise an arm receiving infliximab 7.5 mg/kg, which is the highest approved dose [25].

In summary, optimizing infliximab may be achieved by either increasing the dose or shortening the dose intervals. If increasing exposure to infliximab is beneficial is still a matter of controversy. However, on clinical grounds increasing the dose may worth a try in patients not achieving a satisfactory response, while shortening dose intervals could be more beneficial in patients who experience a symptom relapse before the time of the next scheduled dose (usually at 8 weeks).

Regarding adalimumab, in one clinical trial in RA doses of 40 mg weekly in monotherapy were more effective compared to the usual dose of 40 mg every 2 weeks in terms of achieving a good EULAR response. In fact besides the dose of 40 mg every 2 weeks, the drug has formally been approved for RA at the dose of 40 mg weekly when given as monotherapy [26]. In contrast, in the ARMADA trial, RA patients on background MTX had no additional benefit when prescribed adalimumab 80 mg every 2 weeks compared to 40 mg every 2 weeks [27].

Finally, as far as etanercept is concerned there has been a clinical trial assessing the efficacy of increasing the dose of etanercept to 50 mg twice weekly in RA patients with an inadequate response to etanercept 50 mg weekly and background MTX. In this clinical trial no additional benefit was proved by raising the etanercept dose and, thus, no increase in the drug is recommended in case of inadequate response [28].

4.3. Discontinue TNF- α blockers and continue with DMARDs

Controlled data on the efficacy of replacing failed anti-TNF- α agents with DMARDs or DMARD combinations are virtually lacking. Besides, TNF- α blockers have been introduced to treat patients who, in most cases, have previously failed at least one DMARD. Hence, abandoning TNF- α blockers for DMARDs seems more like a turning back with few chances of success. Some indirect evidence can be traced in the BeSt trial. Indeed, in group 4, patients with early RA who failed initial treatment with infliximab and MTX would further proceed to treatment with sulphasalazine. After 2 years of treatment patients who ended up to sulphasalazine did show some response in terms of disease activity, but yet sulphasalazine was not as effective in reducing disease activity or structural damage progression compared to patients that had responded to infliximab [29].

Table 1
Treatment options after first anti-TNF- α failure.

1. Optimize MTX/DMARDs
2. Optimize anti-TNF- α dose/frequency
3. Discontinue TNF- α blocker, treat with synthetic DMARDs only
4. Add another biologic (not recommended)
5. Switch to another TNF- α blocker
6. Switch to another category of biologics

4.4. Add another biologic

Showing inadequate response to TNF- α blockers may suggest that other pathogenetic mechanisms, different than TNF- α -related, are operative as well. In fact, other biologic treatments such as interleukin (IL) 1 antagonism (anakinra), co-stimulation modulation (abatacept), B-cell depletion (rituximab) and IL-6 blockade (tocilizumab) are especially designed to target diverse non-TNF- α -related pathogenic pathways. These drugs have been effective in treating RA in clinical trials and are currently approved therapies. Combining two biologic drugs would theoretically have an additive or synergistic effect, potentially more effective than each biologic alone. Two randomized trials have been conducted so far examining the effects of such combinations. In the first study, RA patients with an inadequate response to MTX were randomized to receive etanercept or etanercept plus anakinra for 6 months. At the end of the trial, the combined therapy provided no additional benefit to patients, but, instead, was associated with a greater occurrence of serious adverse events [30]. Similarly, in another trial, patients with active RA despite biologic or non-biologic DMARD therapy were randomized to receive additional abatacept or placebo. In the group of patients who received abatacept in addition to background biologic therapy (TNF- α antagonists or anakinra) the frequency of adverse events and serious adverse events was higher compared to patients on placebo plus background biologic or on abatacept plus background non-biologic therapy [31]. Thus, until formal clinical trial data on other biologic DMARD combinations are available, combining biologics is not recommended.

4.5. Switch to another TNF- α blocker

Until the introduction of biologics with novel mechanisms of action, switching between infliximab, etanercept and, later, adalimumab after failure of a previous anti-TNF- α agent was a common practice. The rationale has been that the 3 anti-TNF- α drugs are not identical to each other. Infliximab and adalimumab are IgG₁ monoclonal antibodies that bind two molecules of TNF- α trimers with the potential to form multimolecular complexes. In contrast, etanercept is a fusion of the p75 TNF- α receptor and the Fc fragment of human IgG₁ that only binds a single TNF- α trimer [32]. Moreover, the effects of etanercept binding to membrane TNF- α (complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and reverse signalling) are possibly less pronounced than those of the monoclonal antibodies [32,33]. This probably accounts for the lack of effectiveness of etanercept in granulomatous diseases like Crohn's disease and the apparently safer profile concerning tuberculosis and lymphomas compared to adalimumab and infliximab [34–36]. However, etanercept is the only TNF- α antagonist that binds both soluble and membrane-bound lymphotoxin- α , which probably plays a pathogenic role in RA [32,33,37]. On the other hand infliximab contains murine sequences which probably make it more immunogenic [33]. Furthermore, the 3 drugs have different dosage regimens, different routes of administration and diverse half lives, thus the fluctuation of drug levels in serum and tissues greatly differs among the 3 treatments [32]. Finally, two new drugs enter the market with their own properties: golimumab, a fully humanized anti-TNF- α monoclonal antibody given at a dose of 50 mg subcutaneously once monthly; and certolizumab, an anti-TNF- α monoclonal antibody fragment consisting of a single Fab portion, which has also undergone a pegylation procedure [32].

Concerning the 3 classic TNF- α inhibitors, no formal double blind RCT has been conducted to assess the safety and efficacy of a second or a third TNF- α inhibitor after the first has failed. In contrast, plenty of non-randomized, open-label, uncontrolled or observational studies have been published concerning this issue. The results of these trials have suggested that switching between TNF- α inhibitors produce clinical benefit in a substantial percentage of patients, in some of

whom high levels of response could be observed as well. Indeed, etanercept has been tried after infliximab failure in 2 trials. Both trials showed efficacy of etanercept with 38% and 64% of patients achieving an ACR20 improvement after 12 weeks of treatment [38,39]. Interestingly, one of these studies showed etanercept to be effective despite the specific type of infliximab inefficacy, i.e. lack of response or loss of efficacy [39]. Inversely, infliximab (at 3 mg/kg) has been tried as an alternative in patients with an inadequate response to etanercept. At week 16, 62% of infliximab-treated patients achieved an ACR20 improvement compared to 29% of those maintained on etanercept [40]. Finally, adalimumab has produced favorable responses in patients who had previously failed either infliximab or etanercept. In the ReAct study, which has been a large observational study of RA patients receiving adalimumab after failure of DMARDs and/or biologics, adalimumab has been effective both in anti-TNF- α -naïve patients and in patients who had previously been treated with infliximab or/and etanercept. The percentage of TNF- α -naïve patients attaining ACR 20/50/70 responses after 12 weeks of adalimumab treatment were 70%, 41% and 19% respectively, whereas the ACR 20/50/70 responses of patients who received adalimumab as an alternative TNF- α blocker were 60%, 33% and 13% respectively. Although the responses of patients with previous anti-TNF- α experience were, at least numerically, lower, they were close to those who had previously failed on DMARDs only [41]. On the contrary, in another study, 43 patients having failed on adalimumab were subsequently switched to etanercept ($n=40$) or infliximab ($n=3$). Twenty-one patients achieved at least a moderate EULAR response. The efficacy of the alternative TNF- α antagonist was significantly better, if adalimumab had been stopped due to adverse events or loss of efficacy rather than primary lack of efficacy [42].

However, interesting data concerning switching between TNF- α inhibitors are retrieved from various observational studies or registries of anti-TNF- α use. An observational study based on Spanish hospitals showed that switching from a first to second TNF- α inhibitor may still produce a significant decrease in mean DAS28, while introduction of a third inhibitor after the failure of the second is not followed by a significant DAS28 reduction. Moreover, moving from the first, to a second and a third TNF- α antagonist is characterized by a gradual shift in the distribution of EULAR responses towards moderate or no response [43]. Data from a Swedish registry indicate that patients respond to a second anti-TNF- α significantly better, if the first one had been withdrawn due to adverse events rather than inefficacy, while the efficacy of the third one is even less [44]. This differentiation of effectiveness of the second anti-TNF- α agent depending on the reason for discontinuation of the first is replicated in the ReAct cohort, as well, with 899 patients included. At least numerically, adalimumab was sequentially less effective if the previous drug had been discontinued due to adverse events, loss of response and primary inefficacy [41]. On the contrary, results from two Dutch registries have shown that the second TNF- α inhibitor is effective in reducing DAS28, no matter what the reason for discontinuation of the first had been. In these latter registries, however, only 15–27% of the patients achieved a DAS28 less than 3.2 after 6 months of treatment with the alternative anti-TNF- α agent. Additionally, 39% of patients discontinued the second anti-TNF- α drug after a median 5.1 months. The reason for discontinuation was related to the reason for the discontinuation of the first anti-TNF- α agent: had the first one been discontinued due to primary inefficacy or loss of efficacy, the second would more often be withdrawn due to inefficacy as well; inversely, if the first TNF- α inhibitor were discontinued due to adverse events, the same reason would dictate cessation of the second one too [45]. Similarly, the British registry showed that the reason for discontinuation of the second anti-TNF- α may well be predicted by the reason for discontinuation of the first one, following a similar pattern as observed in the Dutch registries [46].

Overall survival rates of alternative TNF- α blockers have also been described in various registries. In the Danish registry, patients who received a second anti-TNF- α agent remained on the drug longer compared to the time they had stayed on the first agent they had stopped [47]. Moreover, data from the Spanish registry indicate that the survival of the second TNF- α inhibitor is significantly better, had the first one been withdrawn due to adverse events than for any other reason. Further, the survival curve of the second agent was close to that of the first one, whereas the curve of the third was well below the curves of the former two [12].

While controlled data concerning cycling among the classical three TNF- α blockers are lacking, a RCT has been conducted assessing the effectiveness of switching from these inhibitors to a new one, golimumab. Up to now, no such trials have been published for certolizumab.

In the Go-AFTER trial, RA patients who had failed on previous anti-TNF- α agents were randomized to receive either placebo or golimumab 50 or 100 mg once monthly. A significant proportion (58%) of patients had discontinued golimumab due to inefficacy, while 25% had failed at least two TNF- α inhibitors. At week 14, 35%, 16% and 10% of patients on golimumab 50 mg achieved an ACR20/50/70 response respectively, significantly more than the placebo group that achieved the same levels of response in 18%, 6% and 2% of patients respectively. The response rates were maintained at 24 weeks (ACR20/50/70 for the golimumab 50 mg 34%, 18% and 12% respectively) (Fig. 1). Data analysis showed that response to golimumab was better, if patients were co-treated with DMARDs or if they had failed to no more than 2 TNF- α blockers. Moreover, in contrast to previous observations, patients who had discontinued previous TNF- α blockers due to lack of effectiveness responded also better to golimumab than placebo [48].

In summary, observational data support switching between TNF- α inhibitors, while a RCT has established the effectiveness of golimumab after failure of a previous anti-TNF- α agent. It seems that the second TNF- α is not as effective as the first one, but it should be kept in mind that patients failing one TNF- α inhibitor may represent a more

difficult-to-treat subgroup of patients. However, almost all studies agree that adding a third anti-TNF- α drug may not be beneficial. Whether primary inefficacy, loss of efficacy or adverse events of the first agent is the best setting for such a switch is still not clear.

4.6. Switching to an alternative class of biologics

Following TNF- α blockers, several new targeted biologic therapies have entered the market offering new therapeutic options for RA patients: the B-cell depleting agent rituximab, the co-stimulation regulator abatacept and the IL-6 antagonist tocilizumab. All these three drugs are suitable to be administered to patients who have previously been exposed to TNF- α inhibitors.

4.6.1. Rituximab

Although rituximab was introduced in the treatment of RA after TNF- α blockers, the history of the drug goes back several years before the invention of anti-TNF- α drugs, when it was introduced for the treatment of B-cell non-Hodgkin lymphomas. In RA rituximab has been assessed in several clinical trials [49–51] and has been shown to be beneficial. The REFLEX trial [51] included RA patients who had discontinued at least one anti-TNF- α agent (31% had received two and 9% three) most often for inefficacy (90–92%). The patients were randomized to receive rituximab (1 g on days 1 and 15) or placebo with concomitant MTX. The study end-point was ACR20 response at 6 months. Rituximab was shown to be more effective than placebo, since at 6 months ACR20/50/70 responses were achieved by 51%, 27% and 12% in the rituximab group, but in only 18%, 5% and 1% in the placebo group ($p < 0.0001$ for all comparisons of active treatment against placebo) (Fig. 1). Furthermore, based on this trial, rituximab is the only biologic drug so far that has been proved effective in slowing structural damage in this subgroup of patients who have failed TNF- α blockers. Indeed, after one year, patients who had been treated with rituximab showed less radiographic progression in terms of total G \acute{e} nant-modified Sharp score, joint space narrowing score and joint erosion score compared to placebo-treated patients [52]. Finally, in an

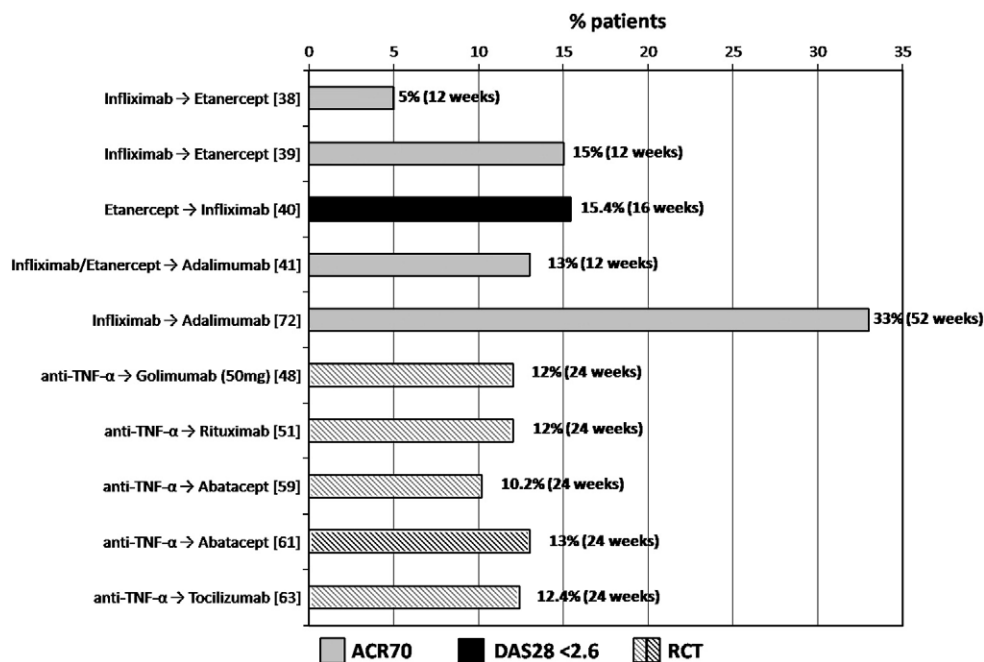


Fig. 1. Rates of high-grade response to treatment in RA patients who have failed on at least one TNF- α antagonist and subsequently switched to another biologic drug across clinical studies. At 3–6 months almost 10–15% of patients achieved either ACR70 or EULAR remission, irrespective of the pair of biologic drugs they had been switched between. In a single study, in which patients were switched between TNF- α blockers, the rate of ACR70 response even reached 33% after 1 year [72]. Numbers next to the bars are percentage of patients achieving a response (time of observation). Grey bars represent rates of ACR70 achievement; black bars represent rates of EULAR remission. Shadowed bars denote that the respective figures were obtained in the context of randomized controlled trials.

open-label follow-up of patients participating in all rituximab studies and who received at least 2 courses of rituximab, the drug has shown sustained efficacy. ACR20/50/70 response 6 months after the first course was achieved by 65%, 33% and 12% of patients previously treated with anti-TNF- α agents, while 6 months after the second course ACR20/50/70 responses were maintained in 72%, 42% and 21% of patients. For comparison, in anti-TNF- α -naïve patients treated with rituximab, ACR20/50/70 responses were achieved by 59%, 27% and 9% six months after the first course and by 73%, 37% and 19% six months after the second course [53].

However, rituximab, by depleting B-lymphocytes, exerts a more sustained influence on the immune system, probably more durable than, if it merely neutralized a single cytokine. An important issue then is if patients failing on rituximab are appropriate to receive another biologic or if they will suffer the combined immune compromising effects of both drugs at the same time. Among 2578 patients who had been exposed to rituximab in clinical trials, 185 received another biologic, among them 153 an anti-TNF- α agent. Median time between rituximab and the alternative biologic was 7 months, with most patients still being peripherally depleted of B-cells. Median time of follow-up after the introduction of the alternative biologic was 11 months. Based on this relatively small sample and this short follow-up duration, the overall incidence for serious infections per 100 patient-years was 4.31 for those exposed to rituximab only, 6.99 in the meantime between rituximab and the alternative biologic, 6.63 in the interval between rituximab and an alternative TNF- α blocker, 5.49 after the alternative biologic and 4.93 after the alternative TNF- α blocker. The type and severity of infections were typical for RA patients [54]. Although data on disease activity, concomitant treatment and statistical comparison of figures are not provided, one cannot help but note that the highest rates of adverse events were seen in the meantime between rituximab and another biologic, apparently reflecting patients who had a substantially active disease.

Shortly after rituximab was licensed for RA treatment, the debate over how to treat anti-TNF- α failures began. In a Swiss cohort of 116 RA patients who had failed on at least one TNF- α inhibitor and subsequently received in a non-randomized fashion either an alternative TNF- α blocker or rituximab, rituximab was shown to be significantly more effective in reducing DAS28, erythrocyte sedimentation rate and the number of tender joints compared to the alternative TNF- α blocker. However, rituximab-treated patients had previously received statistically more TNF- α inhibitors than patients treated with an alternative TNF- α blocker [55]. Few years later analysis of the same cohort that had meanwhile grown larger ($n = 318$ patients) showed that the efficacy of rituximab as opposed to a TNF- α inhibitor replacing a failed TNF- α inhibitor does not seem to be dependent on the number or type of the failed anti-TNF- α drugs. The sole predictor of a better response to rituximab compared to an alternative anti-TNF- α agent was found to be withdrawal of the previous anti-TNF- α agent due to inefficacy rather than toxicity or other reasons [56]. As regards predictors of response to rituximab in general, a recent analysis showed that patients respond better, if they are rheumatoid factor-positive, have a lower baseline Health Assessment Quality (HAQ) and have failed less previous TNF- α blockers [57].

4.6.2. Abatacept

Abatacept is the product of the fusion of the extra-cellular domain of the Cytotoxic T Lymphocyte Antigen-4 (CTLA-4) with the Fc fragment of a human IgG₁. It antagonizes the T lymphocyte receptor CD28 for binding to the CD80/CD86 molecules present on the surface of antigen presenting cells (APC) during the process of (T cell receptor/Major Histocompatibility Complex class II-mediated) antigen presentation to T helper cells. The abrogation of the CD28-CD80/86 interaction prevents APC from conveying a co-stimulatory signal to T cells, thus blocking T cell activation on antigen presentation [58].

Abatacept has been assessed for treating RA patients after failure of a previous TNF- α antagonist in the ATTAIN trial [59]. In this trial, RA patients who had discontinued previous TNF- α inhibitors due to inefficacy were randomized to abatacept or placebo. At 24 weeks, patients on abatacept achieved ACR20/50/70 responses in 50.4%, 20.3% and 10.2% respectively, which was significantly better than those of placebo-treated patients who achieved ACR20/50/70 responses in 19.5%, 3.8% and 1.5% respectively (Fig. 1). Abatacept had a fairly long-standing efficacy, since, after 2 years, 222 out of 317 patients who entered a long-term extension remained on abatacept, while response measures after 2 years remained as high as those observed in the initial 24 weeks [60]. In the ARRIVE trial, the timing for abatacept initiation after discontinuation of a TNF- α inhibitor was evaluated. In this study, patients who had discontinued previous anti-TNF- α agents, because of either inefficacy or adverse events were randomized to receive abatacept either at the time of the next scheduled TNF- α -blocker dose, or after a sufficient wash-out time had elapsed. In both study arms, patients achieved comparable ACR responses (Fig. 1) without significant differences in the rates of adverse events [61]. In conclusion, abatacept is a compelling alternative for patients failing one or more previous TNF- α blockers. Moreover, it is the only drug that has proven its safety if given instead of the next scheduled dose of the discontinued anti-TNF- α agent. This may prove valuable for patients with substantial disease activity, who are expected to get worse, while a new treatment is delayed, until a sufficient wash-out period from the previous TNF- α antagonist has passed.

4.6.3. Tocilizumab

Tocilizumab is a monoclonal antibody targeted against the IL-6 receptor, thus antagonizing the effects of IL-6. IL-6 is a cytokine central to inflammatory response, being responsible for acute phase reaction, B cell activation and terminal differentiation to antibody producing plasma cells and skewing T helper differentiation towards the pro-inflammatory T_H17 phenotype at the expense of the tolerance-inducing T regulatory cells [62]. Tocilizumab has been assessed for use in patients with RA who have failed anti-TNF- α agents in the RADIATE trial [63]. In this trial, RA patients who had previously discontinued TNF- α inhibitors mainly due to inefficacy (95%) were randomized to receive placebo, tocilizumab 4 mg or 8 mg monthly. After 24 weeks, patients who had received the 8 mg dose (the currently approved dose) achieved ACR20/50/70 responses in 50%, 28.8% and 12.4% respectively (Fig. 1). ACR20/50/70 responses of the placebo-treated patients were significantly lower, 10.1%, 3.8% and 1.3% respectively. Interestingly, response to tocilizumab was not influenced by the number or type of previous anti-TNF- α agents. Concerning adverse events patients treated with tocilizumab after anti-TNF- α failure had more often severe neutropenia compared to patients who received tocilizumab after MTX failure.

Table 2

Major safety considerations related to the use of biologic agents in RA.

	Anti-TNF- α	Rituximab	Abatacept	Tocilizumab
Infections	↑	↑	↑	↑
Tuberculosis	↑	No?	Has been described	Has been described
Neoplasms	↑?	No evidence yet	No evidence yet	No evidence yet
Autoimmunity	↑	No evidence yet	No evidence yet	No evidence yet
Caution with	Severe heart failure Hepatitis B Demyelination	Severe heart disease Hepatitis B	Chronic obstructive pulmonary disease	Dyslipidemia Impaired hepatic biology Neutropenia Abdominal infection

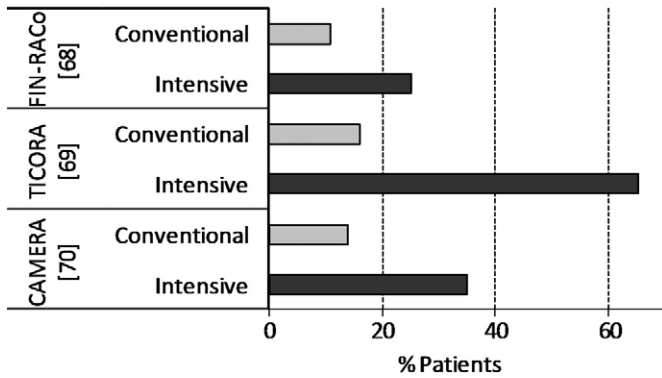


Fig. 2. Comparison of remission rates between patients with RA treated by conventional therapy and patients treated by intensive strategies across studies involving both arms (tight control studies).

Overall, in both controlled and uncontrolled studies the rates of high-grade clinical responses (ACR70, DAS28 remission) after switching between all available biologic agents is in the range 10–15% at 3–6 months of treatment (Fig. 1). However, besides efficacy, safety reasons are central in selecting treatment in patients with RA. Particularly, biologic agents have diverse safety profiles and contraindications. All biologic agents have been associated with infections. Some infections, though, either severe or opportunistic, occur more commonly with some particular class of drugs: anti-TNF- α blockers have been involved in tuberculosis reactivation, while caution is warranted in cases of hepatitis B infection; rituximab has been associated with fatal reactivation of latent hepatitis B infection and, mainly outside the context of RA, with progressive multifocal leukoencephalopathy [64,65]; abatacept has been associated with an increased occurrence

of lower respiratory infections in patients with chronic obstructive pulmonary disease; and finally tocilizumab has been associated with neutropenia and intra-abdominal infections, such as diverticulitis [64].

Moreover, particularities of each biologic drug class preclude or discourage its use in certain subsets of patients. TNF- α antagonists have been associated with central nervous system demyelinating disorders, lupus-like syndromes or even psoriasis-like eruptions [64,66]. TNF- α blockers and rituximab should be avoided in patients with severe heart failure. Tocilizumab has been associated with unfavorable changes in the serum lipid profile and with impaired liver biology, which certainly warrants cautiousness, when used in combination with hepatotoxic drugs [64]. Finally, the potential of these drugs to contribute in other rare adverse events after long-term exposure is not entirely known. As regards anti-TNF- α agents, concerns have been raised about their role in the emergence of hematopoietic malignancies, and caution is advocated before and during the use of these drugs in patients [64]. Only rituximab might be said to be safely administered to RA patients with some forms of underlying blood dyscrasias, due to its already established efficacy in treating various hematologic diseases. Although the use of abatacept has not been associated with cancer so far [67], continuous monitoring is warranted, when RA patients are treated with abatacept, as well as tocilizumab for possible emergence of neoplastic disease (Table 2).

5. Concluding remarks

RA patients failing previous TNF- α blockers represent a difficult-to-treat subset of RA patients. Although facing such a patient one might not be as optimistic as when treating a MTX-naïve RA patient, new biologic drugs have entered the market offering promising results. However, it has to be borne in mind that the best outcomes in RA treatment have been obtained in clinical trials assessing treatment strategies rather than specific drugs. In the FIN-RACO study early RA patients were randomized

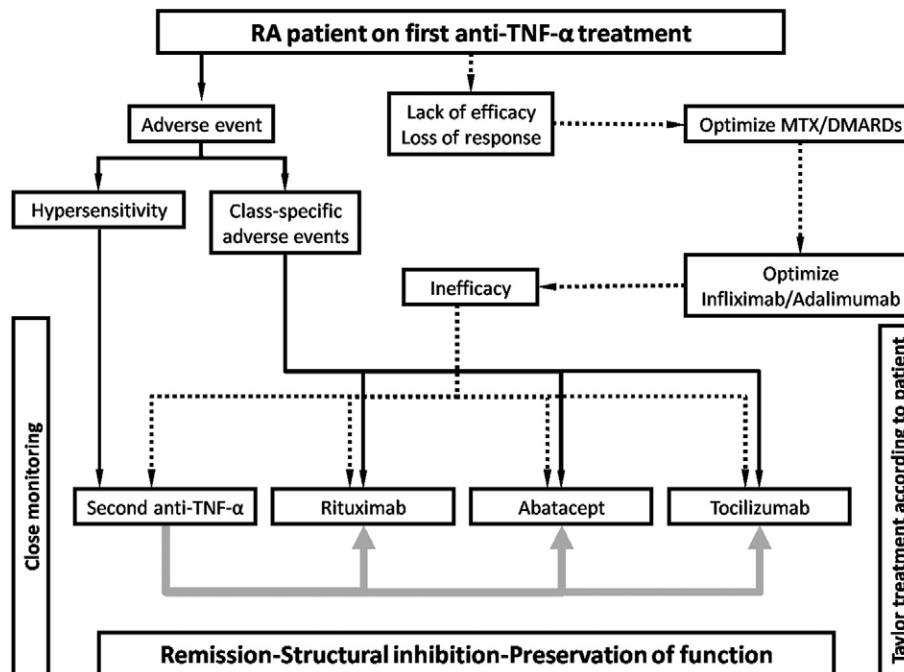


Fig. 3. An approach based on current evidence as regards treatment of RA patients who have failed on the first anti-TNF- α agent. Continuous arrows: A patient on anti-TNF- α treatment may experience adverse events requiring discontinuation of the drug, although it may have been effective. If the event has been drug-specific (e.g. an infusion reaction to infliximab), switching to another TNF- α blocker may abolish the adverse event, maintaining at the same time the benefits of TNF- α blockade. However, if the adverse event has been class-specific (e.g. demyelinating central nervous system disease, worsening heart failure etc), it is safer to switch to another class of biologic drugs that lacks the particular safety issues. Dashed arrows: A patient on anti-TNF- α therapy may not respond adequately or lose the initial good response. The easiest step to take first is to optimize the adjuvant DMARD therapy, i.e. add/increase MTX, switch to injectable MTX in case of intolerance to oral MTX, add leflunomide or CsA in patients intolerant to MTX; subsequently, increasing exposure to infliximab or adalimumab (up to the doses approved) is the last step before withdrawing the drug due to inefficacy. In this case, both controlled and uncontrolled trials support a switch to another biologic, an alternative TNF- α antagonist included; the choice often depends on the specific characteristics of the patients (i.e. abatacept should be avoided in patients with chronic obstructive pulmonary disease). Finally, should a patient fail on a second TNF- α inhibitor, the odds for succeeding on a third are rather limited and, hence, a switch to an alternative class of biologics should be attempted (grey arrows).

to either single-drug therapy or a more aggressive combination therapy with four drugs and were evaluated after one year [68]. In the TICORA and CAMERA studies RA patients were randomized into two treatment approaches: either conventional therapy with less frequent evaluation of patients and more conservative use of drugs; or intensive therapy with frequent evaluation of patients, routine assessment of disease activity and modification of drug regimen as needed and according to a pre-defined protocol [69,70]. Fig. 2 shows the percentage of patients achieving remission among the conventionally and aggressively treated patients across the 3 studies after 12, 18 and 24 months of treatment respectively. The lesson from these trials is that the best physician is not merely the one who prescribes innovative drugs, but the one who uses all the available drugs with prudence. Current rheumatology practice may be summarized into 4 steps: set sustained remission or low disease activity as the goal of treatment; measure disease activity regularly and consider function and structural damage when making decisions; monitor patient closely, especially so long as target is not attained; and treat according to disease and patient characteristics [71].

In Fig. 3 a rational approach is proposed for the treatment of patients intolerant of or not responding to an initial TNF- α antagonist. In any case, time is important. Hence, if a patient fails on an anti-TNF- α agent the treating physician should timely take all the appropriate measures, in order to restore quality of life and function and should not compromise too easily his/her treatment goals. However, treatment changes should be structured, so as every therapeutic alternative to be thoroughly explored and potentially favorable treatments not to be wasted because of hastiness.

Take-home messages

- TNF- α blocking agents have been the mainstay of biologic treatment of rheumatoid arthritis patients who have failed at least one DMARD.
- Up to 40% of patients discontinue the first anti-TNF- α agent in the first year as a result of primary lack of response, loss of response or adverse events. Adverse events may be further classified as drug-specific (e.g. allergic reaction) or class-specific.
- Strategies after failure of first anti-TNF- α agent due to inefficacy include optimization of the concomitant methotrexate/DMARDs, optimization of the infliximab or adalimumab dosing regimen or switching to an alternative biologic agent.
- There are no high quality controlled trials evaluating the effectiveness of switching between infliximab, etanercept or adalimumab after at least one has failed. However, multiple non-controlled or open-label trials have shown that switching to a second TNF- α antagonist may be beneficial after the first has been discontinued, in spite of the reason for discontinuation.
- Golimumab, rituximab, abatacept and tocilizumab have been shown effective in randomized controlled trials after the failure of a previous TNF- α blocker.
- Currently, there are no recommendations as regards the order of alternation of the various biologic agents after a first anti-TNF- α agent has been stopped. However, the optimal therapeutic regimen should be tailored to the individual patient and should be closely monitored aiming at disease remission.

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