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Review

Failure of anti-TNF treatment in patients with rheumatoid arthritis: The pros and cons of the early use of alternative biological agents

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ABSTRACT

The five TNF inhibitors currently approved for the treatment of RA are characterised by differences in their molecular structures, half-lives, administration routes, dosing intervals, immunogenicity, and use in women who wish to become pregnant. TNF inhibitors still represent the first biologic after conventional synthetic DMARD (csDMARD) in the majority of patients according to registry data. This was possibly because they were historically the first biological agents available (biological DMARDS with a different mechanism of action or targeted synthetic DMARDs did not become available until 2006s), and so switching from one to another was frequent in the case of an inadequate response and/or side effects. TNF inhibitors are also efficacious for other inflammatory joint and spine diseases, and have been approved for inflammatory bowel disease, uveitis and psoriasis. In addition, national registries have provided long-term safety data and demonstrated their beneficial effect on cardiovascular morbidity and mortality. However, approximately 30–40% of patients discontinue anti-TNF treatment because of primary failure, secondary loss of response, or intolerance. The options for managing anti-TNF treatment failures include switching to an alternative anti-TNF (cycling) or to another class of targeted drug with a different mechanism of action (swapping).

The aim of this review is to evaluate the pros and cons of whether it is more appropriate to choose a second anti-TNF biological agents after the failure of the first or swap treatment early.

1. Introduction

The development of biological agents and small oral molecules with innovative mechanisms of action aimed at inhibiting specific molecular or cellular targets that are directly involved in disease pathogenesis has changed the perspective, timing and results of pharmacological treatment of systemic rheumatic diseases [1–3]. In particular, rheumatoid arthritis (RA) treatment now includes the use of both conventional and biological therapies such as TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), abatacept, rituximab (RTX), IL-6 inhibitors (tocilizumab [TCZ] and sarilumab), biosimilars and small oral molecules (JAK inhibitors like tofacitinib, baricitinib and the recently approved upadacitinib) [4], alone or combined, with the aim of achieving sustained clinical remission or greatly reducing disease activity [5–7]. However, there is still a need to clarify what to do when the failure of biological agents makes it necessary to switch (use another drug with the same mechanism of action) or swap treatments (use another drug with a different mechanism of action) [8,9].

TNF inhibitors were the first biological agents used after the failure of conventional synthetic disease-modifying drugs (csDMARDs) in 70.2% of the patients in the DANBIO registry, 79.8% in the SCQM-RA registry, and 69.9% in the German RABBIT registry [10–12]. This was possibly because they were historically the first biological agents available (biological DMARDS [bDMARDs] with a different mechanism of action or targeted synthetic DMARDs [tsDMARDs] did not become available until 2006s), and so switching from one to another was frequent in the case of an inadequate response and/or side effects.

The five TNF inhibitors currently approved for the treatment of RA

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are characterised by differences in their molecular structures, half-lives, administration routes, dosing intervals, immunogenicity, and use in women who wish to become pregnant [13]. TNF inhibitors are also efficacious for other inflammatory joint and spine diseases, and have been approved for inflammatory bowel disease (IBD), uveitis and psoriasis. In addition, national registries have provided long-term safety data and demonstrated their beneficial effect on cardiovascular morbidity and mortality [14,15].

However, approximately 30–40% of patients discontinue anti-TNF treatment because of primary failure, secondary loss of response, or intolerance. The options for managing anti-TNF treatment failures include switching to an alternative anti-TNF (cycling) or to another class of targeted drug with a different mechanism of action (swapping), but although most rheumatologists are familiar with the use of TNF inhibitors and there are substantial data indicating what to do in the case of failure, there is still no defined rule.

The aim of this review is to evaluate the pros and cons of whether it is more appropriate to choose a second anti-TNF biological agents after the failure of the first or move on early to another type of biological agent or small molecule with a different mechanism of action [16].

2. The pros of the early use of alternative biological agents after the failure of an anti-TNF drug

In everyday clinical practice, the response of patients starting a TNF inhibitor varies widely: about 60% achieve an American College of Rheumatology 20% (ACR20) response, but a significantly lower proportion achieve remission or a low level of disease activity (LDA); furthermore, other patients may never achieve a response (primary inefficacy), which is probably due to non-TNF inflammatory pathways that may be dominant in individual patients, or may respond and then lose it over time (secondary inefficacy). Patients may also interrupt or discontinue treatment because of side effects. Other potential reasons for the variability include adherence issues, the cessation of methotrexate (MTX) when biological treatment is started, or differences in the drugs' pharmacokinetics.

The European League Against Rheumatism (EULAR) recommendations for the management of RA with tsDMARDs and bDMARDs [17] position both equally for use after failure of csDMARDs and say that, if a bDMARD or tsDMARD fails, treatment with another drug of the same kind should be considered. It is also explicitly stated that, if one TNF inhibitor fails, patients may receive another TNF inhibitor or an agent with a different mechanism of action. As no predictive biomarkers are available, this liberal approach gives rheumatologists considerable room for allowing individualised treatment.

A number of randomised clinical trials have compared the efficacy of biological agents and tsDMARDs with placebo in patients who fail on one or more previous TNF inhibitors, and shown the significantly greater efficacy of RTX (including a radiographic benefit), abatacept, TCZ, sarilumab, tofacitinib, baricitinib and upadacitinib [18–24], and the efficacy of filgotinib has recently been described at international meetings [25].

A few clinical trials suggest the substantial benefit of TNF inhibitor cycling. The GO-AFTER randomised controlled trial compared the efficacy of golimumab and placebo in patients previously failed on at least one TNF inhibitor. The primary endpoint of an ACR20 response at week 14 was achieved by 35% of the patients receiving golimumab 50 mg/month and 38% of those receiving golimumab 100 mg/month, both of which were significantly different from the placebo response rate of 18%. However, overall response rates were low and more stringent endpoints such as an ACR50 response or remission as assessed using using the 28-joint Disease Activity Score (DAS28) were even less frequent [26]. This trial was important as it demonstrated that using a different compound that inhibits the same target may be beneficial in some RA patients. However, the EULAR recommendations clearly advocate shared doctor/patient decision making when defining the treatment goals and considering remission or at least LDA rather an ACR20 response [17].

EXXELERATE was a randomised, controlled head-to-head trial that compared the efficacy of two TNF inhibitors (certolizumab and adalimumab) in RA patients inadequately responding to MTX, and found that ACR20 response rates after 12 weeks were comparable (71% in the adalimumab group and 69% in the certolizumab group). Non-responders were switched to the other drug, and ACR20 response rates were significantly lower in the patients who switched (44% in those switched from adalimumab to certolizumab and 40% in those switched from certolizumab to adalimumab). ACR50 response rates were 17% and 23% [27]. The results of this trial showed that, although a minority of patients benefit from a second TNF inhibitor, the majority are unlikely to achieve the more ambitious endpoints.

This is clearly different from the response rates recorded in patients switching to a bDMARD with a different mechanism of action or a tsDMARD. “Switching or cycling” has been a subject of debate ever since the first non-TNF biological agents were approved almost 10 years ago. The US CORRONA registry compared the clinical efficacy of RTX and a second TNF inhibitor in patients inadequately responding to an initial anti-TNF agent in terms of the proportion of patients achieving remission or LDA, an ACR20, ACR50 or ACR70 response, or an improvement in the Health Assessment Questionnaire (HAQ), and found that RTX was superior in the ACR20, ACR50 and HAQ categories [28]. The Swiss SCQM-RA registry showed that patients failing on a first anti-TNF agent who were switched to RTX showed a greater reduction in disease activity than those switched to a second anti-TNF agent. However, the observed change in the DAS28 was comparable in patients who were switched to a second TNF blocker or RTX for reasons other than inefficacy [29].

One multicentre, prospective, observational study comparing the effectiveness of RTX and an alternative TNF inhibitor in patients who had failed to respond to a single previous TNF inhibitor because of inefficacy (75%) or intolerance (25%) found a significant benefit in favour of RTX in the case of patients who stopped the first TNF blocker because of inefficacy, but no difference between the drugs in those who stopped because of intolerance [30].

Drug retention rates best reflect the efficacy of biological agents in real life. Data from Canada shows that TCZ has a significantly higher 6-year drug retention rate after a first anti-TNF failure than adalimumab or etanercept [31].

The French 52-week open-label, randomised ROC clinical trial compared the efficacy of a non-TNF targeted biological agent with that of a second anti-TNF drug in patients insufficiently responding to a TNF inhibitor; the choice of biological agent within the groups (TNF inhibitor or non-TNF drug) was at the discretion of the treating physician. The primary endpoint was the proportion of patients achieving a good or moderate EULAR response after 24 weeks, and was achieved significantly higher percentage of patients receiving a non-TNF biological agent (69% vs 52%; OR 2.1, 95% CI 1.3–3.4) and this difference was maintained until week 52. It is worth noting that the proportion of patients who developed serious infections was comparable in both groups (5%), but serious adverse events were more frequent in the patients switched to a non-TNF biological agent (11% vs 5%). However, drug retention rates were better among the patients switched to a non-TNF biological agent: 27 patients in the non-TNF group switched to another biological agent during the course of the follow-up (52% because of inefficacy and 44% because of side effects) as against 48 patients (83% because of inefficacy and 13% because of side effects). These findings indicate that the advantage of switching to a second TNF inhibitor might be the lower risk of discontinuation because of side effects, whereas the advantage of switching to a non-TNF biological agent might be the lower risk of discontinuation because of inefficacy [32]. Interestingly, the serum drug and anti-drug antibody (ADA) levels determined in the ROC trial showed that immunogenicity did not explain the majority of inadequate responses to anti-TNF drugs [33].

The cost effectiveness of biological agents is clearly important to payers, but clinical benefits (such as the number of days gained with LDA or remission) are important for patients. Italian data show that, in comparison with a second TNF inhibitor, the use of TCZ leads to a higher number of days gained with LDA or remission, thus reducing costs per day in LDA/remission [34].

In brief, a second TNF inhibitor may be efficacious in patients inadequately responding to a first TNF inhibitor, but the results of randomised controlled trials (RCT)s and observational data show that switching to a bDMARD with a different mechanism of action increases the chances of achieving clinical meaningful improvements and leads to better drug retention rates.

3. The cons of the early use of alternative biological agents after the failure of an anti-TNF drug

The 2016 update of the EULAR recommendations for the management of rheumatoid arthritis suggests considering another bDMARD or a tsDMARD in the case of side effects or a lack or loss of efficacy. If one TNF inhibitor therapy fails, patients can receive another TNF-inhibitor or an agent with another mechanism of action [17].

3.1. Lack of efficacy – primary failure

The levels of disease activity three months after starting bDMARD treatment can predict clinical efficacy and radiographic progression after one year [35], as patients who do not have moderate or low levels after three months are unlikely to have a good one-year outcome [36]. At this time, patients can be classified as responders or non-responders on the basis of the reduction in their DAS28 or DAS28-ESR. Primary failure despite adequate serum drug levels can be considered a non-response [37]. Between 30% and 40% of patients are primary non-responders [38] and, in some cases, dose- or dose frequency modifications may improve clinical responses [38–40]. Non-responders are unlikely to benefit from a second TNF inhibitor and should be switched to a drug with another mechanism of action [30,41], especially in the absence of ADAs. The ACR guideline recommends switching anti-TNF non-responders to a bDMARD or tsDMARD with another mechanism of action, but the current EULAR recommendations say that switching non-responders to a second TNF inhibitor can also be considered [17,42].

3.2. Loss of efficacy – secondary failure

Any biological agent may induce an immune response and lead to the formation of ADAs, and the presence of immune complexes of TNF inhibitors and ADAs can lead to low circulating drug levels [43], which may be due the increased clearance of the complexes or the neutralisation of the functional part of the drug by ADAs. The half-life of IgG antibodies is generally three weeks but, as the half-life of immune complexes is generally shorter [44], they accelerate the clearance of both the drug and the ADAs. Non-neutralising antibodies may also enhance clearance [45]. Antibodies that bind the drug but do not influence the target can also interfere with function and neutralise the effect of the drug: for example, antibodies that block Fc or C1q receptor binding may decrease antibody-dependent cell-mediated or complement-dependent cytotoxicity [46]. The detection of antibodies depends on the amount of ADAs and the administered drug: excess serum drug levels prevent the detection of free ADAs; the same amount of drug and antibody prevents the measurement of both; and antibody over-production only allows the detection of free antibodies. Consequently, antibody measurements should be related to the timing and dose of drug administration [47]. Lower anti-TNF drug doses can permit the development of ADAs, and higher doses may suppress this response: for example, the production of anti-infliximab antibodies is lower in RA patients receiving higher doses of infliximab [48].

The use of MTX 7.5–20 mg weekly decreases the frequency of ADA formation [49], and other csDMARDs (e.g. leflunomide) may be helpful in this respect [50]. Genetic differences such as HLA and IL-10 polymorphisms may influence the development of ADAs [51], the formation of which is also associated with greater baseline disease activity, higher C-reactive protein levels, and a longer disease duration, although it still unclear how these characteristics are related to the development of ADAs [37]. Anti-infliximab antibodies correlate with an increased risk of infusion reactions [52].

It is important to note that ADAs are associated with negative outcomes of adalimumab treatment in RA patients. Twenty-eight percent of patients develop anti -adaliumab antibodies after three years, 67% of whom do so during the first 28 weeks. These patients more frequently discontinue the drug due to treatment failure than those who are antibody negative, and less frequently achieve minimal disease activity or remission [37]. The definition of the failure of anti-TNF drugs is clinical as ADAs cannot be detected in the serum of many non-responders [40,53]. Switching patients with ADAs to another TNF inhibitor is associated with a response in 92% of cases [54].

The findings of the REALISTIC and GO-AFTER trials, which enrolled patients inadequately responding to TNF inhibitors, suggest that using a second TNF inhibitor is clinically beneficial [26,55], although the EXXELERATE study highlight that using another TNF inhibitor (the study compares switch ADA failures to certolizumab and vice versa) after the 1st failure is clinically effective only in a minority of patients [27]. If the second TNF-inhibitor fails, patients should be treated with a drug with a different mechanism of action because TNF is possibly not the main cytokine inducing disease activity [17].

3.3. Side effects of anti-TNF drugs

In the case of the occurrence of TNF inhibitor-related side effects such as severe infection, sepsis, tuberculosis, lymphoma or demyelinating disorders, a drug with another mechanism of action might be considered but, in the case of mild infusion or injection reactions such as skin rash, switching to another TNF inhibitor remains an option [56].

3.4. Pregnancy

The characteristics of placental transfer and drug half-life need to be taken into account when selecting a TNF inhibitor for women of childbearing age. Antibodies can be actively transported through the placenta by Fc receptors on trophoblasts, which start to develop at about week 14. Adalimumab and infliximab should be stopped at week 20, and etanercept at week 32: certolizumab can possibly be given throughout pregnancy as it cannot actively cross the placenta in the absence the Fc part, although there are some data indicating presumably passive transfer. There is a lack of evidence concerning the safety of biological agents with different mechanisms of action [57].

3.5. Comorbidities

In the presence of a TNF-responsive comorbidity such as uveitis, IBD or psoriasis, switching to a second TNF inhibitor in the case of the failure of the first may be beneficial, and a second TNF inhibitor might be considered when other agents are contraindicated (e.g. TCZ in the case of difficult-to-treat diverticulitis). Furthermore. in some cases, a patient's preference and/or a physician's experience may also support the use of a second TNF inhibitor [58].

4. Conclusions

The early and aggressive use of the treat-to-target approach has become the optimal means of managing early-onset RA [59] in order to maintain the lowest possible level of disease activity. In patients who do not achieve LDA or remission, it is necessary to use bDMARDs and then, if the clinical results are insufficient, switch to another biological or

non-biological DMARD or swapping the original for one with a different of action [17,60].

The failure of a first TNF inhibitor may be due to various reasons (9). The complete absence of a clinical response to bDMARD treatment from the beginning is known as *a primary lack of efficacy* (the drug has an inappropriate mechanism of action for the specific immunological subtype of RA) [61]; when the clinical response is only partial and insufficient to ensure clinical remission or a low level of disease activity, the reason is called a *partial lack of efficacy*; the subsequent loss of an initial clinical response is known as *secondary inefficacy* (which may be explained by the development of antibodies against the biological agent) [62]; finally, the *failure of a bDMARD may be due to intolerance or side-effects i*n patients with a good clinical response [63,64].

Choosing a second TNF inhibitor after the failure of a first may sound inappropriate, but the practice of switching from one TNF inhibitor to another (a cycling strategy) is still common and frequently occurs because of a physician's confidence and experience with these drugs [6]: however controversial this may be, it is true that a second agent of the same class may be effective because of individual differences in the drugs' biochemical structures and properties, immunogenicity, bioavailability, and mechanisms of action.

Data supporting a swapping strategy are increasing, but they are still quantitatively and qualitatively limited as the vast majority come from open-label, retrospective, or prospective observational trials; however, a few studies have shown some advantages in favour of a swapping strategy in the case of anti-TNF drug failure [32].

Serious or class-specific side effects should be managed by choosing a differently targeted drug. Swapping to a different mechanism of action is recommended after two or more anti-TNF failures, and the strongest evidence of efficacy in the treatment of anti-TNF failures is currently in favour of RTX and TCZ.

However, no definitive strategy has yet been established, and the available data seem to suggest a personalised approach to each individual patient rather than a standardised approach to all. Before moving to a bDMARD, some partial responders may benefit from the optimisation of their current csDMARD therapy (e.g. increasing the dose or changing the route of administration of MTX). Most patients who insufficiently respond to a TNF inhibitor require a second bDMARD, and both cycling and swapping strategies are supported by data from RCTs and real-life experience. However, the scarcity of head-to-head trials directly comparing these two strategies, and the fact that meta-analyses of individual RCTs have failed to find any significant difference in favour of one or the other, has induced the writers of international guidelines to avoid making any recommendation. In addition, the results of RCTs of small molecules (jakinibs) have introduced a further (non-biological) method of treating otherwise resistant patients.

In conclusion, the results of most observational studies (including well-designed, prospective and randomised trials) indicate the superiority of swapping over cycling (regardless of the chosen mechanism of action); only a few studies have found the comparable effectiveness of the two strategies [9,16].

5. Take-home messages

- Switching or swapping may be a reasonable option of treating RA patients who are resistant to or intolerant of anti-TNF agents;
- Most observational studies (including well-designed, prospective and randomised trials) indicate the superiority of swapping over cycling (regardless of the chosen mechanism of action);
- The presence of anti-TNF drug antibodies may partially explain secondary resistance, but does not fully explain partial or total failure;
- The results of RCTs indicate that small molecules (tofacitinib, baricitinib, upadacitinib) are useful non-biological alternatives for treating resistant patients
- After two or more anti-TNF drug failures, using a drug with to a different mode of action is recommended.

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