Switching Between Anti-TNF: Is it Always Justified?

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New biologic therapies, directed against pathogenic mediators of arthritis, have played an important role in changing paradigms regarding rheumatoid arthritis (RA) and, probably also in other inflammatory rheumatic disease. Directly or indirectly, they have contributed to the fact that 21st century rheumatologists have a tighter control over their patients with inflammatory disease and that they expect more of the drugs, not only in terms of leading to improvement, but that the patients undergo disease remission. Never before had so much information and so many therapeutic options been available, something that seems positive at first glance, but occasionally goes hand in hand with indecision and disinformation. On the other side of the coin, since the rheumatologists have had these new therapeutic weapons at their side, they have become the *enfant terrible* of hospitals, passing from invisible to costly and, therefore, must be monitored closely. The opportunity at hand is to make administrators see that the use given to these drugs is rational and that we have analyzed cost-effectiveness before they have.

We have begun to see situations which 7 years ago would have been unimaginable when biologic therapies started being used in a routine fashion. Such is the case of patients who after a prolonged period of use stop responding to them or who have used several of these drugs. Faced with an unresponsive RA patient or who has stopped responding to biologic therapy, something that happens in up to a third of patients at 2 years and up to half at 5 years,[1] current therapeutic options are basically 4: *a)* temporarily increase the dose or diminish the interval of administration beyond those indicated by the pharmaceutical company; *b)* adding a disease modifying drug (DMARD) or switch the one being combined with the biologic; *c)* switch to another drug with a similar mechanism of action; and *d)* suspending and changing to another drug with another mechanism of action, including other biologics. These options do not necessarily have to be implemented in the order they have been exposed, nor are they the only ones; they are all liable to be combined and subject to be used sequentially and through different routes. The option of increasing the dose, in spite of studies that show transitory improvement in TNF inhibitors—even recently, a randomized, controlled clinical trial[2]—, should not be offered as advice from the security viewpoint, because the existence of a dose-toxicity relationship has been shown, especially on the rate of infections,[3] or, if undertaken, should only be temporarily. The option of switching or adding DMARDs different than methotrexate, which is used in a predefined manner in combination with biologic treatment, has in general received little attention and deserves a detailed analysis because, among other reasons, it is very much used in our environment and it is, probably, a cheaper option, though there is still doubt on its cost-effectiveness. The most employed options are those that propose switching one biologic for another, generally changing among TNF inhibitors but is this option justified?

There is proof that in RA some patients can respond to a TNF inhibitor but not to another. On one hand, we have differences in pharmacokinetics and mechanisms of action. For example, the different half-lives—3 days in the case of etanercept, 10 for infliximab, and 13 for adalimumab—could be translated in differences regarding the degree of TNF neutralization, or on the route of administration can have an effect on efficacy, directly or indirectly because of the influence that this can have on treatment compliance.[4] And there is also the evidence from clinical trials. Since June 2007, in a systematic review by a group of experts of the Spanish Society of Rheumatology Clinical Practice Guide for Rheumatoid Arthritis (GUIPCAR),[5] 35 studies were analyzed in detail with regard on switching one TNF inhibitor to a second one.[6] The majority of studies have limitations regarding design and show great disparity; nonetheless, it can be concluded that: *a)* lack of response to a first TNF inhibitor does not completely predict the lack of response to a second inhibitor; *b)* patients who have experimented loss of efficacy after an initial response—this is secondary failure rather than primary—has more probabilities of responding to TNF inhibitors; and *c)* if failure has occurred with a soluble receptor and an anti-TNF antibody, there is little probability of response to a third TNF inhibitor.

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Apart from the lack of efficacy, there are other reasons to indicate a switch in biologics in RA such as a concrete adverse event, patient preference, supply deficits, or difficulties in access to treatment. In general, data shows that when suspending a TNF inhibitor due to an adverse event, treatment with a second inhibitor does not lead to the same adverse effect, especially when the application of the first drug has been stopped because an administration related event. Other reasons for switching are self-evident.

In any case, it is a proven fact that in clinical practice it is usual to change among TNF inhibitors when faced with primary or secondary failures or due to the adverse events of another anti-TNF drug, especially in patients with RA. In a survey carried out between American rheumatologists, more than 94% indicated that they switched from one anti-TNF to another after detecting a lack of response or side effects.[7] In general, scientific societies, such as the Spanish Society of Rheumatology[8] or the French Society of Rheumatology,[9] support the use of a TNF inhibitor in patients with an insufficient response to the previous one. However, the NICE institute in the United Kingdom has reached the conclusion that, when faced with a reduction in efficacy of the first TNF inhibitor, installing a second one would be out of the cost-effective range and is not to be recommended.[10] From my point of view, this relationship depends on the time that one dedicates to insuring the switch has indeed worked. If treatment is not maintained for more than 3 months in case of an initial partial response, it can fit into the acceptable range, although this implies a tighter control.

Biologics that appeared after TNF inhibitors, such as rituximab or abatacept, have had to show their efficacy in patients with inadequate response to anti-TNFα. That led to clearer proof in favor of switching to another type of molecule because studies were specifically tailored for that. Does this improved quality of the studies mean that switching should be to another type of biologic and not among anti-TNF drugs? In part, yes, but methodology should not blind us; it will all depend on the cost-effectiveness. I know this argument has been employed before, but the ideal should be to have "responder" profiles for each biologic. And, on the other hand, there is truly a lack of studies that compare combined therapy with DMARDs versus biologics, isn't there? This option should be undoubtedly cheaper, but if it is more effective, this is still unknown. Will be resign ourselves to having these so important gaps of knowledge?

But there are other diseases different than RA, in which a decision on biologic therapy might be necessary, especially spondyloarthritis or idiopathic juvenile arthritis, each with less proven alternatives than RA. TNF inhibitors have been proven, apart from arthritis, in spondyloarthritis and in idiopathic juvenile arthritis, and information on switching between molecules is scarce: few studies in few patients. In general, the results seem to back switching from one anti-TNF to another, or at least to avoid discarding them as a therapeutic option. In the Spanish Registry for Adverse Events with Biologic Therapies in Rheumatic Diseases (BIOBADASER), the rate of retention both for the first and second biologic is better in spondyloarthritis than in RA,[11] something that could be explained in part due to the absence of treatment alternatives in spondyloarthritis or a lower rate of adverse events compared to RA, due to the fact that patients are usually younger and have less comorbidities and concomitant treatment.

In general, we can say that switching between TNF inhibitors could be justified once, in the case that there has been an initial response, but then progressed to a lack of response, something that is defined as secondary failure. A second or third switch would not be justified unless previous suspensions of treatments had occurred as the consequence of an adverse event related with administration, or due to diverse causes independent of efficacy, such as patient preference or problems with drug supply. Occasionally, when the patient does nor adequately respond in an initial manner to a TNF inhibitor, the best option would not be switching to another TNF inhibitor, but to another molecule with a different mechanism of action, be it biologic or not.

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