Conventional DMARDs in axial spondyloarthritis: wishful—rather than rational—thinking!

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Conventional synthetic DMARD (csDMARD) therapy in patients with axial spondyloarthritis (SpA) is a matter of continuous debate. Part of this discussion is a dispute about methotrexate (MTX) comedication in patients with axial SpA treated with tumour necrosis factor inhibitors biologicals (TNFi). The dispute seems to be based on perceptions rather than scientific evidence and may have been fuelled by one of the European League Against Rheumatism task force on the management of rheumatoid arthritis (RA) recommendations. This recommendation states that in RA, TNFi-biologicals should be used in combination with MTX,[1] which finds its justification in the results of multiple randomised clinical trials and careful posthoc analyses thereof.

According to the Assessment in SpondyloArthritis International Society (ASAS), however, axial SpA is not a disease in which csDMARDs including MTX should be prescribed.[2] This bold conclusion has been framed by thorough systematic literature research that has failed to find evidence for efficacy of csDMARDs in axial SpA.[3]

Guidelines and recommendations are supposedly clear and unequivocal. However, clinicians prefer to manage 'several shades of grey' rather than 'think in black and white'. They may argue that absence of evidence (for the efficacy of csDMARDs in axial SpA) does not necessarily mean evidence for the absence of such an effect. In fact, and in spite of current recommendations prescribing the opposite, many do treat patients with axial SpA with csDMARDs occasionally.

It must be easier to digest disobedience with guidelines if plausible scientific explanations can be employed to justify non-commitment: immunogenicity of TNF-inhibiting biologicals is one of those attractive theories that scientists may bring up in order to explain why combinations of MTX and a TNFi-biological work better in RA than monotherapy with a biological: MTX may prevent the formation of TNFi-neutralising antibodies, which in turn could be responsible for loss of efficacy.

This is not the time and the place to dispute the relevance of the immunogenicity theory for clinical practice, nor am I the appropriate expert for that, but I need the argument to provide insight into the behaviour of many clinicians: they may easily take up a plausible theory (*here*: neutralising antibodies cause loss of efficacy in RA) and declare it applicable to a different context (*here*: the patient with axial SpA): 'If in RA neutralizing antibodies cause loss of efficacy of a biological, and the co-administration of csDMARDs (MTX) can prevent the occurrence of them, it is reasonable to assume that this will also work in axial SpA!'.

Such an argument assumes a logical string of events. Ideally, there is solid evidence for every link in the string before causality can be accepted and before guidance is formulated for clinical practice. All too often, however, we tend to build up our body of knowledge by aggregating small pieces of evidence in a seemingly logical manner while ignoring the 'greater picture'. By doing so, we preferably use data that are supportive of our hypothesis while we tend to ignore data that are not.

An example of such a string of events starts with data in patients with axial SpA, showing that neutralising antibodies can be detected in patients on a TNFi-biological.[4] Reportedly, these antibodies are associated with clinical non-response![5] Unrelated observations then have suggested that levels of antibodies are lower if tested in patients using csDMARD comedication.[6] A seemingly logical conclusion from such a string of events could be that csDMARD comedication in patients with axial SpA on TNFi-biologicals is associated with better clinical efficacy. I write 'seemingly' here, since the final experiment, the randomised-controlled trial (RCT) in which the effect of csDMARD (*here*: MTX) when added to a TNFi (*here*: infliximab) in patients with axial SpA has been investigated, has provided inconclusive (but negative) results![7] The entire argument has been built by pieces of indirect evidence together with wobbling direct evidence.

At this point I want to make the following two remarks:

- The first is a nuance: in science, the value of indirect or circumstantial evidence is exploring existing hypotheses and generates new ones, which is in fact the basis of scientific research and therefore absolutely justifiable. However, in clinical medicine—where misinterpretations may cause harm to patients—this process of exploration should better start when solid direct evidence is available, not vice versa.
- The second remark is a warning: we should realise that all the pieces of indirect evidence we report about in medical journals will be read by our scientific peers and bodies that have interests beyond science. In the commercially competitive market of modern chronic inflammatory disease management, the producers of expensive medicines will look for arguments of distinction: for example, one biological drug may be less immunogenic than another.[8] Such an argument may commercially suffice to take the short cut and use it as a selling point! Similar motives may pertain to manufacturers of tests of neutralising antibodies. While these companies simply do their commercial job, which is convincing their markets of the virtues of their products, it is the clinical community that has the responsibility to critically weigh and balance all pieces of indirect evidence, and implement only those pieces that have firmly proven their usefulness in clinical practice. That is not a simple task! The world of medicine is full of temptations and there are many competing interests in that world. Easily accessible literature and omnipresent representatives of pharmaceutical industries provide a continuous flow of promising new findings and new insights, all too often built on indirect evidence only.

It is against this background that Lie *et al*[9] report on their analysis that undoubtedly will fuel again the discussion of whether csDMARD should be coadministered in patients with axial SpA on biological therapy.

Lie *et al* have analysed the well-known Swedish biologics register antirheumatic therapy in Sweden (ARTIS) with regard to retention on TNFi therapy in patients

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with AS and SpA. Their careful conclusion is that the use of csDMARD comedication is associated with better 5-year retention to the first TNFi.

In my opinion, Lie *et al* have provided a close-to-perfect set of analyses in their attempt to convince readership that csDMARD comedication may have a positive effect on TNFi-retention. Their analytical approach and their sensitivity analyses are beautiful, and Lie *et al* give evidence of a commendable insight in methodology when they state that they have 'only' found an association between csDMARD comedication and retention of the first TNFi, not a causal relationship. They are aware that their study does not give a decisive answer to the clinical question if—from now on—patients with axial SpA on a TNFi-biological should be cotreated with a csDMARD, and do therefore not explicitly recommend this.

Why not?

First, Lie's study is a cohort study, not an RCT. In ARTIS, one cannot be confident that csDMARDs have been prescribed in an unbiased manner. While guidance tells us that there is no place for csDMARDs in the treatment of axial SpA, we do know that it is rather common in many countries to occasionally prescribe csDMARDs to patients with axial SpA. The reasons for this behaviour are largely unknown. It is likely a matter of beliefs. Some physicians simply practice csDMARDs in axial SpA and others do not. There may occasionally be a very acceptable reason in a patient with axial SpA to prescribe a csDMARD, such as the presence of peripheral arthritis or psoriasis. But whether the indication is based on beliefs or on solid evidence, the prescription of csDMARDs in a cohort-like ARTIS is biased by default, creating prognostic dissimilarity between those that are on csDMARDs and those that are not, and *confounding by indication* is luring. Any conclusion about csDMARDs stemming from observational cohorts should therefore be interpreted with great caution.

Second, the investigators have not measured efficacy or safety directly. They have measured a 'proxy' of combined efficacy and safety, being TNFi-retention. In fact, TNFi-retention is a rather vague construct. Under the assumption that TNFi-retention is a reflection of the sum of 'all the good and all the bad' that TNFi may provide, drug-retention likely says something about the benefit-risk profile of a particular treatment. Therefore, a patient on a TNFi may stop for reasons of efficacy, tolerability or because of some intangible combination (interaction) of both, or for even completely unrelated reasons. It is rather speculative to assume that an epidemiological association between csDMARDs and TNFi-retention is a real and meaningful association with clinical implications, without having further data available to explain it. Disease activity during treatment has not been measured in this study, nor antibody-formation, treatment compliance or comedication with other drugs, and there has not been any attempt to couple TNFi-retention to the occurrence of side effects to treatment. Admittedly, the authors do not speculate unacceptably, but my fear is that—in the absence of solid direct evidence and plausible explanatory evidence—readers will start speculating and fill in the existing gaps with theories such as the neutralising antibody formation theory.

Third, it should not be forgotten that Lie's analysis includes a mixture of patients who were already on csDMARDs while starting TNFi, patients who have started csDMARDs at the same time as the TNFi and patients who have started their csDMARD after the start of the TNFi. In addition, patients were using several types of csDMARDs and TNFi. It must be very difficult—if not impossible—to disentangle all these different effects in one analysis, how sophisticated this analysis may be.

Fourth, the authors found the usage of csDMARD comedication being dependent on the type of TNFi that was used (eg, csDMARD usage was far higher in case of infliximab than that of etanercept). The choice of the type of TNFi, in turn, was likely dependent on several factors, such as start date (eg, infliximab was on the market far before adalimumab) and beliefs about potency (eg, many clinicians may consider infliximab more potent in cases with difficult AS, or in cases with concomitant psoriasis). Such a chain of mutually dependent clinical choices, often based on beliefs, preferences and timing rather than on a rational balance of all potential options, is so complicated that appropriate statistical adjustment is likely impossible, and confounding cannot be ruled out.

Taken together, Lie's study is an example of an observational study in which residual confounding seems a far too likely explanation for the association between TNFi-retention and csDMARD comedication to justify implementation in clinical practice. However, absence of evidence for a particular hypothesis is not the same as evidence for the absence of such a hypothesis! The best experiment to test the hypothesis that csDMARDs in axial SpA improve TNFi-retention is the well-powered RCT that randomises patients with axial SpA to either monotherapy with a biological or to combination therapy of a biological plus a csDMARD, follow them blindly for some time and compare clinical efficacy, safety and drug-retention in both arms. Such a trial is feasible, but costly, hard to fund and unfortunately not in the interest of pharmaceutical industries. This may explain why this trial likely will not be performed in near future. That is truly a pity, since for the benefit of our patients and the affordability of our healthcare systems we urgently need unequivocal answers to simple but extremely relevant clinical questions.

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