

## INFLIXIMAB OR BIOSIMILARS IN SARCOIDOSIS; TO SWITCH OR NOT TO SWITCH?

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### INTRODUCTION

Sarcoidosis is a systemic, granulomatous disorder that can affect multiple organs and has a variable clinical course (1). Because the etiology of sarcoidosis remains unknown, no curative treatment exists. It is important to state that not all patients require treatment. In the literature the need for systemic treatment varies between 20-70% (2-4). Main treatment indications are risk of organ failure and substantial impact on quality of life. If there is a treatment indication, the first step is usually oral glucocorticoids such as prednisone or prednisolone (5).

In steroid-refractory cases and in the presence of steroid-associated side-effects, second-line disease-modifying antisaroid drugs (DMASDs), with steroid-sparing potency, are available. If the patient has disease progression or toxic effects of glucocorticoids an antimetabolite such as methotrexate (MTX), azathioprine, mycophenolate or leflunomide should be started. Nevertheless, in some sarcoidosis patients the available first- and second-line therapeutics do not provide the optimal result. In those refractory

sarcoidosis cases third line therapy with targeted TNF- $\alpha$  inhibition can be considered (6).

### *Anti-TNF treatment in sarcoidosis*

There are many different TNF- $\alpha$  inhibitors available, however not all successful in sarcoidosis. Treatment with TNF- $\alpha$  inhibitors etanercept or golimumab did not show positive outcomes in patients with sarcoidosis (7, 8). In contrast, adalimumab was found effective in cutaneous, pulmonary and intraocular inflammatory sarcoidosis (9-12). The most experience with TNF- $\alpha$  inhibitors in sarcoidosis however is with infliximab (Remicade®). These include a large case series (13) and double blind placebo controlled trials (14, 15). In a comparison of etanercept, adalimumab, and infliximab, infliximab was the most potent treatment for sarcoidosis, etanercept the least, and adalimumab in between (16). This is in line with the findings in patients with moderate to severe Crohn's disease. Etanercept appeared to be not effective, infliximab effective, and adalimumab effective only with higher doses than those used for rheumatoid arthritis (17). These studies support the concept that the potency of drug therapy to suppress TNF is particularly important for granulomatous diseases such as sarcoidosis and Crohn's disease. These findings are similar to the risk for tuberculosis, with the highest risk of reactivation for those treated with infliximab and lowest for those treated with etanercept (18).

Based on these studies and the results of a Delphi study amongst world's leading sarcoidologists,

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practical recommendations for the use of TNF- $\alpha$  inhibitors in sarcoidosis were established (19). These recommendations with emphasis on indications, dosage and discontinuation regimens have been developed to support the clinician in the management of refractory sarcoidosis patients. Based on this experience in the field and recent studies infliximab is now considered as the main third-line treatment option in sarcoidosis (13, 19-21).

### *Biosimilars*

A similar biologic medicinal product, referred to as biosimilar, is a copy version of an approved original biologic medicine whose data protection has expired. Since the biosimilar approval in 2005 several biosimilars such as filgrastims, epoetins and somatropins have been licensed and become available. Biosimilars are the equivalent of chemical generics, with an important difference however. Biological medicines are derived from living cells or organisms and consist of large and complex molecular structures which are difficult to fully characterize. Based on variability of the biologic system and manufacturing process, a resulting biological medicine will display a certain degree of variability, even between different batches of the same product. Although the amino acid sequence is expected to be the same, due to inevitable differences in manufacturing processes biosimilars will not be entirely identical to the reference biological medicine. If structural and functional characteristics analyses as well as clinical performance of both products are the same, we can state that both medications are "similar" (22).

### *Biosimilars of infliximab*

Treatment with infliximab is expensive, creating a barrier that limits universal access to this effective therapeutic agent. Recently, biosimilars of infliximab have become available. These infliximab biosimilars have brand-names Remsima<sup>®</sup> and Inflectra<sup>®</sup> and are less expensive. In the Netherlands for example, the prices of Remicade<sup>®</sup> and Inflectra<sup>®</sup> are € 590/100 mg vs. € 332/100 mg, respectively. Implementation of biosimilars in our treatment regime could lower the costs of TNF- $\alpha$  inhibitors in sarcoidosis.

At present, no data of sarcoidosis patients being treated with infliximab biosimilars are available. In the PLANETRA trial, the equivalence in efficacy

and safety of the infliximab biosimilar Remsima<sup>®</sup> was compared with the reference infliximab Remicade<sup>®</sup> in patients with rheumatoid arthritis (23). In this randomized double blind study 606 patients with active rheumatoid arthritis were randomized to receive 3 mg/kg infliximab biosimilar or 3 mg/kg reference infliximab. In both groups, MTX and folic acid were given as co-medication. The infliximab biosimilar was well tolerated and demonstrated equivalent efficacy to the reference infliximab at week 30, with a comparable pharmacokinetic profile and immunogenicity (23). In patients with Crohn's disease, a retrospective analysis also revealed also no differences in treatment outcome between infliximab biosimilar Remsima<sup>®</sup> and infliximab reference product Remicade<sup>®</sup> (24).

### *Infliximab biosimilars in sarcoidosis patients who never received anti-TNF treatment*

Based on the data of the PLANETRA trial and the experience of implementation of other biosimilars such as filgrastims, epoetins and somatropins without any problems it can be expected that treatment of sarcoidosis patients with infliximab biosimilars will be effective and safe. However, some critical remarks have to be made before extrapolating data from other systemic inflammatory disease like rheumatoid arthritis and Crohn's disease to our population of sarcoidosis patients, the most important one being immunogenicity.

In sarcoidosis, positive tests for anti-infliximab antibodies have been reported in 6-29% of patients (13, 25, 26). To prevent antidrug antibody formation during TNF- $\alpha$  inhibitor treatment, concomitant immunosuppressive therapy (MTX, azathioprine or glucocorticosteroids) is recommended (19).

When extrapolating data from the PLANETRA trial regarding immunogenicity it is important to realize that both infliximab and MTX dose are different compared to sarcoidosis. In the PLANETRA trial infliximab is dosed at 3 mg/kg compared to 5 mg/kg in sarcoidosis. More importantly, the mean dose of MTX in rheumatoid patients was 15 mg per week compared to 7.5 mg MTX per week in sarcoidosis (23). Therefore, we should be cautious to state that when treating sarcoidosis patients with biosimilars there will not be a difference in immunogenicity.

Moreover, a recent study in RA shows that adalimumab levels are influenced by concomitant MTX use: patients on adalimumab monotherapy had a lower adalimumab level of compared with patients concomitantly taking MTX ( $p < 0.001$ ). A better clinical response was present for patients using both adalimumab and MTX (27).

However, to our opinion sarcoidosis patients who never received TNF- $\alpha$  inhibitors before may be safely treated with infliximab biosimilars instead of the infliximab reference product. A clinical registry looking at the outcome of patients treated with biosimilar versus infliximab should be performed before a final recommendation can be made

#### *Infliximab biosimilars in sarcoidosis patients currently receiving TNF- $\alpha$ inhibitors*

In order to further reduce the costs of TNF- $\alpha$  inhibitors one could consider switching the infliximab reference product to an infliximab biosimilar in patients who are currently being treated with infliximab. A major problem in active switching of infliximab is its pharmacological half-life, which is around 9 days. During treatment even some accumulation occurs resulting in the fact that infliximab can be detected in serum during a period of 12 weeks (28). The normal dosing interval of infliximab in sarcoidosis patients is 4 weeks. In theory, when during active switching anti-infliximab antibodies are formed, it can't be determined if these antibodies are against the reference product of infliximab or the biosimilar. Based on the high risk of relapse it also is not advisable to stop the infliximab reference product for 3 months before starting the infliximab biosimilar (29). Moreover, when considering active switching of infliximab therapy we have to bear in mind that TNF- $\alpha$  inhibitors is often seen as last-resort therapy in patients with severe, refractory and threatening sarcoidosis. If those patients achieved a good response on the infliximab reference product it will be obviously hard to switch to an infliximab biosimilar for both clinicians and patients themselves. Furthermore, patients should not get the feeling that finance is more important than their well-being.

Currently, in rheumatology or inflammatory bowel disease also no data on active switching to infliximab biosimilars are available. At present, the NOR-SWITCH study is recruiting patients. The

purpose of this study is to assess the safety and efficacy of active switching from the infliximab reference product Remicade® to the infliximab biosimilar treatment Remsima® in patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease and chronic plaque psoriasis (30). The results of this RCT are expected at the end of 2016.

Therefore, we recommend to avoid active switching to infliximab biosimilars in sarcoidosis patients who are currently being treated with the infliximab reference product. Including sarcoidosis patients in the ongoing NOR-SWITCH study would provide important information regarding the safety of such a switch.

## CONCLUSION

Biosimilars of infliximab are here to stay and will obviously become important in the treatment of patients with sarcoidosis. However, both economic and clinical issues are complex indicating that continuous education on the subject is warranted (31, 32). Considering the working mechanism of the original biological and that of the biosimilars it is highly likely that the therapeutic effect is comparable of both agents. Therefore, in our opinion sarcoidosis patients who were not treated before with the TNF- $\alpha$  inhibitor infliximab may safely start with infliximab biosimilars instead of the reference product infliximab. A clinical registry looking at the outcome of patients treated with biosimilar versus infliximab should be performed before a final recommendation can be made. Switching the infliximab reference product to an infliximab biosimilar in patients who are currently receiving infliximab therapy until clinical trials addressing this issue become available should be avoided.

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