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Efficacy and safety of infliximab biosimilar Inflectra® in severe sarcoidosis

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ABSTRACT

Background: Infliximab, a monoclonal antibody against tumor necrosis factor alpha (TNF-α) is effective third-line therapy in severe sarcoidosis. The originator product of Infliximab, Remicade®, is expensive, limiting universal access. Recently, a less expensive biosimilar of infliximab, Inflectra®, has become available, but the efficacy and tolerability has not been studied in sarcoidosis.

Methods: In this retrospective cohort study, 29 patients treated with the infliximab biosimilar Inflectra®, were analysed. Patients received Inflectra® intravenously monthly at a dose of 5 mg/kg. We measured trough levels before every infusion. Before and after 6 months of induction therapy pulmonary function and disease activity were evaluated using Standardised Uptake Value (SUV) of the ^{18}F-fluorodeoxyglucose by positron emission tomography (^{18}F-FDG PET), soluble interleukin-2 receptor (sIL-2R), angiotensin converting enzyme (ACE) and health-related quality of life (HRQOL).

Results: In patients with pulmonary sarcoidosis as main treatment indication (n = 15) the predicted FVC improved with 8.1%, $p < 0.05$. Furthermore, in the whole group HRQoL improved significantly ($p < 0.001$), whereas SUVmax and sIL-2R significantly reduced ($p < 0.001$ and $p = 0.001$ respectively). Hospitalisation due to infections occurred in four patients. None of the patients discontinued Inflectra® due to side-effects. Furthermore, all patients had detectable trough levels indicating development of neutralizing antibodies.

Conclusion: Infliximab biosimilar Inflectra® seems effective in the treatment of refractory sarcoidosis with a comparable safety profile to the reference product Remicade®. Inflectra® can be considered as an alternative and less expensive option for patients with refractory sarcoidosis.

1. Background

Sarcoidosis is a multisystem granulomatous disease of unknown aetiology. Moreover, the course and prognosis of sarcoidosis is heterogeneous. Not all patients with sarcoidosis require therapy: most patients have a spontaneously resolving course of disease, while in others the disease can be progressive and even life-threatening [1]. Treatment of sarcoidosis has a multistep approach. Corticosteroids have proved to be effective as initial treatment for sarcoidosis [2–4]. In steroid-refractory cases or in the presence of steroid-associated side effects second-line treatment can be commenced using drugs such as methotrexate, azathioprine, mycophenolate or leflunomide [5–9].

Nevertheless, in some sarcoidosis patients the available first- and second-line therapeutics do not provide the optimal result. In those refractory sarcoidosis patients third-line therapy with targeted TNF-α inhibition can be considered [10].

Several randomized clinical trials [11–14] and retrospective studies [15–18] have shown the efficacy of infliximab in refractory sarcoidosis using the originator product Remicade®.

The expensive therapy with anti-TNF-α agents remains a large issue in health care costs. However, with the expiring of the patent of Remicade®, biosimilars of infliximab have become available. Biosimilars are comparable to its reference product in terms of quality, safety and efficacy [19]. Various reports described promising results of the use of biosimilars of the originator product Infliximab (Remicade®), in the treatment of rheumatoid arthritis, psoriasis, ankylosing spondylitis and inflammatory bowel disease [20–23]. Furthermore, the European Medicines Agency (EMA) considers Inflectra® similar to its reference product in efficacy and safety based on two trials: the PLANETA study in patients with ankylosing spondylitis and the PLANETRA study in patients with Rheumatoid Arthritis [20,22]. However, in these studies a much lower dose of Inflectra® and a higher dose of methotrexate

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was used than currently used in sarcoidosis. Furthermore, it is uncertain whether these data can be extrapolated to the use of the biosimilar Inflectra® in refractory sarcoidosis.

A third point of concern of introducing biosimilars in sarcoidosis is immunogenicity. Formation of neutralizing drug antibodies is related to low trough infliximab serum levels and subsequently are associated with treatment failure [24].

In this study we report the first cohort of sarcoidosis patients treated with the infliximab biosimilar Inflectra® addressing efficacy and safety.

2. Methods

This study is a retrospective cohort study. In 2015 an update of the position paper how to use TNF-α blockers in sarcoidosis patients was published by the Dutch Association of Pulmonologists. In this paper, it was recommended to treat patients with an indication for TNF-α blockers with Inflectra® instead of Remicade® in order to reduce the health care costs and increase accessibility to this drug [25,26]. Therefore, since November 2015 all patients with refractory sarcoidosis with an indication for third line therapy were started on the biosimilar Inflectra® in our hospital.

Sarcoidosis was defined as refractory when organ damage persisted while receiving second-line immunosuppressive treatment (Table 1). Furthermore, refractory sarcoidosis was also defined when second-line therapy had to be discontinued due to toxicity.

In this study all patients received an intravenous infusion of 5 mg/kg Inflectra® at weeks 0 and 2, and subsequently every four weeks. Sarcoidosis was diagnosed when clinical findings were supported by histologic evidence, and after exclusion of other causes of granuloma [1].

The following data from patients were registered: sex, age at the start of Inflectra®, ethnicity, smoking history, prior and current immunosuppressive drug use, duration of disease, main treatment indication and, extra-pulmonary manifestations. Study data were collected and managed using REDCap electronic data capture tools hosted at St. Antonius Hospital, Nieuwegein [27]. The study was approved by the local institutional review board of St Antonius Hospital Nieuwegein, The Netherlands, with registration number LTME/Z-12.33.

2.1. Organ function

Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), diffusing capacity of the lung for carbon monoxide (DLCOc) and the 6-min walking distance were determined at baseline and after 26 weeks of Inflectra® treatment as previously described in the study of Vorselaars et al. [18]. An increase of 5% of FVC, FEV1 and DLCOc (% predicted) was considered as clinically relevant.

Functional response in patients with a pulmonary treatment indication was based on an improvement of 5% of FVC (% predicted).

In patients with extra-pulmonary treatment indications, improvement of organ function (functional response) was based on either:

1. Improvement of neurologic symptoms or improvement of pain
2. Improvement of lesions in the central nervous system seen on MRI
3. Improvement of cardiac ejection fraction by more than 5%
4. In patients with PET-positive cardiac localisations and prior arrhythmias, absence of arrhythmias during treatment with Inflectra® was defined as functional response.

Table 1
Definition of refractory sarcoidosis.

Refractory sarcoidosis was defined when despite first and second line treatment the following occurred:	N (number of patients)
Progressive pulmonary sarcoidosis defined by a decrease of FVC > 5% of predicted and/or decrease DLCO > 5% of predicted	5
Progressive pulmonary fibrosis in the context of persistent inflammatory activity defined by positive PET-scan	10
Persistent inflammatory activity of cardiac localisation defined by positive PET-scan	3
Persistent symptomatic sarcoidosis of central nervous system	8
Persistent severe pain due to small fiber neuropathy or osteolytic lesions	3

2.2. Inflammatory activity and HRQoL

^{18}F-fluorodeoxyglucose by positron emission tomography/computed tomography (^{18}F-FDG PET/CT), genotype corrected angiotensin converting enzyme (ACE), serum soluble interleukin-2 receptor (sIL-2R) were measured as previously published in the study of Vorselaars et al. [18].

A decrease of 40% of SUVmax and a decrease of 40% of one of the biomarkers was considered as a clinically significant response to Inflectra® [18].

In patients with a pulmonary treatment indication we measured the maximum Standardised Uptake Value (SUVmax) in the lung parenchyma and in the mediastinal/hilar lymph nodes. In patients with cardiac sarcoidosis the SUVmax was measured in the mediastinal (including anterior, visceral and posterior mediastinum) and perihilar region. In patients with neurosarcoidosis, small-fibre neuropathy and skeletal sarcoidosis the SUVmax was measured in target lesions and in mediastinal and hilar lymph nodes.

The health-related quality of life was determined by the 36-Item Short-Form Health Survey (SF-36) and the Visual Analogue Scale (VAS).

The RAND 36-Item Healthy Survey contains eight domains: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health. We used only the subscale physical functioning (as reported by Vorselaars et al. [18]), the scale consists of 10 items and is transformed to a 0 (worse score) to 100 scale (best score) [28]. The dimension physical functioning gives an indication of the limitations of patients due to their physical health. Although in some studies an increase of 5 points of the SF-36 was considered clinically relevant [31], we decided to use a more robust increase of 10 points as clinically relevant as previously published [18].

The Visual Analogue Scale is a scale measuring the burden of disease also used in the DAS28 in rheumatology [29], ranging from 0 (worst) to 100 (best) [30]. An increase of 10 points of VAS [32] was also considered as a clinically significant response of health-related quality of life to Inflectra®.

2.3. Adverse events and immunogenicity

Side effects and symptoms were evaluated at every visit to the outpatient clinic. Serious infections side effects were defined as infections associated with death, hospitalization, or the use of intravenous antibiotics.

Trough infliximab serum levels were measured prior to Inflectra® infusion using enzyme-linked immunosorbent assay (ELISA). Antibodies to infliximab (ATIs) were measured in case of suspected treatment failure or adverse reactions. ATIs were detected using radioimmunoassay as previously described [18].

2.4. Composite overall response

Composite overall score was measured as previously published by Vorselaars et al. [18] and includes the following dimensions: functional response, inflammatory response and response of health-related quality of life. Measurement of these responses was performed as described in the previous paragraphs.

Composite overall response was considered excellent when patients showed improvement in all three dimensions, good when patients showed improvement in 2 out of 3 dimensions and response in one