



The Non-medical Switch from Reference Adalimumab to Biosimilar Adalimumab is Highly Successful in a Large Cohort of Patients with Stable Inflammatory Rheumatic Joint Diseases: A Real-Life Observational Study

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ABSTRACT

Introduction: The adalimumab biosimilar (ADAbio) Amgevita® has a similar efficacy and safety profile as the adalimumab reference (ADA) Humira®. We studied the clinical consequences of a non-medical switch from ADA to ADAbio in adult patients with mainly established rheumatoid arthritis (RA), psoriatic arthritis (PsA), and spondyloarthritis (SpA).

Methods: Patients that received treatment with ADA for at least three months were switched to ADAbio. Data was collected retrospectively from 1 year before the switch up to 6 months after.

Results: A total of 603 patients were switched from ADA to ADAbio (switch group). During a 1-year follow-up, over 93% of all patients underwent a successful transition in terms of disease activity and safety from ADA to biosimilar, supporting the bioequivalence of both drugs in patients with stable inflammatory rheumatic joint diseases. Forty patients (6.6%) switched back to ADA (re-switch group). There

were no objective changes in disease activity score in 28 joints using C-reactive protein (DAS28-CRP), or adverse effects before and after the switch between both groups.

Conclusions: In line with earlier reports, the transition to ADAbio went successful in the majority of patients with stable inflammatory rheumatic joint diseases. Patient-reported symptoms without objective signs that indicate a flare of disease activity after the switch to ADAbio are probably explained by nocebo effects. A pre-emptive approach to counteract nocebo effects and stimulate placebo response may have a positive impact on health outcomes for patients and preserve the economic benefits of cost savings that can be achieved by prescribing a biosimilar instead of the reference drug.

Keywords: Biosimilar; Adalimumab; Anti-TNF; Inflammatory rheumatic joint diseases; Disease activity; Nocebo effects

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Key Summary Points

Patient-reported symptoms upon the non-medical switch from adalimumab reference (ADA) to biosimilar adalimumab (ADAbio) are probably explained by nocebo effects since there were no objective changes in disease activity score or adverse effects observed in our cohort of patients with established inflammatory rheumatic joint diseases, comprising RA, PsA, and SpA.

With the growing numbers of available biological disease-modifying anti-rheumatic drugs (DMARDs) against various targets and their biosimilars in the field of rheumatic inflammatory joint diseases, a pre-emptive strategy to counteract nocebo effects and stimulate placebo response may have a positive impact on health outcomes for patients and preserve the economic benefits of cost savings by switching from a reference drug to the less-costly biosimilar.

INTRODUCTION

With a trial in experimental sepsis over 20 years ago, the first tumor necrosis factor (TNF) inhibitor was introduced with cA2 monoclonal antibody, now known as infliximab [1], which was later followed by a randomized study in patients with rheumatoid arthritis (RA) [2]. From then, TNF inhibitors (TNFi) that neutralize TNF as central orchestrator of the pathogenesis of multiple inflammatory diseases [3, 4] revolutionized the treatment strategy in patients with RA, psoriatic arthritis (PsA), and spondyloarthritis (SpA) [5–10].

Since then, a new era has arrived with the advent of innovative medications that have many different drug targets and a growing number of available biosimilars. After the launch of Inflectra® and Remsima®, the biosimilar versions of TNFi infliximab (2013),

and subsequently Benepali® (2016), an etanercept biosimilar to the Dutch market [11–14], Amgevita® (ABP 501; Amgen Inc., Thousand Oaks, CA, USA) was approved as adalimumab biosimilar in the Netherlands. It was registered in 2017 for the same indications and with a similar safety profile as the adalimumab reference (ADA) Humira® (AbbVie Inc., North Chicago, IL, USA) [13].

A large number of studies, including randomized control trials, have demonstrated that switching from a reference TNFi to its biosimilar has no significant effect on disease activity, safety, and immunogenicity, suggesting therapeutic equivalence [15–27]. As TNFi are prescribed in large numbers of patients with various chronic inflammatory disorders including the musculoskeletal system, gastro-intestinal tract, and skin, non-medical switching from a reference biomedicine to a biosimilar could have a large socioeconomic impact [28–30]. Beyond the economic advantage, expansion of the biosimilar market may lead to further improvements of the reference drug, including the design of the injection device and product service.

Despite these benefits, switching from reference biomedicine to biosimilar may introduce subjective symptoms or adverse effects in patients otherwise classified as stable disease. In the absence of any objective clinical data, this alteration in the patient-reported outcomes may be explained by nocebo effects that challenge the principle of interchangeability from the patient's point of view, and may be detrimental to patient confidence and drug compliance [31–34].

The aim of our study is to evaluate the non-medical transition from ADA to ADAbio in a cohort of patients with established and stable inflammatory rheumatic joints disease involving RA, PsA, and SpA.

METHODS

Patients and Disease Activity Score

In November 2018, a total of 603 adult patients in the Maastad Hospital, Rotterdam, The

Netherlands were treated with ADA. All patients had an established diagnosis of either RA, PsA, SpA, or incidentally juvenile idiopathic arthritis (JIA) and sarcoidosis.

Stable disease was defined as disease remission or low disease activity (DAS28 2.6–3.2) during treatment with ADA for at least 3 months before the switch to ADAbio.

In November 2018, all patients underwent a non-medical switch of ADA to ADAbio after being informed by a formal letter in November 2018 and, on request, via additional face-to-face consultation with the nurse practitioner or rheumatologist. There were no exclusion criteria for eligibility for this study except age of at least 16 years or older. Clinical data, including age, sex, disease duration, smoking habits, co-medication, and disease activity scores in 28 joints (DAS28) C-reactive protein (CRP) in patients diagnosed with RA and PsA was collected from the electronic medical/health record system (HIX, Chipsoft, The Netherlands) retrospectively in the 1-year period before the switch up to 6 months after the switch. Disease activity indicated by the composite index DAS28-CRP in all switchers with RA and PsA was determined between May 2019 and November 2019.

The last measured DAS28-CRP before and after the non-medical switch were determined in the 1-year period before the switch up to 6 months after the switch.

All eligible patients, when admitted to our outpatient clinic, agreed that their clinical and laboratory data may be used for clinical practice analysis to improve care in an anonymous manner (opt-out procedure). Therefore, this study has been granted an exemption from requiring ethics approval. Personal data was handled in compliance with the Dutch Personal Data Protection Act and the privacy regulations of the Maastricht Hospital. This study was conducted in accordance with the Declaration of Helsinki of 1964 and its later amendments.

Design and Statistical Analysis

The basis of our report was the Strengthening the Reporting of Observational Studies in

Epidemiology (STROBE) statement [35]. Data were analyzed using SPSS software (version 23 for Windows; SPSS, Inc.).

Comparative statistical evaluations were performed by Wilcoxon signed-ranks tests, Kruskal–Wallis tests, independent sampled *t* tests, and Mann–Whitney test. Data are reported as means \pm SEM. In all analyses, a two-sided *p* value < 0.05 was considered statistically significant.

RESULTS

A total of 603 patients with the established diagnosis RA, PsA, and to a lesser extent SpA, and few others involving patients with JIA and sarcoidosis underwent a non-medical transition of ADA to ADAbio (switch group). The average duration of ADA therapy before the switch was 88 ± 8 months, and ADA was primarily used as first or second bDMARD in these patient cohorts. At the initiation of the transition, the average age was 55 years (range, 41–82 years), and 56.5 percent of the patients were female and the majority were Caucasian. Co-medication was used in 69.1% of all patients, including conventional DMARDs (cDMARDs) methotrexate, leflunomide, sulfasalazine, and/or hydroxychloroquine (28.1%), glucocorticoids (9.1%) and NSAIDs (13.9%).

In the 1-year follow-up, the transition to ADAbio went successfully in terms of disease activity and safety in over 93% of the patients with stable inflammatory rheumatic joint diseases. However, 40 patients (6.6%) of this group gradually switched back to the bio-originator (re-switch group) by using shared decision-making. To get a better understanding of the clinical arguments for this re-switch, we compared the clinical characteristics of the re-switch group ($n = 40$) with that of the patients ($n = 563$) that continued their use of ADAbio (listed in Table 1).

The distribution of median age, sex, race, and smoking status were comparable in both groups. RA, PsA, and SpA were the most common inflammatory rheumatic joints diseases amongst the re-switch group and switch group. In the re-switch group, however, the percentage

Table 1 Patient characteristics of the re-switch group ($n = 40$) and switch group ($n = 563$)

	Re-switch group ($N = 40$)	Switch group ($N = 563$)	<i>P</i> value
Demographic data			
Age range, median (years)	41–82, 55	16–88, 55	0.47
Sex, female (%)	22 (55)	318 (56.5)	0.86
Race, Caucasian (%)	40 (100)	553 (98.2)	0.40
Smoking, yes/stopped (%)	19 (47.5)	252 (44.8)	0.74
Co-medication			
None (%)	16 (40)	179 (31.8)	0.28
NSAID/COX inhibitor (%)	5 (12.5)	78 (13.9)	
Glucocorticoids	4 (10.0)	51 (9.1)	
cDMARD* (%)	14 (35)	158 (28.1)	
NSAID/COX inhibitor + cDMARD	5 (12.5)	147 (26.2)	
Median disease duration (months)	122	104	0.094
Rheumatological disease			
Rheumatoid arthritis (%)	13 (32.5)	248 (44.0)	0.22
Psoriatic arthritis (%)	13 (32.5)	156 (27.7)	
Spondyloarthritis (%)	13 (32.5)	154 (27.3)	
Other			
Juvenile idiopathic arthritis (%)	1 (2.5)	3 (0.5)	
Sarcoidosis	–	2 (0.4)	

of RA patients was lower as compared to the switch group, whereas PsA and SpA were slightly more present ($p = 0.22$).

The treatment schedule and dosage of adalimumab 40 mg every other week was not significantly different in either of the groups, which was 87.5% of the patients in the re-switch group versus 83.7% in switch group ($p = 0.52$). In the re-switch group, 35% of the patients used cDMARDs in addition to TNFi as compared to 28.1% of the patients in the switch group ($p = 0.35$). The total percentage of patients without co-medication was higher in the re-switch group (40%) than in the switch group (31.8%, $p = 0.28$). The mean dosage of glucocorticoids (prednisolone or equivalent) was 12 mg daily in the re-switch group (10.0%) versus 9.5 mg daily in the switch group (9.1%).

There was no statistically significant difference in median disease duration between the re-switch and switch group, respectively (122 vs. 104 months; $p = 0.094$). The median duration of ADA use before the switch to ADABio was 2.8 years in the switch group, and 7 years in the re-switch ($p = 0.018$). We set out to address the clinical impact of the re-switch on the disease activity score, as indicated by the composite index DAS28-CRP, in the patients with RA and PsA. SpA patients were not included in this analysis because of missing values in the composite disease activity scores.

In the re-switch group, the disease activity was measured as the last available clinical score within a period of 1 year before and 6 months after the switch back to ADA. As shown in Fig. 1, no significant difference in disease activity

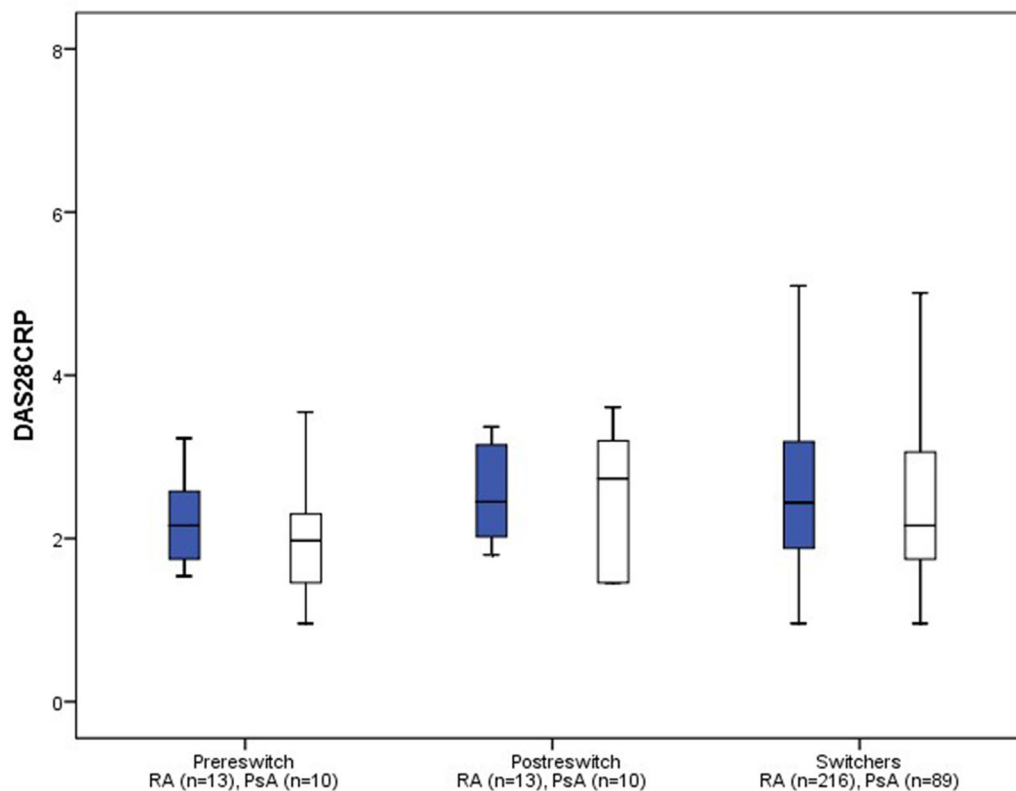


Fig. 1 Pooled measurements of disease activity scores in 28 joints (DAS28) C-reactive protein (CRP) in patients with rheumatoid arthritis (RA) and psoriatic arthritis

(DAS28-CRP) was observed in these RA ($n = 13$) and PsA patients ($n = 10$, data not available for 3/13 patients) before and after the non-medical switch ($p = 0.31$). In addition, there were no significant differences in swollen joints (SJ), tender joints (TJ) and, visual analog scale (VAS) between RA and PsA patients, respectively ($p = 0.20$, $p = 0.76$, $p = 0.66$). DAS28 and CRP did not change in patients that not reswitch (non-reswitchers).

The most important reasons for switching back to ADA, as predominantly instigated by the patient, included an increase in arthralgias with or without stiffness ($n = 28$; 70%), decrease in therapeutic efficacy in a broader sense ($n = 2$, 5%), unpleasant experience with the injection device (an auto-injection pen versus prefilled syringe; $n = 2$, 5%), self-reported worsening of psoriasis in PsA ($n = 1$, 2.5%), and various other subjective causes (see pie chart Fig. 2).

(PsA) before and after the switch back from ADABio to reference adalimumab

In the re-switch group, 24 patients (60%) experienced clinical improvement after the switch back to ADA, which cannot be explained by a relevant difference in disease activity between the re-switch group and switch group. Seven patients (17.5%) of the re-switch group did not notice any differences in their symptoms. Finally, three of these seven patients switched to therapies with other modes-of-action. One patient started with another TNFi, and two other patients switched to cDMARD monotherapy.

DISCUSSION

To the best of our knowledge, this is one of the largest single-center, real-life observational studies that report on the clinical follow-up data upon the non-medical transition from ADA to ADABio in a cohort of 603 patients with an

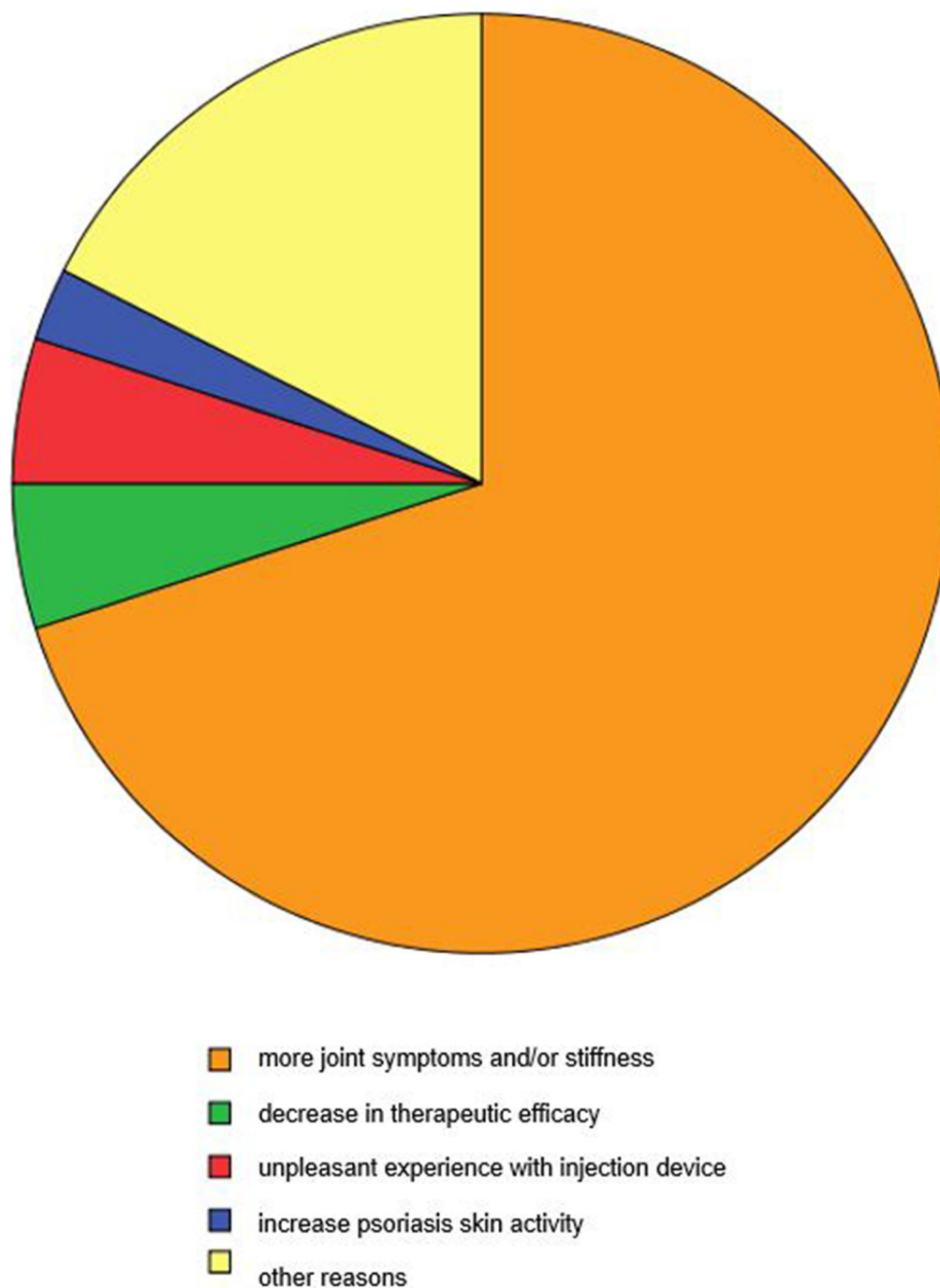


Fig. 2 The most important reasons for switching back to reference adalimumab (ADA). $N = 28$ (70%), $N = 2$ (5%), $N = 2$ (5%), $N = 1$ (2.5%), $N = 7$ (17.5%)

established diagnosis of primarily RA, PsA, and SpA [36–39]. Using a comprehensive approach, we are the first to report on successful non-medical switch from adalimumab reference

Humira® (ADA) to adalimumab biosimilar Amgevita® (ADAbio) that rendered stable disease activity after transition.

A total of 40 patients (6.6%) were gradually shifted back to the bio-originator, which was largely instigated by patients that reported an increase in arthralgias and stiffness without measurable enhancement of disease activity. Since the disease activity indicates no flare of disease after the transition to ADABio, we believe that patient-reported symptoms that triggered the switch back to the bio-originator are probably explained by nocebo effects. RA, PsA, and SpA were evenly distributed amongst the re-switch group and the remaining patients of the cohort that underwent the initial transition to the biosimilar.

Our findings indicate that over 93% of the patients in our cohort comprising RA, PsA, and SpA readily underwent the transition to ADABio and experienced no signs of flare of disease activity or adverse effects. Our observation highly supports the therapeutic equivalence of ADA and ADABio and is in line with earlier studies [16–18, 21–23, 25, 39]. Six patients refused to switch, and of 86 patients (14.3%) disease activity is not well controlled.

We believe that our department has achieved this success by the huge efforts to carefully inform and educate our patients and operational staff including nurse practitioners, nursing staff at the day hospital, residents and medical doctors on the interchangeability of both biomedicines and the economic benefits in this growing sector of expensive drugs in advance to the transition [39, 40].

We were unable to find differences in clinical characteristics including co-medication, smoking habits, gender, and disease duration that could explain the switch back to the bio-originator between the patients that continued the use of ADABio and the re-switch group.

In addition, we noted that there was no significant change in clinical scores of disease activity in the RA and PsA patients of the re-switch group upon switching back to the bio-originator, which is in line with other studies [15–26, 39].

In the majority of patients that re-switched to the bio-originator, the decision was instigated by largely patient-reported symptoms. In none of these patients was a re-challenge with

the ADABio performed, although this strategy would have provided evidence for a causal link. Given the absence of measurable worsening of disease activity, nocebo effects probably played an important role in the shared decision between patient and rheumatologist to switch back to the bio-originator. However, discriminating between nocebo effects and true adverse effects, fluctuations in clinical course, and loss of therapeutic efficiency could be difficult, particularly in patients with established inflammatory rheumatic joint diseases that may be less capable to comprehend scientific data and biased because of loss in therapy response and adverse effects in the past [41].

As a shortcoming of this study, we noted that the documentation of disease activity scores including the DAS28-CRP before and after transition to ADABio was suboptimal in a few cases. This may have been caused by the magnitude of this operation in our large cohort of established inflammatory rheumatic joint diseases. Another limitation of our study is that we could not objectify patient-reported response outcomes. Implementation of instruments to measure patient-reported response outcomes in RA patients was only recently realized and not yet in PsA and SpA patients.

In our local hospital, the costs of adalimumab reference is about three times that of its biosimilar. As anticipated, the costs savings and socio-economic impact that resulted from the transition to ADABio was indisputably considerable. However, the emerging costs that accompanied the re-switch to the bio-originator threatened to overshadow the initial success. This finding warrants the decision to switch for (non-)medical and economic reasons to other biosimilars on a case-by-case basis.

CONCLUSIONS

In conclusion, this large real-life observational study demonstrates that the transition to ADABio went successfully in the majority of patients with stable inflammatory rheumatic joint diseases. The absence of objective measurements, indicating increased disease activity, which could have supported the patient-

reported symptoms after the switch to ADAbio, suggests that nocebo effects most likely played a decisive role in the shared decision between patient and rheumatologist to switch back to the bio-originator. A pre-emptive approach to counteract nocebo effects and stimulate placebo response may have a positive impact on health outcomes for patients and preserve the economic benefits of cost savings that can be achieved by prescribing a biosimilar instead of reference drug.

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Disclosures Roxanne C.S. van Adrichem, Hanneke J.E. Voorneveld, Geeke J. Waverijn, Marc R. Kok, and Radjesh J. Bisoesndial have nothing to disclose.

Compliance with Ethics Guidelines All eligible patients, when admitted to our outpatient clinic, agreed that their clinical and laboratory data may be used for clinical practice analysis to improve care in an anonymous manner (opt-out procedure). Therefore, this study has been granted an exemption from requiring ethics approval. Personal data were handled in compliance with the Dutch Personal Data Protection Act and the privacy regulations of the Maasstad Hospital. This study was conducted in accordance with the Declaration of Helsinki of 1964 and its later amendments.

Data Availability Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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