TITLE: Cohort study on drug survival and tolerability of adalimumab biosimilar transitioning: pharmaceutical properties do matter.

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ABSTRACT

There are no clinically meaningful differences between bio-originators (BO) and their biosimilars (BS) in safety and efficacy. However, differences in pharmaceutical properties, such as volume and excipient can occur. This study aims to compare outcomes between patients transitioning from the modernised adalimumab BO (0.4ml/no citrate) to BS1 (0.8ml/citrate) and from BS1 to BS2 (0.4ml/no citrate) and outcomes for new starters. In this retrospective exploratory cohort study of RA, PsA and axial SpA patients receiving adalimumab, the (adjusted) 12-month drug survival rates were compared between the transition from the modernised BO to BS1 (cohort 1,2021) and from BS1 to BS2 (cohort 2, 2023) in existing users, and for adalimumab naïve new starters of the originator and BS1 and BS2 (cohort 3 to 5). Subanalyses included drug survival separately for inefficacy and intolerability. In existing users, (983 patients transitioned to BS1, 1,082 patients to BS2, with 659 patients in both cohorts), drug survival rates at 12 months were 73% (95%CI: 70% to 76%) and 90% (95%CI: 88% to 92%), respectively (p<0.001), adjusted Hazard Rate Ratio (HRR) 0.32 (95%CI:0.26-0.40) in favour of BS2. The HRR for discontinuation due to inefficacy and tolerability were 0.50 (95%CI 0.37-0.67) and 0.20 (95%CI 0.14-0.28) respectively, both favouring BS2. In adalimumab naïve new starters also, better survival for the originator and BS2 were seen compared to BS1. In conclusion, adalimumab BS1 showed a significantly lower drug survival compared to BS2, primarily due to lower tolerability. These findings suggest that pharmaceutical differences can have an important impact on drug survival.

INTRODUCTION

Biologicals have an increasingly important place in the treatment of inflammatory rheumatic diseases, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA). Expiration of patents for original biologicals (bio-originators) in the last few years have led to the introduction of many biosimilars. Biosimilars are very similar but not fully identical to their originator, with small variations in structure arising from differences in the production process (1), but very similar efficacy and safety.

Adalimumab is a Tumor Necrosis Factor inhibitor (TNFi), used to treat various diseases, including RA, PsA and axSpA. The bio-originator (BO) of adalimumab is Humira ® and has been approved by the Food and Drug administration (FDA) since 2002 and by the European Medicines Agency (EMA) since 2003. After the compound patent on the BO expired, several adalimumab biosimilars have been introduced (2, 3).

Extensive research shows similarity between adalimumab originator and the many adalimumab biosimilars in effectiveness and safety, both for patients starting adalimumab treatment and for patients transitioning from originator to biosimilar and even in patients undergoing multiple transitions between originator and biosimilars (4-10). Data on patients undergoing multiple transitions supports the idea of interchangeability of biosimilars, which in turn can help with cost-effectiveness and worldwide accessibility of biologicals (11). Interestingly, although pharmacologically the adalimumab originator and the adalimumab biosimilars are similar in terms of structure, function, safety and effectiveness, there are some pharmaceutical differences. These include concentration and volume of the solution, type of excipients, administration devices and needle characteristics. These different pharmaceutical properties might drive differences in patient reported outcomes such as tolerability. Literature shows, the use of different excipients (specifically citrate) and injection volume are important factors for tolerability of biosimilars(12, 13). The total patent portfolio of Humira ® illustrates this, as it encompasses over 70 patents regarding indication, dosing and comedication, in addition toinjection volume and excipients use like citrate. In the last two decades, evergreening (making incremental improvements to extend patent protections and commercial drug lifecycle) of the original Humira®, with a 0.8 ml injection volume and use of citrate as an excipient, has led to the development of the current modernized Humira ®, with a 0.4 ml injection volume and no use of citrate. As patents expire

after a set period, this means that early adalimumab biosimilars were based on the initial Humira ® formulation , which could lead to small differences in pharmaceutical properties from the more recent biosimilars based on the modernized Humira ®.

In the Sint Maartenskliniek the Netherlands in January 2021, all patients receiving treatment with adalimumab transitioned from the modernized Humira ® to Idacio ®, Biosimilar 1 (BS1), approved by the EMA in 2019 based on PK/PD data and clinical data(14). In 2023, all patients receiving adalimumab transitioned from Idacio ® to Yuflyma ®, Biosimilar 2 (BS2), approved by the EMA in 2021 based on PK/PD models and clinical data of RA patients(15). Both transitions were made for non-medical economic reasons. Idacio ®, used between 2021 and 2023, is an adalimumab biosimilar with 0.8 ml volume and citrate excipient, and is comparable to the original Humira ®. Yuflyma ® shares pharmaceutical properties with modernized version Humira ®, with small differences in pharmaceutical properties such as a 0.4 ml injectable volume, and absence of citrate (16). These two centre wide transitions, and availability of long-term data on outcomes of all drug variants on both adalimumab naïve new starters and existing users, offer the opportunity to study the effects of transitioning from an originator to a biosimilar with either similar or small differences in pharmaceutical properties. This allows for the evaluation of the effect of these transitions on treatment outcomes including drug survival and tolerability in a real world observational dataset.

Based on literature, the use of citrate and a larger volume are among the pharmaceutical differences that may impact tolerability of the drug and differ between the BO and the different biosimilars. Therefore in this study we looked specifically at these two factors. Our hypothesis was that the use of citrate as an excipient and a larger volume would contribute to a lower tolerability of the drug. We explored whether these differences in citrate use and injection volume would contribute to differences in drug survival between BS1 and BS2 and hypothesized that BS1 might have a , lower drug survival compared to BS2 in existing users. Additionally, given the established clinical evidence of similarity in efficacy among biosimilars and the bio-originator, we did not expect differences in drug survival related to effectiveness or mean disease activity.. Finally, we expected no difference in drug survival in patients who newly started the drug and never experienced a transition from the lower volume/ no citrate concentration, since those patients have not been exposed to the differences of excipients and volume.

PATIENTS AND METHODS

Study design and patients

This retrospective exploratory observational cohort study, consisted of two cohorts of existing adalimumab users, and three cohorts of new adalimumab starters (Figure 1). General inclusion criteria were all patients who were at least 18 years old at index date (date of transitioning to a BS, or date of starting adalimumab), had a clinical diagnosis of RA, PsA, or axSpA and were treated at any time with adalimumab between April 2012 and May 2024 at the rheumatology department of the Sint Maartenskliniek, the Netherlands.

For the existing user cohorts, only transitioning users were included. Cohort 1 included all patients who transitioned from the modernized BO to BS1, while cohort 2 included all patients who transitioned from BS1 to BS2. Cohort start dates were June 8 2021 for cohort 1 and March 20 2023, for cohort 2. For each individual patient, the index date (T=0) was the first time they received BS1 or BS2 after the respective transition. Patients could be included in both cohorts in the case of multiple transitions, therefore patients in cohort 2 could have begun their treatment with BS1 or in case of a second transition with the BO.

For the incident new starter cohorts, three additional cohorts were identified (cohort 3 to 5). Firstly, cohort 3 including all adalimumab naive starters of the BO of adalimumab from April 2021 to June 8 2021, thus before introduction of the first adalimumab biosimilars in the Sint Maartenskliniek. Secondly, cohort 4, which consisted of adalimumab naive BS1 starters, before introduction of BS2. And finally cohort 5, which included all adalimumab naïve BS2 starters. Patients of these cohorts did not transition before cohort entry. Patients included in these three cohorts were censored when they were transitioned, so in these cohorts patients did not experience change between adalimumab versions with different pharmaceutical properties.

The follow-up period was censored at 12 months (or earlier in case of loss to follow up or death) for each patient, starting from their index date. The local ethics committee (METC-Oost Nederland, 2024-17267) assessed this study and provided exemption, as ethical approval for this type of study is not required under Dutch law. Anonymized data from electronic health records was used for analyses, but patients who previously chose not to have their data used for scientific research were excluded, according to Dutch law and guidelines (GDPR, WGBO 758.2).

Treatment

All patients included in this study were being treated according to usual care. Treatment decisions regarding indication, dose, comedication and tapering were made through shared decision making between patient and rheumatologist. Adalimumab has been the first or second choice biologic Disease Modifying Anti-Rheumatic Drug (bDMARD) for patients with RA, PsA, and axSpA during the study period. However, individual patient characteristics allowed for choice of other bDMARDs.

All existing adalimumab users transitioned from the originator to BS1, and subsequently from BS1 to BS2. Transitioning was in part mandatory, but physicians had the option to offer patients the possibility of transitioning back to the previous drug in case of objective side effects or loss in efficacy. All such cases were reviewed in a staff meeting prior to this transition to prevent too lenient transitioning back. All new patients started on the preferential adalimumab version in the Sint Maartenskliniek at that specific moment in time, as these preferences changed multiple times over time.

Assessments

The data used for this study were extracted from the locally developed integrated rheumatology information system (IRIS) and electronic patient health records. Data extraction included limited and pseudonymised patient demographics, disease characteristics, and disease activity and treatment related information. For patients with RA and PsA, disease activity was determined using the Disease Activity Score, including 28 joint count and C-reactive protein (DAS28-CRP) score. Remission was defined as DAS28-CRP ≤2.4 and low disease activity as DAS28-CRP > 2.4 and ≤ 2.9 (17). For patients with axSpA, the Axial Spondyloarthritis Disease Activity Score (ASDAS) score was used. Inactive, moderate, high and very high disease were defined as an ASDAS score< 1.3, ≥ 1.3 and <2.1, ≥ 2.1 and ≤ 3.5 and > 3.5 respectively. All disease activity measurements were extracted between baseline and 12 months follow-up for each patient. The disease activity measurements closest to the index date and at 12 months were included in the analysis, with a maximum of 4 months prior to, and a maximum of 1 month after the supposed index and 12-month follow-up date. Treatment related data included the version of adalimumab, rheumatic co-medication, DMARD history, and time since start of adalimumab. Reasons for discontinuation of adalimumab were extracted from patients' health records, since these reasons are specifically noted in the system. Determination of inefficacy and intolerability was based on physicians' judgement alongside disease activity measurements.

Outcomes

Outcomes of this study were the comparison of the 12-month drug survival between cohort 1 and cohort 2, and between cohorts 3, 4, and 5. Furthermore, numbers and reasons for treatment discontinuation with BS1 and BS2, specifically discontinuation due to intolerability and inefficacy, and changes in disease activity between baseline and 12 months, were compared between both cohorts.

Statistical analyses

All statistical analyses were performed using STATA/IC 17.1. Descriptive analyses are, depending on the distribution of the data, presented using frequencies and/ or percentages, mean and standard deviation, or median and interquartile range. Survival analyses were conducted for several outcomes. Transitioning back to the BO, switching to another BS of adalimumab or discontinuation of adalimumab due to inefficacy or intolerability were considered events. Discontinuation due to pregnancy, comorbidities or remission was not counted as an event but was censored at the time of occurrence. Other reasons for early censoring were death of the patient, lost to follow-up from the Sint Maartenskliniek, or when the follow-up time of 12 months was not completed before data extraction (May 2024). A multivariate Cox regression analysis was performed to test for significant differences in drug survival between cohort 1 and 2. To account for the dependency between some subjects included in both cohorts, a variance estimator incorporated into the analysis. In addition, baseline characteristics were compared between cohorts to identify possible confounders. Potential imbalances between cohorts were adjusted for in the multivariate cox regression analysis. Reasons for discontinuation of adalimumab were analysed using hazard rates (HR), and differences were expressed as hazard rate ratios (HRR).

Change in disease activity between baseline and 12 months within cohorts were compared using a Wilcoxon signed-rank test. Differences in change in disease activity between cohorts were tested with a two-sample T-test or Mann-Whitney U test, depending on the distribution of the data. Only patients who had both a baseline measurement and a follow-up measurement were included in this analysis.

RESULTS

A total of 983 and 1082 patients were included in the first or second cohort. 659 patients were included in both cohorts. Patients in cohort 1 had a significantly higher disease duration, a significantly lower ASDAS score at baseline, a significantly higher duration of adalimumab use and significantly less previous bDMARDs use compared to cohort 2 (Table 1). Cohort 3 had a significantly longer disease duration, less previous bDMARDs use, less patients on standard adalimumab dosing and less concomitant csDMARDs use, compared to both cohort 4 and cohort 5. Baseline characteristics between cohort 4 and cohort 5 did not differ.

D**rug survival**

The 12-month drug survival rates were 73% (95%CI: 70% to 76%) and 90% (95%CI: 88% to 92%) ($p<0.001$) for cohort 1 and 2 respectively (Figure 1A). In our study, a significantly lower risk of discontinuation of treatment was observed for BS2 compared to BS1 with an adjusted HRR of 0.32 (95%CI:0.26-0.40).

In cohort 1, 263/983 (26.8%) patients discontinued BS1, of whom 71.5% transitioned back to the BO. In cohort 2, 106/1082 (9.8%) patients discontinued BS2, of whom 17.9% transitioned back to the BO. No patients transitioned from BS2 back to BS1, since BS1 was no longer available in the Sint Maartenskliniek during that time period. The remaining patients who discontinued either BS1 or BS2 transitioned to a different b/tsDMARD.

Discontinuation proportions due to inefficacy (as a percentage of the population of the whole cohort) were 11.9% (117/983) for BS1 and 6.6% (71/1082) for BS2, and due to intolerability 14.6% (146/983) for BS1 and 3.2%% (35/1082) for BS2. The HRR for discontinuation due to inefficacy between cohorts was 0.50 (95%CI 0.37-0.67) favouring BS2. For discontinuation due to intolerability the HRR was 0.20 (95%CI: 0.14-0.28) favouring BS2 (Figure 1B and 1C). The most commonly reported tolerability issue of BS1 was increased injection site pain experienced by patients compared to the BO.

A total of 163, 614 and 446 naive adalimumab users started the BO, BS1, and BS2 respectively. Comparison of all adalimumab naive new starters shows a significant lower 12 month drug survival for adalimumab naive BS1 starters 68% (95%CI: 64% to 71%), compared to adalimumab naive BS2

starters 81% (95%CI: 78% to 85%) and the BO 84% (95%CI: 77% to 89%) (both p<0.001, vs BS2), but no significant difference between adalimumab naive starters of BS2 and BO (p=0.46) (Figure 2).

Disease activity

There were no significant differences in median disease activity between baseline and 12 months follow up for both cohort 1 and cohort 2 (Table 2). Comparison of the changes in disease activity between cohorts also showed no significant differences. For RA and PsA the differences were -0.01 (95%CI: -0.21 to 0.19) (p=0.89) and 0.21 (95%CI -0.04 to 0.46) (p=0.10) DAS28 points respectively, and for axSpA 0.12 (95%CI -0.15 to 0.39) (p=0.39) ASDAS points.

DISCUSSION

The results of the study are in line with our hypothesis that adalimumab BS1, with citrate as an excipient and a higher volume of 0.8ml, has a lower drug survival compared to adalimumab BS2, without citrate as an excipient and a volume of 0.4ml. The main reason for discontinuation of BS1 was indeed intolerability, mostly injection site reactions. Unexpectedly, the same differences between BS1, and BS2 and the BO were seen for new starting patients, suggestingthat the patient preference for low volume, no citrate injections may be independent of previous exposure to low volume no citrate versions.

In addition to a higher risk of discontinuation due to intolerability of BS1 in cohort 1 (after transition) in our study, discontinuation due to inefficacy of BS1 in cohort 1 also seems more frequent compared to discontinuation due to inefficacy of BS2 in cohort 2 (after transition). This could be interpreted as lower effectiveness of BS1 compared to BS2. However, we do not think the lower drug survival for efficacy is driven by true pharmacodynamic differences between the drugs, given the extended evidence of similarity in efficacy of biosimilars compared to bio-originators. Also, our study shows no differences in disease activity between baseline and 12 months follow-up. The most likely explanation therefore of the noted small difference in efficacy might be caused by the ‘reverse halo effect’ causing a drug with lower tolerability also to be perceived as less effective (18). Alternatively, the occurrence of new injection discomfort might have swayed the risk benefit trade off decisively in patients who would otherwise have accepted suboptimal efficacy to some extent.

Similarity in efficacy between originator and biosimilars has been extensively researched previously, however, pharmaceutical properties and differences have rarely been the study focus. Our study shows that when transitioning (existing and new starters) from BO to BS, or from BS to BS, it is important to account for possible pharmaceutical differences. Current literature on drug survival rates of biosimilars are somewhat difficult to compare to our study, since there are many different biosimilars available of adalimumab and different population groups are being investigated. When comparing bio-originators to different biosimilars most studies show equivalent drug survival(19, 20). Drug survival rates of BS1 in existing literature were somewhat higher compared to our study (21). A study by Rella et al. shows similar results to our study with higher drug survival for the bio-originator compared to biosimilars. Additionally, discontinuation due to intolerability was more common compared to

discontinuation due to inefficacy (22). In contrast to our study, a study by Edwards et al. showed no differences in injection site reactions between BS1 and the bio-originator. This study investigated BS1 with an acetate-buffered formulation, while the BS1 used in our clinic contained an citrate-buffered formulation. This difference in pharmaceutical properties might explain the difference in findings (23).

Interestingly, in a recent systematic review investigating efficacy and safety of biosimilars of adalimumab in transitioning patients with different inflammatory diseases, open label data shows a higher number of transitioning patients reporting injection pain in non-randomized studies compared to blinded RCTs, suggesting the possible presence of a nocebo effect. (5, 24) This nocebo effect is also seen when transitioning to a biosimilar of other bDMARDs (25, 26). Using optimized communication strategies when transitioning from bio-originator to biosimilar, or from biosimilar to biosimilar shows positive results in drug survival and might help overcome these nocebo effects to some extent, although in our center this somewhat lower drug survival was seen in spite of optimal evidence based communication (27, 28). Also, a nocebo effect would not explain the same difference in drug survival between BS1 and the bio-originator and BS2 in new starters in our study. BS1 seems to be associated with more injection pain across the different cohorts, regardless of the previous drug that was used. Therefore, the higher incidence of intolerability in BS1 is more likely to be largely real, and not driven solely by a nocebo effect.

This study has several strengths and limitations. Strengths firstly include the large sample size of this study. Due to the two non-selective transitions in our clinic, both cohorts contained a large amount of patients across different diseases without selection bias, leading to the opportunity to assess differences in drug survival in these specific biosimilars. In addition, the use of data from routine clinical practice makes the study more generalizable.

Limitations of this study include the potential survival bias in the second cohort. Since patients could be included in both cohorts, a substantial number of patients in cohort 2 already survived cohort 1. We controlled for this possible bias in two ways: firstly, a variance estimator was added to the multivariate cox regression analysis to control for dependency in data. Secondly, the drug survivals of naïve adalimumab starters with both biosimilars and the bio-originator were assessed separately and compared. As in these patients the significant difference in drug survival is seen also, the better drug survival of BS2 cannot only be explained by survival bias. A second limitation is, that there are some

imbalances between cohorts that could have biased our results. Although, we did adjust for these imbalances in cohort 1 and cohort 2, by adding them in the final analysis as possible confounders, the presence of residual confounding cannot be excluded. A third limitation is the large number of missing disease activity measurements. Because it is expected that patients with stable disease activity have less frequent visits compared to patients experiencing a possible flare, this might lead to an overestimation of disease activity. In addition, differences between disease activity were seen between both cohorts, but due to the high number of missing data, this has not been taken into account in the final analysis adjusted for possible confounders. However, in this study the median disease activity for both patients with RA, PsA and axSpA was very low, making overestimation unlikely. Finally, the DAS28-CRP was used both in RA and PsA patients. This disease activity measurement however is not optimal for PsA patients. Therefore, non-joint disease that could have driven different treatment choices in these patients might have been missed.

In conclusion, adalimumab BS1 (0.8ml/citrate) showed a significantly lower drug survival rate compared to BS2 (0.4ml/no citrate), both in existing and new users, likely driven by lower tolerability. While all biosimilars included in this study have been approved and meet the standards of clinical equivalence, these findings suggest that pharmaceutical differences, such as volume and the use of certain excipients, should be considered to be taken into account in decision making on a hospitals bio-originators/biosimilar portfolio of choice. With many more biosimilars on the horizon, and frequent changes in formulation of biologicals over their commercial lifespan, it is important to take possible pharmaceutical properties into consideration , especiallywhen contemplating use of early ‘first wave’ biosimilars.

Study highlights:

What is the current knowledge on this topic? Biologicals have an important place in the treatment of different inflammatory rheumatic diseases. Over the last two decades, multiple biosimilars have been developed for the biological adalimumab. These biosimilars have been proven to be equally as safe and effective as their bio-originators, both in new starting patients and patients undergoing multiple transitions. Biosimilars are very similar (but not identical) to their bio-originators, apart from small pharmaceutical differences.

What question did this study address? Although, the proven equivalency in safety and efficacy of biosimilars, pharmaceutical properties do differ. This might have an impact on tolerability and therefore drug survival. **This study addressed these possible impacts.**

What does this study add to our knowledge? Biosimilars of adalimumab with a lower volume and without citrate as an excipient have a significantly better drug survival compared to biosimilars with a higher volume and containing citrate. Both in transitioning users as in adalimumab naïve new starters. This difference is mainly due to intolerability.

How might this change clinical pharmacology or translational science? With many more biosimilars to come, it is important to take pharmaceutical properties into account**.**

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A.C.D.P., M.H.M.W., W.D.M., D.F.T.C., L.C.C., B.J.F.v.d.B., N.v.H. and A.A.v.B. wrote the manuscript;

A.C.D.P., M.H.M.W., W.D.M., D.F.T.C., L.C.C., B.J.F.v.d.B., N.v.H. and A.A.v.B. designed the research;

A.C.D.P., M.H.M.W., W.D.M. N.v.H. and A.A.v.B. performed the research (This is a retrospective study, existing data was extracted from electronic patient health records and the integrated rheumatology information system (IRIS). Thereafter, the data was cleaned and analyzed mainly by the previously named authors); A.C.D.P., M.H.M.W., W.D.M., N.v.H. and A.A.v.B. analyzed the data. **Conflict of interest:** LCC: LCC has received grants/research support from Abbvie, Amgen, Janssen and UCB; worked as a paid consultant for AbbVie, Amgen, Bristol Myers Squibb, Eli Lilly, Enlivex, Janssen, Moonlake, Novartis, Pfizer, Takeda and UCB; and has been paid as a speaker for AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer and UCB.

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TABLES:

Table 1. Baseline characteristics of all 5 cohorts

Characteristics	Cohort 1: transition to BS1 (n=983)	Cohort 2: transition to BS2 (n=1082)*	Cohort 3: New starters bio-originator(n=163)	Cohort 4: New Starters BS1 (n=614)	Cohort 5: New starters BS2 (n=446)
Diagnosis, n (%)					
RA	441 (44.9%)	524 (48.4%)	65 (40%)	351 (57%)	242 (54%)
PsA	313 (31.8%)	326 (30.1%)	53 (33%)	177 (29%)	125 (28%)
axSpA	229 (23.3%)	232 (21.4%)	45 (28%)	86 (14%)	79 (18%)
Female, n (%)	526 (53.5%)	563 (52.0%)	91 (56%)	344 (56%)	262 (59%)
Age in years, mean (sd)	56.6 (14.7)	56.3 (14.5)	56 (15)	54 (15)	53 (15)
Disease duration in years, median (25th-75th percentile)	8.1 (4.3-16.5)	7.0 (3.5-16)	5 (1.35 to 12.16)	2 (0.65-7.55)	2 (0.69 – 6.48)
Disease activity, mean (sd) **					
DAS28-CRP, RA, median (IQR)	2.2 (1.6-2.9) (121 missing, 27%***)	2.1 (1.6 - 3.0) (118 missing, 23%)			
DAS28-CRP, PsA, median (IQR)	1.9 (1.6-2.7) (128 missing, 41%)	2.0 (1.5-2.6) (111 missing, 34%)			
ASDAS, axSpA, median (IQR)	1.8 (1.3- 2.4) (114 missing, 52%)	2.2 (1.6-2.8) (115 missing, 50%)			
Previous bDMARDs n (%)					
0	782 (79.6%)	901 (83.3%)	117 (72%)	535 (87%)	394 (88%)
1	171 (17.4%)	146 (13.5%)	40 (25%)	50 (8%)	37 (8%)
2	22 (2.2%)	24 (2.2%)	4 (2%)	19 (3%)	6 (2%)
3 or more	8 (0.8%)	11 (1.0%)	2 (1%)	10 (2%)	9 (2%)
Duration of adalimumab use in years, median (25th-75th percentile)	3.4 (1.7-6.0)	2.6 (1.1-5.5)	n.a.	n.a.	n.a.
Adalimumab standard dose, n (%)*****	543 (54.9%)	628 (58.0%)	133 (82%)	611 (99%)	441 (99%)
Adalimumab DDD% , mean	80% (24%)	81% (24%)	99% (7%)	99% (3%)	99% (4%)

(sd)					
Concomitant csDMARD use, n (%)	442 (44.7%)	530 (49.0%)	59 (36.2%)	334 (54.4%)	269 (60.3%)

Baseline characteristics of patients included all cohorts. Baseline for cohort 1 and 2 is defined as the first time patients received BS1 or BS2 after transition. In case of multiple transitions and thus inclusion in both cohort 1 and 2, baseline characteristics for the same patients were assessed again at the time of inclusion in the second cohort.

Baseline for cohort 3, 4 and 5 is defined as the first time patients received adalimumab.

***659 (61%) of the patients in cohort 1 also belong to cohort 2.**

**** Disease activity was not assessed for cohort 3, 4 and 5. Since we were only interested in disease activity, and the change in disease activity, in the transitioning cohorts.**

*****Percentage of missing disease activity measurements relative to the total RA, PsA or axSpA population in the study.**

******The standard dose of adalimumab is 40mg once every 2 weeks (100%).**

Disease duration, disease activity, duration of adalimumab treatment, bDMARD use prior to initiation of adalimumab treatment, were significantly different between cohort 1 and 2.

Disease duration, bDMARD use prior to initiation of adalimumab treatment, number of patients on standard dosing, and concomitant csDMARD use were significantly different in cohort 3 compared to both cohort 4 and 5.

Abbreviations: RA Rheumatoid Arthritis, PsA: Psoriatic Arthritis, axSpA: axial Spondyloarthritis, DAS28-CRP: Disease Activity Score in 28 joints calculated with C-reactive protein, ASDAS: Ankylosing Spondylitis Disease Activity Score, bDMARD: biological disease modifying anti-rheumatic drug, csDMARD: conventional synthetic disease modifying anti-rheumatic drug, DDD%: percentage of the Daily Defined Dose of 40 mg every 2 weeks, sd: standard deviation.

475 **Table 2. Disease activity in patients with RA, PsA and axSpA included in cohort 1 and in cohort**
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		RA	PsA	axSpA
Cohort 1	**Disease activity at baseline**			
	Number of patients (n)*	320	185	115
	DAS28-CRP, median (IQR)	2.2 (1.6-2.9)	1.9 (1.6-2.7)	
	ASDAS, median (IQR)			1.8 (1.3-2.4)
	Disease activity at 12 months follow-up			
	Number of patients (n)*	347	232	125
	DAS28-CRP, median (IQR)	2.1 (1.6-2.9)	1.9 (1.5-2.8)	
	ASDAS, median (IQR)			2.0 (1.6-2.7)
	Δ disease activity, mean (sd) (p-value)**	-0.004 (1.13) (P=0.95)	0.09 (0.9) (p=0.21)	0.02 (0.69) (P=0.81)
Cohort 2	**Disease activity at baseline**			
	Number of patients (n)*	406	215	117
	DAS28-CRP, median (IQR)	2.1 (1.6-3.0)	2.0 (1.5-2.6)	
	ASDAS, median (IQR)			2.2 (1.6-2.8)
	Disease activity at 12 months follow-up			
	Number of patients (n)*	227	111	71
	DAS28-CRP, median (IQR)	2.2 (1.6-3.1)	1.9 (1.5-2.7)	
	ASDAS, median (IQR)			1.8 (1.2-2.6)
	Δ disease activity, mean (sd) (p-value)**	0.01 (1.00) (p=0.89)	-0.11 (0.96) (p=0.27)	-0.10 (0.74) (p=0.40)

Disease activity measurements at baseline and 12 months follow-up and the difference for patients with RA, PsA and axSpA in cohort 1 and cohort 2.
***Number of patients with an available disease activity measurement at that timepoint per diagnosis for both cohorts.**
**** Mean change in disease activity between baseline and 12 month follow-up per diagnosis for both cohorts.**
Abbreviations: RA; Rheumatoid arthritis, PsA; Psoriatic arthritis, axSpA; axial Spondyloarthritis, DAS28-CRP; Disease Activity Score, including 28 joint count and C-reactive protein, ASDAS; Axial Spondyloarthritis Disease

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FIGURE LEGENDS

FIGURE 1 – LEGEND:

Overview of the different cohorts that were analysed in this study. Cohort 1 and cohort 2 were used to analyse patients who transitioned. In addition, adalimumab naïve starters of BO, BS1 and BS2 were analysed, including patients who did not undergo a transition previous to cohort entry.

FIGURE 2 – LEGEND:

Kaplan-Meier curves showing the drug survival rates of the two biosimilars. Transitioning from BO to BS1 (0.8ml/citrate) (cohort 1) and from BS1 to BS2 (0.4ml/no citrate) (cohort 2) (A). Divided into discontinuation due to intolerability (B) and inefficacy (C). The numbers between brackets are the numbers who discontinued the drug in that time period.

Abbreviations: CI Confidence Interval.

FIGURE 3 – LEGEND:

Figure 3. Kaplan-Meier curve showing drug survival rates of adalimumab naïve patients starting either the BO (0.4ml/no citrate), BS1 (0.8ml/citrate) or BS2 (0.4ml/no citrate). The numbers between brackets are the numbers who discontinued the drug in that time period.

Abbreviations: CI Confidence Interval.