Therapeutic drug monitoring (TDM) as a tool in the switch from infliximab innovator to biosimilar in rheumatic patients

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BRIEF REPORT

Therapeutic drug monitoring (TDM) as a tool in the switch from infliximab innovator to biosimilar in rheumatic patients: results of a 12-month observational prospective cohort study

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Abstract The objective of this study is to apply therapeutic drug monitoring (TDM) as an objective tool to monitor the switch from infliximab innovator (INX) to infliximab biosimilar (INB) in our diverse rheumatic cohort in daily clinical practice. All rheumatic patients on INX treatment (Remicade®) and ≥18 years were switched to INB (Inflectra®) as part of routine care, but in a controlled setting. Patients were monitored by taking blood samples just before the first infusion of INB (T1), and after the second (T2), fourth (T3), and seventh (T4) infusion of INB. T4 reflects the patients' status after ~12 months. Infliximab trough levels, antibodies-to-infliximab (ATI), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and validated disease activity scores (if possible) were measured. Our population consisted of 27 patients with seven different rheumatic diseases who had received INX for 143 (58–161) months (median (IQR)). Half of the patients (52%) received concomitant immunosuppressives. We found widely varying infliximab levels, with only 56% within the proposed therapeutic range of 1–5 μg/mL. One patient had very high ATI levels (>880 au/mL), and two had low ATI levels (≤30 au/mL). After switching to INB, seven patients (26%) discontinued the therapy, partially due to subjective reasons. No difference in infliximab levels, CRP levels, and disease activity scores was found between the four time points ($p \geq 0.2460$). In conclusion, no pharmacokinetic or clinical differences were found between INX and INB in our diverse rheumatic cohort. TDM is a helpful tool to monitor patients switching from INX to INB.

Keywords Biosimilars · Infliximab · Rheumatology · Switch study · Therapeutic drug monitoring

Abbreviations

ATI	Antibodies to infliximab
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
IFX	Infliximab
INX	Infliximab innovator
INB	Infliximab biosimilar
IQR	Interquartile range
TDM	Therapeutic drug monitoring
TNFα	Tumor necrosis factor alpha

Introduction

Infliximab (IFX), a therapeutic antibody against tumor necrosis factor alpha (TNFα), has been successfully used to treat patients suffering from inflammatory disorders for many years. It is very effective in those who did not respond well to conventional immunosuppressive medication. Although the majority of patients does well on IFX therapy, non-response or loss of response is common [1]. This can be due

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to different reasons, e.g., the formation of antibodies-to-infliximab (ATI), inadequate dosing, or pharmacodynamic problems. Moreover, IFX therapy is expensive and thus a burden on healthcare costs.

In February 2015, the patent of IFX innovator (INX; Remicade®) expired, and much cheaper IFX biosimilars (INB; CTP-13, brand names Inflectra® and Remsima®) entered the market. Registration studies in rheumatic populations showed comparable pharmacokinetics, efficacy, safety, and immunogenicity for INX and INB, both on short- and long-term [2–7]. However, data from daily, more diverse clinical practice is still scarce.

Therapeutic drug monitoring (TDM) is widely advocated in literature to optimize IFX therapy and can serve as an objective tool to monitor patients who are switched from INX to INB [8]. In many hospitals, including ours, this is not yet routine practice though. In this study, we used TDM of IFX to monitor the switch of INX to INB in our diverse rheumatic cohort to register their clinical performance.

Materials and methods

Patients and study design

All patients from the Department of Rheumatology of Máxima Medical Center on Remicade® treatment and ≥18 years were included. The switch to biosimilar Inflectra® was introduced as part of routine care. All patients agreed to this change in treatment after being informed by their rheumatologist. The switch was done in a controlled setting: blood samples were taken just before the first infusion (just before switch; T1), and after the second (just after switch; T2), fourth (~6 months after switch; T3), and seventh (~12 months after switch; T4) infusion of Inflectra®. IFX trough levels, ATI, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and validated disease activity scores (if possible) were measured at these time points.

Infliximab and ATI measurements

IFX levels were measured using an Infliximab ELISA kit (apDia, Turnhout, Belgium), which was implemented on an automated ELISA processor in our lab [9]. When a patient's IFX concentration was <0.5 μg/mL, ATI were determined by the in-house ELISA of Sanquin Diagnostics (Amsterdam, the Netherlands) [10].

Disease activity scores

For rheumatoid arthritis patients, DAS28 scores were calculated using the ESR value, the visual analogue scale, and the swollenness/tenderness of 28 joints. For ankylosing spondylitis patients, ASDAS scores were calculated using the amount of back pain, duration of morning stiffness, peripheral pain/swelling, the patient's global health, and CRP value.

Statistical analysis

Infliximab, CRP, ESR levels, and disease activity scores were compared between the different time points using non-parametric Friedman analysis, the Wilcoxon signed rank test, and the Wilcoxon Mann-Whitney test.

Results

Patients

Our cohort of rheumatic patients receiving infliximab innovator (INX) consisted of 27 patients. All were switched to the biosimilar (INB) as part of routine care. Our population suffered from different rheumatic diseases and had been using INX for many years. Half of the patients received immunosuppressives (see Table 1).

Status on Remicade therapy

The first measurement (T1) was immediately before switching to INB and reflected the patients' status at INX therapy. IFX levels ranged from very low to very high (see Fig. 1, black columns). Three patients had IFX levels >12 μg/mL (upper

Table 1 Demographics of our rheumatic cohort. Data are represented as "number (percentage)" or "median (interquartile range)"

Sex [*n* (%)]	
Male	10 (37%)
Female	17 (63%)
Age (years)	60 (48–68)
Indication [*n* (%)]	
Rheumatoid arthritis (RA)	14 (52%)
Psoriatic arthritis (PsA)	5 (19%)
Ankylosing spondylitis (AS)	4 (15%)
Spondylo arthritis (SpA)	1 (3.7%)
Psoriasis (PsO)	1 (3.7%)
Polyarthritis with ulcerative colitis	1 (3.7%)
Periferal arthritis with ulcerative colitis	1 (3.7%)
IFX dose (mg)	300 (300–400)
Interval (weeks)	7 (6–8)
Immunosuppressive comedication	
Methotrexate	13 (48%)
Azathioprine	1 (3.7%)
Duration IFX therapy (months)	143 (58–161)

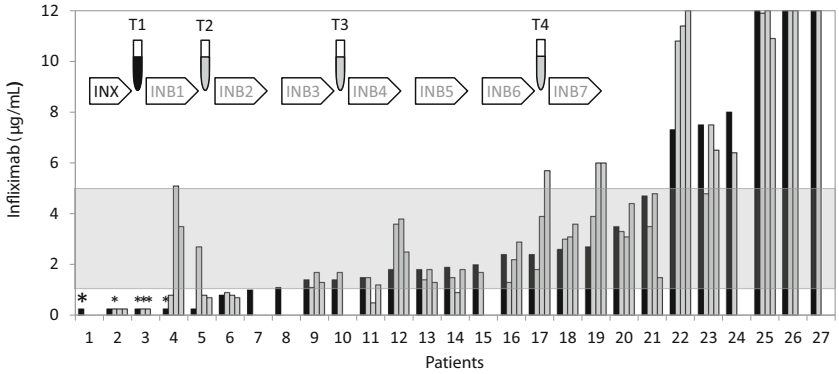

Fig. 1 Infliximab levels of our rheumatic cohort on infliximab innovator (INX, T1, *black*) and after switching to infliximab biosimilar (INB, T2-T4, *gray*). The proposed therapeutic range (1–5 µg/mL) is depicted with the *gray rectangle*. Antibodies-to-infliximab (ATI) are depicted with *stars above the columns*; a *big star* indicates high ATI levels; *small stars* indicate low ATI levels

limit of the assay). Five patients had IFX concentrations <0.5 µg/mL, of which one patient had very high ATI (>880 au/mL), two had low ATI levels (≤30 au/mL), and two had no detectable ATI. Infliximab therapy was immediately discontinued for the patient with very high ATI. Therapy was continued for the two patients with low ATI levels, since it was shown that these can be transient and thus not necessarily have negative influence on the therapy [11, 12].

Disease activity was monitored by measuring CRP and ESR and calculation of disease activity scores. CRP or ESR levels were elevated for nine patients (six patients had both elevated). A slight negative correlation of CRP with IFX levels could be observed, but this was not the case for ESR and IFX levels. DAS28 scores were calculated for 14 patients and ASDAS scores for five patients. Median DAS28 and ASDAS values were 2.6 and 1.8, respectively. No correlation between disease activity scores and IFX levels could be observed, but there was association between disease activity scores and CRP and ESR levels.

Switching to IFX biosimilar: comparison of different time points

After switching to INB, patients were monitored three times during the first year. The therapy was discontinued by seven patients (26%), which happened mostly during the first 6 months after switching. Characteristics of these patients can be found in Table 2. Only one had undetectable levels of IFX, while three had IFX levels above the therapeutic range. Three patients used immunosuppressive co-medication. Interestingly, one of these patients developed high ATI levels. Two patients experienced high disease activity after switching to INB, which indicates lower response to INB than to INX or subjective increase in disease activity. For one of these patients, this was objectified (DAS28 increased from 2.3 (T1) to 4.5 (T2) to 6.3 at (T3)), but for the other patient, there was no DAS28 score measured before discontinuation. However, this patient had already reported higher disease activity on INX treatment. One patient discontinued INB due to suspected vasculitis. This could be switch related; however, this patient had already high drug levels on INX therapy. In one case, hyperventilation occurred during the first infusion of INB. This could be related to the switch but could also a subjective response. In three cases, discontinuation was not switch-related (2× different disease, 1× high ATI to INX).

Infliximab levels before switching (T1) were no predictor of subsequent failure of switching. The median INX level of patients who continued INB therapy (2.0 µg/mL, IQR 1.3–2.9) was not different from patients who discontinued INB therapy (1.4 µg/mL, IQR 1.1–10) (p = 0.1819). ATI levels were also no predictor of switch failure, both patients with low ATI levels at T1 successfully continued biosimilar therapy.

Table 2 Characterization of the patients who discontinued biosimilar therapy

Disease	Co-medication	Infliximab level (µg/mL)	ATI level	Drop-out switch related	Reason drop-out
PsA	None	1.1	n.a.	Possibly related	Hyperventilation
PsA	None	1.7	n.a.	Not related	Different disease
PsA	Methotrexate	>12	n.a.	Possibly related	Suspected vasculitis
RA	Methotrexate	1.0	n.a.	Not related	Different disease
RA	None	6.4	n.a.	Probably related	Higher disease activity (DAS28 2.3 → 6.3)
PsO	Methotrexate	<0.5	>880	Not related	High ATI level
SpA	None	>12	n.a.	Not related	Higher disease activity, but not in remission with Remicade either

IFX levels were very constant for some patients, while they varied between the four time points for others (see Fig. 1). Median IFX levels were not statistically significantly different at the four time points (p = 0.3487, see Fig. 2). One patient with low ATI at T1 had also continuously low ATI levels after switching to INB. The other patient with low ATI at T1 had a prolonged dosing interval at T1; after switching to INB, drug levels increased to >0.5 μg/mL (see patient 4 in Fig. 1). None of the patients developed ATI after switching to INB.

CRP and disease activity scores were not significantly different at the four time points (DAS28: p = 0.4779; ASDAS: p = 0.3916; CRP: p = 0.2460, see Fig. 2). It has to be noted that there were very few data points for the ASDAS scores though. ESR levels were significantly higher at T3 than at T1 (p = 0.0056) and T2 (p = 0.0077), although median ESR levels did not show much variation (see Fig. 2). Disease activity scores, CRP and ESR, did not correlate with IFX levels. However, both CRP and ESR were associated with disease activity scores: patients with elevated CRP or ESR had higher disease activity scores than patients with normal CRP or ESR ($p \leq 0.0173$, except for ESR vs ASDAS p = 0.0593).

Discussion

In this study, TDM was used as a tool to monitor patients who were switched from infliximab innovator to biosimilar. Despite (empiric) optimization of infliximab therapy by our rheumatologists, we found a broad range of IFX concentrations, ranging from very high to very low. In literature, a therapeutic range between ~1–5 μg/mL has been suggested [13]. Only 56% (15 patients) in our cohort had IFX levels within this range. Also, one

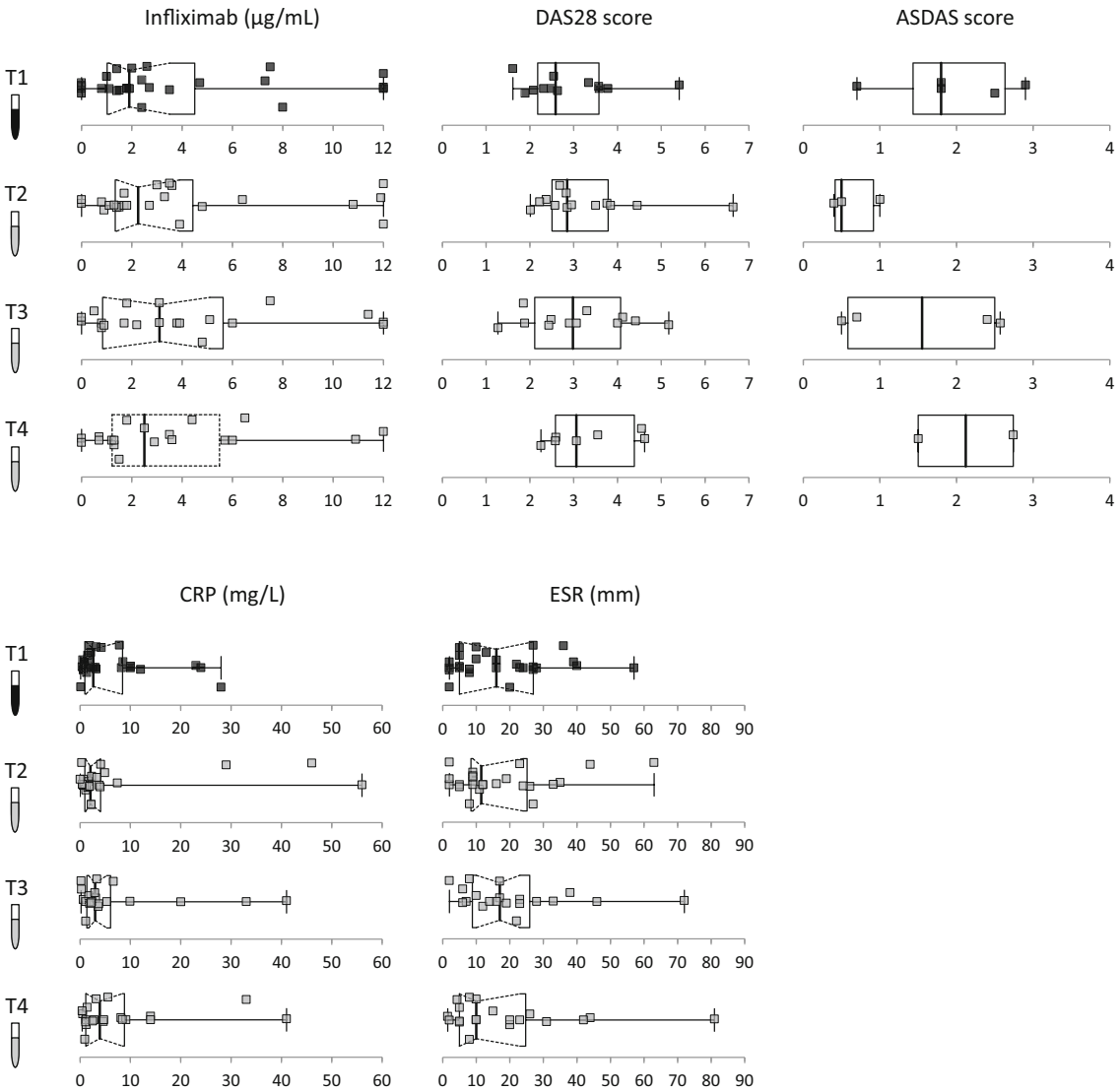

Fig. 2 Infliximab concentrations, DAS28 scores, ASDAS scores, CRP, and ESR values on IFX innovator (T1, *black*) and after switching to IFX biosimilar (T2-T4, *gray*). *Boxplots* show the median values, interquartile range, and total range

patient with very high ATI and two patients with low ATI were identified. This shows that TDM can aid to further optimize infliximab therapy, also in patients who seem clinically stable and have received IFX for a long time. When patients have higher disease activity, TDM aids to optimize therapy efficiently. Patients with low IFX levels (<1 μg/mL) and no or low ATI levels could receive dose escalation to achieve therapeutic levels, while patients with high ATI levels should be switched to a different anti-TNFα drug. Patients with high IFX levels (>5 μg/mL) could be switched to a different drug. If patients feel well while they have high IFX levels, they could receive dose reduction, since this reduces costs while clinical efficacy is maintained [14–16]. Complete discontinuation of anti-TNFα therapy while maintaining remission is possible for some but not for all patients [17–19].

Upon switching to INB, no significant differences in drug levels and disease activity scores were observed. This is in accordance with recent literature. However, one-quarter of our patients discontinued INB therapy during the first year after switching. This happened mostly during the first 6 months after switching. These numbers are similar to those reported in literature [18–20]. All switch studies we found reported that discontinuation of biosimilar therapy was partly due to subjective reasons, which could be due to the "nocebo effect" (disease worsening due to negative expectations). In our study, this was probably the case for one or two patients, which is not as much as reported in other studies. The nocebo effect could be reduced by routinely performing TDM and measurement of disease activity scores can serve as an objective tool to diminish this effect.

A noticeable difference between our switch study and those reported in literature [19–23] is that we had very few patients with ATI. This could be due to the fact that our population was receiving INX for the longest time, leading to a selection bias in favor of pharmacologically stable patients.

In conclusion, we found that TDM is a helpful tool to monitor patients switching from innovator infliximab to biosimilars, and we believe thus that TDM should always guide dosing of IFX therapy. No differences in drug levels and disease activity scores were observed between INX and INB in our small but diverse cohort of patients with rheumatic diseases. Switching to biosimilar and performing TDM can make IFX therapy much more cost-effective.

Compliance with ethical standards

Disclosures None.

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