Switching from infliximab innovator to biosimilar in patients with inflammatory bowel disease

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Switching from infliximab innovator to biosimilar in patients with inflammatory bowel disease: a 12-month multicentre observational prospective cohort study

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Summary

Background: Infliximab biosimilars have become available for treatment of inflammatory bowel disease (IBD). However, data showing long-term safety and effectiveness of biosimilars in IBD patients are limited.

Aim: To study prospectively the switch from infliximab innovator to biosimilar in an IBD cohort with 12 months follow-up to evaluate safety and effectiveness.

Methods: Adult IBD patients from two hospitals treated with infliximab innovator (Remicade; Janssen Biotech, Horsham, Pennsylvania, USA) were switched to infliximab biosimilar (Inflectra; Hospira, Lake Forest, Illinois, USA) as part of routine care, but in a controlled setting. Blood samples were taken just before the first, second, fourth and seventh infusion of biosimilar. Infliximab trough levels, antibodies-to-infliximab (ATI), CRP and ESR were measured and disease activity scores were calculated.

Results: Our cohort consisted of 133 IBD patients (64% CD, 36% UC). Before switching we found widely varying infliximab levels (median 3.5 μg/mL). ATI were detected in eight patients (6%). Most patients were in remission or had mild disease (CD: 82% UC: 90%). After switching to biosimilar, 35 patients (26%) discontinued therapy within 12 months, mostly due to subjective higher disease activity (9%) and adverse events (AE, 9.8%). AE included general malaise/fatigue (n = 7), arthralgia (n = 2), skin problems (n = 2) and infusion reactions (n = 2). No differences in IFX levels, CRP, and disease activity scores were found between the four time points (P ≥ .0917).

Conclusions: We found no differences in drug levels and disease activity between infliximab innovator and biosimilar in our IBD cohort, indicating that biosimilars are safe and effective. The high proportions of discontinuers were mostly due to elective withdrawal or subjective disease worsening.
INTRODUCTION

Inflammatory bowel disease (IBD) is characterised by chronic inflammation of the gastrointestinal tract, with two main subtypes: Crohn’s disease (CD) and ulcerative colitis (UC). IBD patients often experience disease flares and significantly decreased quality of life.\(^1,2\) The introduction of biological therapies two decades ago revolutionised the treatment of moderate to severe IBD.\(^3\) Two years ago, a new landmark in IBD treatment was set with the introduction of the first biosimilars. Biosimilars are highly similar to the innovator biologics, but much cheaper.

In 2015, the patent of infliximab (IFX), the first anti-tumour necrosis factor (TNF\(_\alpha\)) biological, expired and two infliximab biosimilars entered the market: Inflectra and Remsima (both CTP-13). Registration studies in patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS) showed that IFX innovator (Remicade) and IFX biosimilar (CTP-13) had comparable pharmacokinetics, efficacy, safety and immunogenicity\(^4-7\) and that it was safe to switch from IFX innovator to biosimilar.\(^8,9\) Treatment approval was extrapolated to include all indications approved for treatment with the innovator, which also includes IBD. However, data on the use of biosimilars in IBD patients are still scarce and many healthcare professionals and patients are yet to be convinced. Several concerns have been raised\(^10\): the different dosing (5 mg/kg in IBD and 3 mg/kg in rheumatic disorders), the use of different concomitant immunosuppressive medication (which is more common and different in rheumatic diseases than in IBD), and the potentially different mechanism of anti-TNF\(_\alpha\) biologics in rheumatic conditions and IBD.\(^11-13\)

There are currently only a few studies available that show data of IBD patients who were treated with a biosimilar. Moreover, these studies often have a limited amount of patients, limited information about drug levels and anti-drug-antibodies, and often only show short-term data. Therefore, we prospectively studied the switch from infliximab innovator to biosimilar in a large cohort of IBD patients with a 1 year follow-up to evaluate long-term safety and effectiveness.

MATERIALS AND METHODS

2.1 | Patients and study design

All adult IBD patients treated with infliximab in Máxima Medical Center (Veldhoven, the Netherlands) and Elkerliek hospital (Helmond, the Netherlands) were included. Patients were switched from innovator Remicade to biosimilar Inflectra as part of routine care. In both hospitals the same switching protocol was used. All patients received a letter from their gastroenterologists which described that the infliximab treatment changed from Remicade to Inflectra, a different brand, and that studies showed that these drugs are highly similar. Essentially, patients were switched to biosimilar unless there were severe doubts. In these rare cases, the physician gave the patient a thorough explanation of the biosimilar concept, which could persuade them to switch. All patients agreed to this change in treatment.

The switch was performed in a controlled setting (Figure 1): blood samples were taken just before the first infusion (T0), and after the second (T1), fourth (T2) and seventh (T3) infusion of Inflectra. These time points reflect the patient’s status just before and after the switch and after approximately six and twelve months. The following parameters were measured in blood: IFX trough levels, antibodies to infliximab (ATI, only if IFX < 0.5 \(\mu\)g/mL), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Concomitantly, disease activity scores were determined.

Since the switch was done as part of routine care, actions could be taken as a consequence of the measured IFX levels if necessary. For example, patients with high ATI levels were switched to a different therapy, and patients who had undetectable IFX levels and deep sustained remission (stop criterion defined by the Dutch gastroenterologist’s society\(^14\)) discontinued IFX therapy.

2.2 | Infliximab and ATI measurements

IFX levels were measured in-house using an Infliximab ELISA kit (apDia, Turnhout, Belgium) on an automated ELISA processing
2.3 Disease activity scores

Validated disease activity scores were calculated to determine the disease activity. For CD patients the Crohn’s disease activity index (CDAI) was used.\textsuperscript{18} The Truelove-Witts disease activity index (TWDAI) was used for UC patients.\textsuperscript{19}

2.4 Statistical analysis

First, data were analysed with the Shapiro-Wilk test to determine if it was normally distributed. This was not the case, so non-parametric statistical analysis was used. Comparison of infliximab, CRP and ESR levels between the four time points was done using Friedman analysis. If Friedman analysis returned a statistically significant difference, the Wilcoxon signed rank test was subsequently used to analyse differences between all time points in pairs. For comparison of the disease activity scores, the score at T0 was compared to the average score after switching to biosimilar therapy. This was done using the Wilcoxon Mann-Whitney test. $P < .05$ were considered statistically significant.

3 RESULTS

3.1 Patients

Our cohort consisted of 133 IBD patients, of which approximately two-third had CD and one-third had UC. They had been receiving infliximab innovator therapy for a median of 52 months before switching to the biosimilar. Half of the patients received concomitant immunosuppressive therapy (48%), of which thiopurines were most common. More details can be found in Table 1.

3.2 Status on Remicade therapy

Before switching to biosimilar therapy, the patients’ status on innovator therapy was determined (T0). We found widely varying IFX levels, ranging from undetectably low to very high (Figure 2). The median IFX level of the whole cohort was 3.5 $\mu$g/mL (3.7 $\mu$g/mL for CD patients and 2.9 $\mu$g/mL for UC patients). The proposed therapeutic range for IBD patients is 3.7 $\mu$g/mL.\textsuperscript{20-23} If we apply this range to our cohort, 40% of all CD patients had levels within the therapeutic range, whereas 27% of the UC patients reached adequate levels. In both populations, 21% had high IFX levels ($>7$ $\mu$g/mL). Low IFX levels ($<3$ $\mu$g/mL) were found in 39% of the CD patients, 9% had even undetectably low levels ($<0.5$ $\mu$g/mL). For UC patients, we found that 52% had low IFX levels, 21% had undetectably low levels.

Antibodies-to-infliximab (ATI) were measured in eighteen patients. Ten patients (four CD, six UC patients) had no detectable ATI, while eight patients (four CD, four UC patients) had detectable ATI. Two of these eight patients (one CD, one UC patient) had very high ATI levels ($>880$ au). Infliximab therapy was discontinued in patients with very high ATI. Therapy was continued for the patients with low ATI levels, since it was shown that ATI can be transient and thus not necessarily have negative influence on the therapy.\textsuperscript{24,25}

CRP levels were elevated for 25 patients (19%). Disease activity scores at T0 were available for 65 CD patients (76%) and 29 UC patients (60%). The great majority of patients was in remission or had mild disease (82% of CD patients and 90% of UC patients). The rest, a minority, had moderate disease (see Figure 3, T0). No patients had severe disease activity. No statistically significant correlation could be found between drug levels and disease activity scores.

3.3 Switching to IFX biosimilar: comparison of different time points

To determine effectiveness and safety of infliximab biosimilar, we firstly analysed if there were differences in IFX levels, CRP and disease activity scores between IFX innovator and biosimilar. Dose and frequency were never changed between T0 and T1. Also during the rest of the study, patients stayed on the same dose and frequency during the study, apart from a few exceptions. Median IFX levels varied from 3.5 to 4.2 $\mu$g/mL, median CRP levels varied from 1.4 to 2.0 mg/L. Both were not statistically significantly different between the four time points (IFX: $P = .4106$ and CRP: $P = .0981$, Figure 4). Disease activity scores before and after switching were also not statistically significantly different (CDAI: $P = .5657$ and TWDAI: $P = .7609$). This is supported by Figure 3, which shows that the amount of patients that had no/low disease activity and patients

### TABLE 1 Demographics of our IBD cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>52 (60%)</td>
<td>22 (46%)</td>
</tr>
<tr>
<td>Male</td>
<td>34 (40%)</td>
<td>25 (52%)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>41 (29-51)</td>
<td>49 (42-60)</td>
</tr>
<tr>
<td>Infliximab dose (mg)</td>
<td>400 (300-400)</td>
<td>400 (300-400)</td>
</tr>
<tr>
<td>Interval (wk)</td>
<td>8 (6-8)</td>
<td>8 (8-8)</td>
</tr>
<tr>
<td>Duration infliximab therapy (mo)</td>
<td>53 (33-74)</td>
<td>50 (35-65)</td>
</tr>
<tr>
<td>Immunosuppressive comedication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>46 (54%)</td>
<td>22 (47%)</td>
</tr>
<tr>
<td>thiopurines</td>
<td>33 (39%)</td>
<td>22 (47%)</td>
</tr>
<tr>
<td>corticosteroids</td>
<td>4 (5%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>thiopurine + corticosteroids</td>
<td>1 (1%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>methotrexate</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Data are represented as [n (%)] or [median (IQR)]. IQR = interquartile range.
that had moderate disease activity were comparable between the four time points.

After switching to biosimilar therapy, patients were monitored at three time points during the first year. The therapy was discontinued by 35 patients (26%) in total, 23 CD patients (26%) and 13 UC patients (27%). Approximately half of those patients used concomitant immunosuppressive medication, which is similar to the whole population. Most patients discontinued due to higher disease activity or adverse events (Table 2). The majority discontinued biosimilar therapy due to adverse events (9.6% of the cohort). The most common adverse event was general malaise and/or fatigue (n = 7). Other adverse events were arthralgia (n = 2), skin problems (n = 2), infusion reaction to the first biosimilar infusion (n = 2), anaphylactic response to biosimilar infusion (n = 1) and suspected delayed allergic reaction (n = 1). Furthermore, 12 patients (9% of the cohort) experienced higher disease activity. In the majority of cases, complaints about higher disease activity were not objectified with higher disease activity scores or increased CRP (n = 8). Increased disease activity was only objectified in two patients. In two cases, patients also had high disease activity on infliximab innovator therapy. Last, five patients (3.8% of the cohort) discontinued biosimilar therapy because they were in remission, one was switched to vedolizumab and two were switched back to infliximab innovator therapy.

Different follow-up strategies were applied for the patients who stopped biosimilar therapy. The majority of discontinuers (63%) were switched back to infliximab innovator therapy. Four patients (11% of discontinuers) switched to vedolizumab (Entyvio; Takeda Pharmaceuticals, Osaka, Japan), an α4β7 integrin antibody. Nine patients (26% of discontinuers) discontinued biologics therapy completely because they were in remission (n = 5), because they already had complaints while receiving infliximab innovator (n = 2), because they had high ATI levels (n = 1) or because they were expecting labour (n = 1).

At T0, eight patients had detectable ATI. After switching, only two of these patients stayed on biosimilar therapy during the first twelve months (2% of continuers); one continued to have detectable ATI, while ATI disappeared for the other. The other six patients with detectable ATI at T0 discontinued biosimilar therapy during the first 12 months after switching to biosimilar (17% of discontinuers). Three of these patients discontinued biosimilar because they were in remission, one was switched to vedolizumab and two were switched back to infliximab innovator therapy. The relative risk (RR) of discontinuing biosimilar therapy for patients with detectable ATI before switching was 3.2 (95% CI 1.9-5.4) compared to patients with no ATI before switching. This indicates that patients with autoimmune response to IFX have a statistically significantly higher risk on therapy discontinuation.

Three patients developed ATI after switching to biosimilar therapy. One of these patients had a low ATI level after the first infusion of biosimilar, but they disappeared after the second infusion. The second patient experienced an allergic reaction to the first biosimilar

![FIGURE 2](image1.png) Trough levels of infliximab (IFX) and antibodies-to-infliximab (ATI) of our IBD cohort before switching to IFX biosimilar (T0). Data are split into Crohn’s disease patients (left) and ulcerative colitis patients (right). The proposed therapeutic range of 3–7 µg/mL is indicated with the light grey rectangle. The percentage of patients with IFX levels within, below or above the therapeutic range are indicated. ATI levels are indicated with yellow, orange and red bars.

![FIGURE 3](image2.png) Disease activity scores for Crohn’s disease patients (left) and ulcerative colitis patients (right) before switching to infliximab biosimilar (T0) and at the different time points after switching to biosimilar (T1-T3).
infusion, after which we found a high ATI level. The third patient had continuously undetectable IFX levels, but only detectable ATI during the last measurement, indicating that the immune response against IFX was recently triggered.

4 | DISCUSSION

The use of infliximab biosimilars could greatly reduce treatment costs of IBD patients. Infliximab biosimilars are highly similar to infliximab innovator but less expensive (estimated up to 40%) due to competition in the market.\textsuperscript{24} However, data demonstrating its clinical safety and effectiveness in real-life IBD patients are still limited and further studies are needed to support the use of infliximab biosimilar in IBD patients (reviewed in\textsuperscript{26,27}). Therefore, we switched our IBD cohorts receiving IFX innovator to biosimilar as part of routine care, but in a controlled setting, using therapeutic drug monitoring (TDM).

In our study, we first determined the patients’ status at IFX innovator therapy. Despite (empiric) therapy optimisation by the gastroenterologists, a broad range of IFX levels was found. Approximately one-third of the patients had concentrations within the proposed therapeutic range of 3.7 \(\mu\text{g/mL}\).\textsuperscript{20-23} Most patients had IFX levels below this therapeutic range, for UC patients this was even half the population (52%). However, we also found that the majority of our patients was in remission or had low disease activity.

No correlation between IFX levels and disease activity was found. A possible explanation for this is that our cohort did not include patients with high disease activity. Also, TDM was already applied on a part of this cohort 2 years ago,\textsuperscript{28} which ‘dilutes’ the concentration-activity relationship.

Antibodies to infliximab (ATI) were detected in eight patients (6% of the total cohort). This number is somewhat lower than usually reported in literature for IBD patients.\textsuperscript{24,29,30} This could be due to our gastroenterologists’ policy to sometimes perform TDM as part of routine care, especially when a patient has higher disease activity.

![Infliximab (IFX) and C-reactive protein (CRP) concentrations for all patients before switching to biosimilar (T0) and after switching to IFX biosimilar therapy (T1-T3). The box and whisker plots show the median IFX values, interquartile range and total range](image)

**TABLE 2** Characteristics of the patient group who discontinued biosimilar therapy. Percentages are calculated with respect to the whole population (n = 133)

<table>
<thead>
<tr>
<th>Reason drop-out</th>
<th>n (%)</th>
<th>Probably switch-related</th>
<th>Possibly switch-related</th>
<th>Not switch-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher disease activity</td>
<td>12 (9.0%)</td>
<td>2</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Adverse events</td>
<td>13 (9.8%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>- infusion reaction</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>- delayed allergic response</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>- general malaise/tired</td>
<td>—</td>
<td>—</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>- arthralgia</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>- skin problems</td>
<td>—</td>
<td>—</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Antibodies to infliximab</td>
<td>2 (1.5%)</td>
<td>—</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>In remission</td>
<td>5 (3.8%)</td>
<td>—</td>
<td>—</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>3 (2.3%)</td>
<td>—</td>
<td>—</td>
<td>3</td>
</tr>
</tbody>
</table>
This could make this population slightly biased towards lower disease activity or lower number of patients with detectable ATI. However, some studies do not report IFX and/or ATI levels at all, which makes comparison difficult.

Six of the eight patients who had detectable ATI at T0 discontinued biosimilar therapy within the first 12 months. We found that patients with detectable ATI before switching had a relative risk of 3.2 for discontinuation of biosimilar therapy compared to patients with no ATI. This indicates that patients with autoimmune response to IFX have a statistically significantly higher risk on therapy failure. It was shown that antibodies to IFX innovator are highly similar to antibodies to the biosimilar, so these patients would probably also have experienced therapy failure if they would have stayed on innovator therapy.

No statistically significant differences in drug levels, disease activity scores or inflammation marker CRP were found between IFX innovator and biosimilar. This indicates that safety and effectiveness of the biosimilar are good and that switching from IFX innovator to biosimilar is feasible. However, 26% of patients in our cohort discontinued biosimilar therapy, which was mostly due to adverse events (9.8% of the cohort) or higher disease activity (9.0% of the cohort). Higher disease activity was objectified in only two patients (1.5% of the whole cohort). The high amount of patients discontinuing biosimilar therapy with non-objectified lack of effectiveness or general malaise could be explained by the low threshold that was applied to switch back to innovator therapy for the first biosimilar switch in our hospital. Patients were easily put back on innovator treatment if they had complaints that could possibly be switch-related due to the lack of experience with biosimilars in clinical practice. Objective measurement of disease activity using questionnaires is not yet part of routine care in our hospitals and was thus unfortunately not always applied before making the decision to discontinue biosimilar therapy. Besides, the novelty of biosimilars could induce the nocebo effect in patients (disease worsening due to negative expectations), so disease worsening is not necessarily due to a lack of effectiveness. This is a drawback of nondouble-blinded studies and we believe this is an important cause of finding such high numbers of biosimilar discontinuation.

Another important reason for discontinuation is the occurrence of adverse events (9% of the population). Increased fatigue, skin problems and arthralgia were most commonly mentioned by patients. These could possibly be switch-related, but also be induced by the nocebo effect. There was one patient (0.8% of the cohort) who experienced an infusion reaction, which is similar to other studies. Infusion reactions reported in literature were 6.9% in the PROSIT-BIO study, 2% in the NOR-SWITCH study and none in the study by Arguelles-Arias et al. and Smits et al.

Five patients (3.8%) discontinued biosimilar therapy because they experienced deep sustained remission and met the STOP criteria. Several studies showed that most patients who discontinue anti-TNF therapy in deep sustained remission continue to be in remission, especially when patients have undetectable IFX levels before discontinuation. Three of our five patients who discontinued IFX maintained remission, while the other two experienced mild disease worsening. None of the patients restarted IFX therapy; four are taking different medication and one is medication-free.

The number of dropouts in our study is higher than usually reported in literature. In the NOR-SWITCH study, the only randomised double-blind trial available, 1.2% of patients discontinued biosimilar therapy due to lack of effectiveness and 3.0% due to adverse events within the first 12 months. However, the double-blind setup of the NOR-SWITCH study excludes possible bias caused by the nocebo effect. In our study both patient and gastroenterologist knew about the switch from innovator Remicade to biosimilar Inflectra. This could explain the higher drop-out rate in our study. Moreover, all patients included in the NOR-SWITCH study were in remission at the start of the study, while only 84% of our patients had no/mild disease activity. Several other switch studies report similar numbers of patients who discontinue biosimilar treatment to the NOR-SWITCH study, though it has to be noted that the duration of all these studies was shorter than twelve months. However, there are also several switch studies which reported similar numbers of patients that discontinued biosimilar therapy as our study. These switch studies were performed in real-life cohorts and reported that a significant amount of patients discontinued due to elective withdrawal or subjective disease worsening.

In conclusion, we found no differences in drug levels and disease activity between infliximab biosimilar and innovator in our IBD cohort, indicating that the biosimilar is safe and effective. A relatively high proportion of patients discontinued biosimilar therapy within the first year, but this is probably due to the nonblinded setup of our study and the fact that a real-life cohort was monitored rather than a well-defined and pre-selected population, which induces the nocebo effect. Switching to biosimilar and performing TDM as part of routine care can optimise IFX therapy efficiently and make it more cost-effective.

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AUTHORSHIP

Guarantor of the article: Derijks Luc JJ.

Author contributions: Schmitz, Ellen Maria Hubertina, performed the research, collected and analysed the data, wrote the paper; Boekema, Paul, designed the research study, commented on the paper; Straathof, Jan-Willem, designed the research study, commented on the paper; van Renswouw, Dein, collected the data, commented on the paper; Brunsveld, Luc, designed the research study, commented on the paper; Schamnhorst, Volker, designed the research study, commented on the paper; van de Poll, Matthijs, collected the data, commented on the paper; Broenen, Maarten, designed the research study, wrote the paper; Derijks, Luc JJ, collected the data, designed...
the research study, wrote the paper. All authors approved the final version of the manuscript.

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