Survival and safety of infliximab bio-original and infliximab biosimilar (CT-P13) in usual rheumatology care

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Abstract

Objective

Reports to-date indicate similarity between infliximab biosimilar (IB) and infliximab bio-original (IO) in clinical efficacy and safety. This study examines the survival of IB and IO using routinely collected data over a 2-year period.

Methods

Routinely collected clinical data inputted directly in an electronic database at a large rheumatology centre were analysed. Adult patients taking IO or IB for any rheumatological diagnosis were included. Kaplan-Meier survival analyses were used to examine IB and IO survival, with a sub-group analysis among those starting infliximab from 2008 onwards.

Results

Out of 395 patients analysed, 53% (n=209) were female; the majority had rheumatoid arthritis (31%) followed by spondyloarthritis (28%). Ninety-nine patients had IB as the first infliximab drug. Patients who started on IB vs. IO as their first infliximab product, had better survival over the first 2 years (log rank=0.001). Discontinuation due to inefficacy was much commoner in IO versus IB users (18 vs. 5%). In patients switching from IO to IB, drug survival was better versus those receiving IB as the first infliximab drug (log rank=0.073).

Conclusion

IB was well-tolerated and comparable to IO, with no additional safety signals identified. The results suggest superior survival of IB over IO over the first 2 years.

Key words
infliximab, biosimilar, CT-P13, safety, side effects

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Introduction

Biological drugs have undoubtedly changed the face of many autoimmune, inflammatory conditions and have been heavily studied in the past one and half decades, especially in the context of rheumatoid arthritis (RA). However, their high costs represent an important barrier to their use, resulting in inequity in their uptake across countries. This has prompted the development of biosimilar drugs with the intention of providing similar clinical benefits to bio-original drugs, but at lower costs.

The infliximab biosimilar (IB) was the first to make it into the market in Western countries. Its efficacy and non-inferiority as well as similar safety profile when switching from infliximab originator (IO) have already been supported using clinical trial data and observational, real-life data (1-4). Beyond inflammatory arthritis, similar findings are reported in other diseases such as inflammatory bowel disease (5, 6).

We have previously reported using data from our centre on the clinical effectiveness of IB in both patient-reported outcomes (PROs) and disease-activity measures, which was comparable to IO during the first year of switching, with no immediate safety signals (7).

We now report on two-year data from our centre, based on real-life patients with various rheumatic conditions and their unique individual characteristics, comorbidities and disease-related features. The objective of the study was to analyse the survival of IB (CT-P13) and IO over a two-year period, exploring reasons for drug discontinuation in both patients who started on either of the two drugs from the beginning or those who switched from IO to IB.

Patients and methods

Study population

Patients with rheumatic diseases seen in central Finland at Jyväskylä Central Hospital and receiving treatment with IO were studied. Patients seen at this centre have their demographic, clinical and self-reported data collected as part of the normal infra-structure of the outpatient clinic using the electronic monitoring tool GoTreatIT (8).

Clinical and laboratory data

Clinical and laboratory data are recorded at every patient visit as previously described (7). This included PROs, extra-articular manifestations, comorbidities, surgical joint history, medication history including use of glucocorticoids and conventional synthetic and biologic disease-modifying anti-rheumatic drugs (cDMARDs and bDMARDs) including start and end date, reasons for discontinuation and a record of adverse events at all severity levels are recorded.

Study design

A clinical database in one rheumatology center was analysed for IB and IO survival, including a sub group analysis among those who started an infliximab in 2008 or later. Reasons for discontinuation were analysed. The primary study outcome was drug survival. This enabled the study of individual medical and patient-related reasons for drug discontinuation including safety, efficacy and compliance, among others.

Statistical analysis

Descriptive statistics were used to compare baseline characteristics and diagnoses in each treatment group. Kaplan-Meier analyses were used to study drug survival in each of the groups, with a sensitivity analysis undertaken for the subgroup of patients who started IO from 2008 onwards. The log-rank, non-parametric hypothesis test was used to compare the survival distributions across the different treatment groups. Reasons for drug discontinuation were recorded and compared across each group.

Results

Patient demographics

Data from 395 patients were analysed; 53% (n=209) were female. From these, a quarter (n= 99) received IB as the first infliximab drug. Across both IB and IO groups, the majority used concomitant methotrexate. The majority of patients had rheumatoid arthritis (31%), followed by ankylosing spondylitis (AS)/spondyloarthritis (SpA) (28%). Table I shows patient characteristics in the IO and IB groups, as well as the IO sub-

Table I. Infliximab original (IO) or infliximab biosimilar (IB) as the first infliximab product.

Patient characteristics.	IO	IB	Total (IO + IB)	IO subgroup*
Number of patients	296	99	395	190
Gender, n (%) female	153 (52%)	56 (57%)	209 (53%)	89 (47%)
Age, mean (SD)	41.6 (16)	43.4 (13)	42.0 (15)	42.1 (16)
Diagnosis				
RA	105 (36%)	18 (18%)	123 (31%)	51 (27%)
AS/SPA	78 (26%)	31 (31%)	109 (28%)	55 (29%)
PsA	50 (17%)	21 (21%)	71 (18%)	38 (20%)
JIA, adults	35 (12%)	4 (4%)	39 (10%)	22 (12%)
IBD/REA	10 (3%)	6 (6%)	16 (4%)	9 (5%)
Undifferentiated/other	18 (6%)	19 (19%)	37 (9%)	15 (8%)
Concomitant MTX	236 (80%)	82 (82%)	318 (80%)	147 (77%)
First initiation	May 1999	January 2014		January 2008

*IO subgroup only includes a subgroup of patients (extracted from the main IO group) who started IO from 2008 onwards.

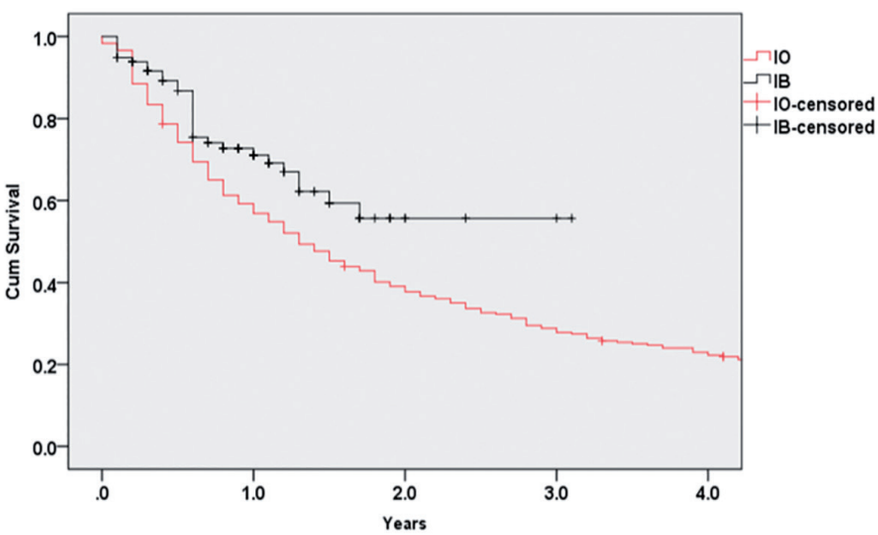

Fig. 1. Survival of infliximab original (IO) or infliximab biosimilar (IB) as the first infliximab product.

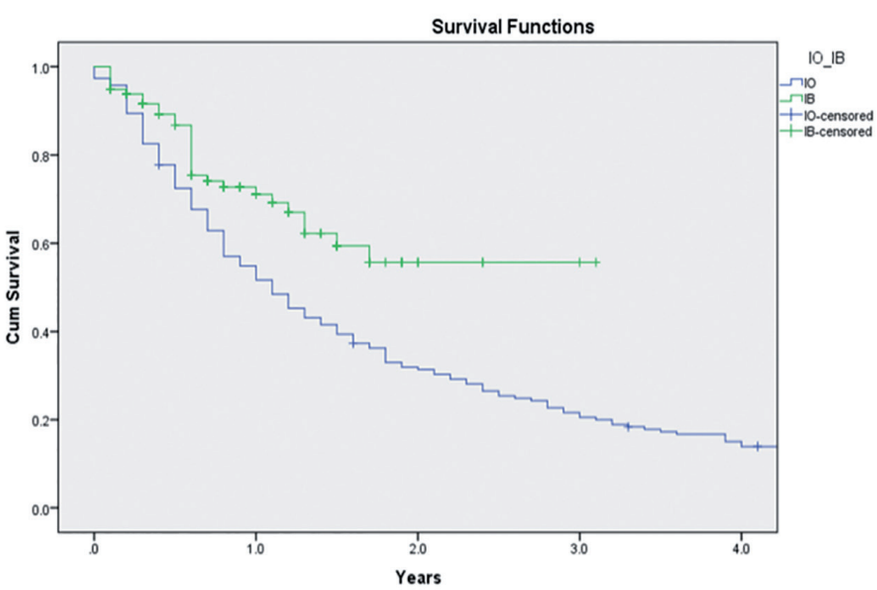

Fig. 2. Sub-group of patients who started an infliximab IO or IB in 2008 or later. Log rank p=0.001.

group of patients receiving IO from 2008 onwards.

First infliximab users: IO or IB

Across all disease groups, patients who started on IB compared to those who started on IO as their first infliximab product had better survival over the first 2 years (Fig. 1). In a sensitivity analysis on patients who commenced infliximab IO from 2008 onwards, results remained the same (Fig. 2).

In the IO and IB groups, 62% and 30% respectively discontinued their medication over the first 2 years; reasons for drug discontinuation are shown in Table II. Inefficacy was a common reason for discontinuation in the IO group, whereas in the IB group the commonest reasons were inefficacy, side effects (Table III) or antibody formation.

IO switchers to IB

From the patients switching from IO to IB, drug survival was better compared to the group who started IB as their first infliximab medication (Fig. 3). Reasons for discontinuation after switching are shown in Tables IV and V.

Discussion

Our study presents real life data on the use and safety of IB in patients with inflammatory joint disease, the majority with RA or AS/SpA. The study demonstrates that in patients starting IB as the first infliximab product, or switching from IO, drug survival and tolerance was generally better compared to drug survival of IO. More than double the number of patients discontinued their medication in the IO group compared to the IB group, with inefficacy being a much commoner reason for discontinuation in the IO group. Other reasons for drug discontinuation included the achievement of disease remission, comorbidity and pregnancy, among other. Several other studies to date are in support of our own data, showing that switching from bio-originals to biosimilars is safe and feasible (9-12). In a recent report on data from fifty-three switching studies (13), efficacy and safety data generally showed no differences between patients who switched treatments *versus* those who did not.

Table II. Reasons for discontinuation of IO and IB for the first 2 years of treatment.

Reasons for discontinuation	IO, n=296	IB, n=99
Inefficacy	53 (18%)	5 (5.0%)
Side effects*	27 (9.1%)	5 (5.0%)
Antibodies$	6 (2.0%)	5 (5.0%)
Comorbidity	5 (1.7%)	1 (1.0%)
Switch^/other	71 (24%)	10 (10%)
Remission	6 (2.0%)	1 (1.0%)
Pregnancy	3 (1.0%)	1 (1.0%)
Not known	12 (4.1%)	2 (2.0%)
Total	183 (62%)	30 (30%)

*See details in Table III.
$ Antibody formation only routinely checked post 2013.
^Switch to biosimilar due to local hospital policy.

Table III. Side effects as the reason for discontinuation of IO and IB, during the first 2 years of treatment.

Side effects in detail	IO, n=296	IB, n=99
Infusion reaction	4 (1.4%)	0
Infection*	10 (3.4%)	3 (3.0%)
Tuberculosis	4 (1.4%)	0
Liver enzyme elevation	2 (0.7%)	1 (1.0%)
Skin reaction	4 (1.4%)	1 (1.0%)
Not known	3 (1.0%)	0
Total	27 (9.1%)	5 (5.0%)

*Excluding tuberculosis.

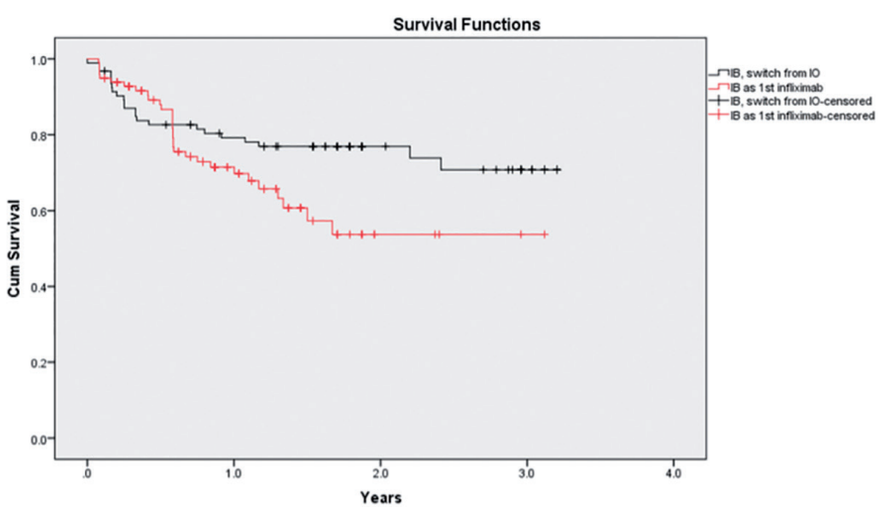

Fig. 3. Survival of IB as the first infliximab (n=99) *vs*. switch from IO (n=93). Log rank, p=0.073.

Although the precise designs in these studies varied, overall no differences were seen pre- and post-switch. Other recent studies have also confirmed comparable clinical measures of safety between non-switched and switched groups, in line with our findings (14, 15).

A study that deserves particular attention is the randomised, non-inferiority, double-blind, phase 4 NOR-SWITCH trial (n=482) (12). This study with 52 weeks of follow-up examined patients across six relevant disease groups, using disease worsening as the common primary outcome and demonstrated that the rate of adverse events was similar between bio-original and biosimilar CT-P13 groups for serious adverse events and overall adverse events, as well as for adverse events leading to discontinuation (12). In the NOR-SWITCH study, patients switching were in stable disease states, making it particularly relevant in current financial climates since it demonstrated that patients on stable treatment with an originator drug could safely be switched to the biosimilar. Reflecting on our data, the remarkably good tolerance to IB as a first infliximab agent or as a switch from IO reinforces the messages from existing cohort and trial studies to date. Evidence suggests no difference in antibody incidence between bio-original infliximab and the biosimilar equivalent (11). Antibody formation in our study was recorded more frequently in the IB group compared to the IO group and represented one of the commonest reasons for drug discontinuation in the IB group. This was not an unexpected observation in our analyses though, since antibodies were not routinely checked in the clinic until after 2013. Therefore, the results cannot be used to make comparative inferences regarding antibody formation between the IO and IB groups. However, in those patients switching from IO to IB, antibodies

Table IV. Reasons for discontinuation of IB over the first 2 years of treatment, after switch from IO.

Reason for discontinuation	IB after switch from IO, n=93
Inefficacy	3 (3.2%)
side effects	5 (5.4%)
Antibodies$	2 (2.1%)
Comorbidity	1 (1.1%)
Switch^/other	6 (6.5%)
Remission	0
Pregnancy	1 (1.1%)
Not known	4 (4.3%)
Total	22 (24%)

$ Antibody formation only routinely checked post 2013.
^Switch to biosimilar due to local hospital policy.

Table V. Side effects as the reason for discontinuation of IB over the first 2 years of treatment, after switch from IO.

Side effects in detail	IB after switch from IO, n=93
Infusion reaction	0
Infection*	1 (1.1%)
Tuberculosis	1 (1.1%)
Liver enzyme elevation	0
Skin reaction	2 (2.1%)
Not known	1 (1.1%)
Total	5 (5.4%)

*Excluding tuberculosis.

were always tested prior to the switch and antibody formation in this group remained low, around 2%. The more frequent testing for antibody formation, as well as the checking of drug trough levels in IB users as part of the current policy of our clinic is an important aspect of patient management, guiding dose changes according to the drug trough levels and the presence/absence of the antibodies. Although speculative, this might in turn explain the better drug survival in the case of IB, observed in our study.

Infection as a reason for drug discontinuation was a commoner phenomenon in the IO group, with one patient suffering tuberculosis (none in the IB group as the first infliximab). After switch from IO, the commonest reason for discontinuation of IB over the first 2 years of treatment were side effects, with skin reactions being the commonest although numbers were small for undertaking statistical comparisons. The better drug survival of IB in patients switching from IO is interesting, since evidence suggests that generally drug efficacy of subsequent biologics of the same 'family' tends to reduce. Our findings contrast those from the DANBIO registry where 1-year IB (CT-P13) retention rate was slightly lower than for IO (1). It is likely that these differences reflect the policZy of the clinic to meticulously and in a standardised way monitor all aspects of disease and laboratory findings including antibody formation and drug trough levels among other, taking prompt action where indicated and minimising the risk of adverse outcomes.

Limitations of our study include the small patient numbers, confounding by indication, short follow-up and the single-centre nature of the study. Patients initially started IO as early as 1999, compared to patients starting IB in 2014, and therefore people receiving IO *versus* IB may represent different patient populations. Therefore, we ran sensitivity analyses including only patients who started IO in 2008 or later. We acknowledge that the latter may not have overcome actual differences in the IO *versus* IB groups and therefore, our results need to be interpreted with caution.

The single-centre nature of the study could be perceived as a strength since it resulted in a clear structure of clinical procedures uniformly adopted across the centre, enabling close and ongoing monitoring of clinical outcomes over time. Furthermore, the real-life setting without the stringent inclusion/exclusion criteria of randomised controlled trials represents an important strength of the data presented. The scope of the study was to undertake a descriptive analysis of real-life data, thus adding to the existing literature based on observational data.

In conclusion, this study of routinely collected, real-life clinic data, suggests that IB is generally well tolerated and comparable to IO, with no additional safety concerns identified. Considering the high costs of bio-original infliximab, IB represents a safe and well-tolerated alternative reducing, in particular, financial burdens of restricted healthcare budgets and improving universal access and use of these treatments.

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