Infliximab use in the Netherlands: Uptake and characteristics of originator and biosimilars over time

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Human studies and subjects

As the current study uses data without any direct enrolment of subjects, ethical approval or informed consent is not necessary according to the Dutch law regarding human medical scientific research (Wet medisch-wetenschappelijk onderzoek met mensen [WMO]), which is enforced by the Central Committee on Research involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek, CCMO). There was no Principal Investigator.

Running head

Originator and biosimilar infliximab use in the Netherlands

Keywords

Infliximab, originator drug, biosimilar, market uptake

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Abstract

Aims: The objective of this retrospective cohort study was to provide an overview of the utilization of originator and biosimilar infliximab in the Netherlands.

Methods: All infliximab dispensings were selected from the PHARMO In-patient Pharmacy Database from 2002-2018. Descriptive analyses were performed in order to characterise initiators and to describe switching patterns over time.

Results: Overall, 3,840 patients with 61,274 infliximab dispensings were identified. 2,496 patients initiated an originator infliximab and 777 patients initiated a biosimilar infliximab. Overall, 57% of the patients was female and mean age was 43.2 years. Both originators and biosimilars were mostly prescribed by gastroenterologists, followed by internists and rheumatologists. After market authorization of the first biosimilar the proportion of new patients initiating the biosimilar increased from 39% in 2015 to 91% in 2018. Out of 704 patients eligible for switching 34% switched. Among switchers, the proportion of females was 60% and mean age at index was 45.1 years. Among non-switchers, 55% was female and mean age was 39.8 years. The median time to switch was 1.7 years and switchers were most frequently initiated on infliximab by a rheumatologist (42%), while non-switchers were most frequently initiated by a gastroenterologist (42%).

Conclusions: The results of this large population-based cohort show an increase in biosimilar initiation in daily clinical practice. The number of switchers remains relatively low as non-medical switch is not encouraged in the Netherlands.

Keywords

Infliximab, originator drug, biosimilar, market uptake

Introduction

Therapeutic monoclonal antibodies, particularly tumour necrosis factor alpha (TNF-α) inhibitors such as infliximab, etanercept and adalimumab, have revolutionized the management of Immune Mediated Inflammatory Diseases.[1,2] Originator Infliximab Remicade® was first approved by the European Medicines Agency (EMA) in June 1999.[3] CT-P13 (Remsima®/Inflectra®) was the first biosimilar of a complex monoclonal biologic approved by the EMA in 2013. SB2 (Flixabi®) was the second biosimilar of infliximab to be approved by the EMA in May 2016,[4] followed by PF-06438179 (Zessly®) in 2018.[5]

Despite effectiveness in managing prevalent and impactful chronic conditions, biologics are expensive drugs which could potentially limit their uptake. Thus, when originators come off patent, the new biosimilar agents could be an opportunity for increasing market competition resulting in significant cost savings and improving access to biologic therapies.[6-9] Studies showed that use of biosimilars in Europe may result in savings between €11.8 to 33.4 billion between 2007 and 2020, and around $44.2 billion in the US between 2014 and 2024.[10,11] The European Union has a common regulatory system for approving biosimilars,[12,13] but it is at discretion of individual member states to fulfil market approval, and to announce reimbursement practices and incentives, or interchangeability and substitution policies.[14] In most countries substitution of biological medicines is not allowed, but in some countries, physician incentives have been incorporated in pricing and reimbursement mechanisms to stimulate biosimilar uptake. For instance, physicians in Norway must follow tender based recommendations and use the cheapest product, which often is a biosimilar. With this system, biosimilar infliximab has reached market share above 95%.[15] In countries without tendering or automatic substitution

policies (e.g. the Netherlands) some other factors such as physicians concerns over the efficacy and safety of biosimilars might be more influential than the potential cost savings, and this may limit the uptake of these biosimilars.[15-17]

To date there is limited data available regarding the general utilisation of infliximab and the uptake of its biosimilars in Europe. Furthermore, the studies that do have this information available have focused on only one centre or one indication.[18,19] The nature of the data of PHARMO's In-patient Pharmacy Database allows for distinction between originator and biosimilar and the assessment of multiple centres and indications at once. The current study provides an overview of the utilization of originator and biosimilar infliximab in the Netherlands in terms of uptake over time and switching patterns.

Methods

Study Design

A retrospective cohort analysis was conducted using data from the In-patient Pharmacy Database (IPD) of the PHARMO Database Network (PHARMO).[20] PHARMO is a population-based, patient-level network of healthcare databases linking data from different healthcare settings.[21,22] The IPD contains information on drugs dispensed by hospital pharmacies. The dispensing records include information on type of drug, date of dispensing, written dose instruction, type of prescriber, article codes. All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) Classification. The IPD covers a catchment area representing 2.0 million residents (~10% of the Dutch population).

Study Population

All dispensings for infliximab (ATC code: L04AB02) in the IPD were selected between 01 January 2002 (date of first infliximab dispensing in the data) and 31 December 2018 (end data availability). Patients with missing data on age or sex were excluded (n=3). The date of the first dispensing was defined as the index date. Treatment at index date (originator vs. biosimilar) was defined as the index treatment. Patients were considered a new user at the time of index date. No exclusion criteria were applied.

Originator-biosimilar Identification and Switching

Originator will be used throughout this article when referring to Remicade® and biosimilar will be used when referring to Remsima®, Inflectra®, Flixabi® or Zessly®. All dispensings prior to 01 January 2015, date of market approval of the first biosimilar infliximab in the Netherlands, were identified as originator. Following this date, a dispensing is classified as originator, biosimilar or unknown based on articles codes and free text notes. Patients were deemed eligible for switching when they had at least one dispensing of infliximab after 01 January 2015. Patients with a dispensing of originator at index date and a dispensing of biosimilar during follow-up were defined as switchers. Switches to unknown or from biosimilar to originator were disregarded. Among originator initiators, characteristics of patients switching to biosimilar infliximab and characteristics of patients not switching to biosimilar infliximab were determined.

Analysis

At index date, the following descriptive information was summarised: sex, age, year of index date, total number of dispensings and prescriber. These characteristics were presented separately for originator and biosimilar infliximab initiators and separately for originator infliximab initiators switching and those not switching to biosimilar infliximab during follow-up. For the latter group, also time to switch and the number of originator biosimilar dispensings prior to switch was presented. Time to switch was calculated as the number of days between the first date switching was possible and the dispensing date of the first biosimilar infliximab. The first date switching possible was defined as the maximum date of index date and 01 January 2015 (date of market approval of the first biosimilar infliximab in the Netherlands). The number of dispensings during the time to switch were summed per patient. Uptake was plotted as number of new users over time. Furthermore, the distribution of originator vs. biosimilar dispensings per year was presented. Categorical variables are presented as counts with percentages, continuous data as means with standard deviation (SD) or median with interquartile range (IQR), as appropriate. Data were analysed using SAS version 9.3 (SAS Institute Inc. Cary, NC, USA).

Results

We identified 3,840 patients with 61,274 infliximab dispensings in the IPD between January 2002 and December 2018. Of these dispensings, 67% were classified as originator, 17% as biosimilar and 16% was classified as unknown. 2,496 patients initiated originator treatment and 777 patients initiated biosimilar treatment (Table 1). Characteristics of patients initiating infliximab classified as unknown were not included (n=567). Overall, 57% of the patients was

female and mean (± SD) age was 43.2 (± 17.5) years. Both, originators and biosimilars were mostly prescribed by gastroenterologists (31% and 45%, respectively), followed by internists (24% and 27%, respectively) and rheumatologists (both 16%).

Table 1. Demographic characteristics at index date of new users of originator and biosimilar infliximab between 2002-2018

[Table 1]

Uptake

The monthly trend in new infliximab users is visualized in Figure 1. Spikes in uptake were observable for new users of infliximab in mid-2006, early 2008, early 2014, early 2015 and end 2016/early 2017.

[Figure 1]

Figure 1. Monthly number of new infliximab users between 2002-2018

As shown in Figure 2, after market authorisation of the first biosimilar in 2015 the proportion of new patients initiating the originator rapidly decreased to 45% in 2016, 26% in 2017 and less than 20% in 2018.

[Figure 2]

Figure 2. Distribution of new originator vs biosimilar infliximab users over time

Switching

Out of 2,496 patients initiating originator infliximab, 704 patients had at least one infliximab dispensing after 01 January 2015 and were therefore eligible for switching to biosimilar infliximab. Following the introduction of biosimilars, 238 out of 704 patients (33.8%) switched from originator infliximab to biosimilar infliximab. The median (IQR) time to this switch was 1.7 (0.6-2.1) years. Table 2 presents the demographic characteristics of switchers between originator and biosimilar infliximab and non-switchers among patients initiating originator infliximab. The proportion females was similar in patients who switched (60%) compared to non-switchers (55%). Patients who switched to a biosimilar were slightly older at index (mean ± SD: 45.1 ± 16.7 years) compared to non-switchers (mean ± SD: 39.8 ± 17.0 years). Switchers were most frequently initiated on infliximab by a rheumatologist (42%), while non-switchers were most frequently initiated by a gastroenterologist (42%).

Table 2. Demographic characteristics of (non-)switchers initiating on originator infliximab

[Table 2]

Discussion

In this population-based cohort study we characterised the use of originator infliximab and biosimilar in the Netherlands over time. Several spikes in the uptake were observed. The majority of these spikes could directly be related to the extension of the label or market authorisation of new biosimilars. Possible other explanations may include recording of practices, policy, and reimbursement changes.

Furthermore, no immediate switch from originator to biosimilar following the introduction of the first biosimilar (CT-P13) in the Netherlands in January 2015 was observed. However, the proportion of patients initiating on a biosimilar exceeded the proportion of patients initiated on the originator from 2016 onwards. These findings are in line with the Dutch guidelines, which state that patients initiating infliximab, or any other biologic agent, should start on the cheapest agent.[23] Regarding switching, the Dutch guidelines state that switching from originator to biosimilar should only be considered for prevalent users under controlled circumstances and conditions and in consultation with the patient.[24] Of the prevalent infliximab users eligible for switching approximately one third switched to a biosimilar.

The points of view in the guidelines are currently being reconsidered following the "NOR-SWITCH" study. The "NOR-SWITCH" study was a 52-week, randomized, double-blind, non-inferiority trial across indications and showed that switching from infliximab originator to CT-P13 was not inferior to continued treatment with infliximab originator according to a pre-specified non-inferiority margin of 15%.[25] These results are confirmed in the DANBIO registry.[26] This study showed that disease activity and flare rates were largely unaffected by non-medical switching to infliximab biosimilar. Despite the evidence from these studies, the uptake of

biosimilars is limited due to a lack of trust and knowledge by patients and healthcare providers, concerns regarding immunogenicity and policies on interchangeability and non-medical switching.[27,28] More studies regarding switching can provide valuable evidence for long-term safety and efficacy, increasing the trust and knowledge on biosimilars and ultimately increasing the uptake.

The current study contributes to the knowledge on biosimilars in daily practice but has also several limitations which should be taken into consideration when interpreting the results. For a proportion of patients (15%) it could not be determined whether they initiated an originator or biosimilar infliximab. These patients were categorised as unknown and not included in the current study. In addition, use of infliximab could not be stratified by indication as indication is not recorded in PHARMO's IPD. However, prescriber can be used as a proxy, but information regarding prescriber was not recorded for all patients. Using prescriber as a proxy for indication has also limitations as patients with the same indication may be treated by different specialties, depending on the hospital. Furthermore, the IPD only captures medication use administered during hospital stay; therefore, no information regarding outcomes was available in this study. Lastly, the IPD covers approximately 10% of the Dutch population which limits the extrapolation of the results to the Netherlands.

CONCLUSION

This large population-based cohort provides insight in the daily clinical practice of infliximab uptake and switching in the Netherlands. Complete traceability of originator or biosimilar, registration of indication and expansion of PHARMO's IPD would increase the

applicability and validity of the current results. Furthermore, these improvements will make it possible to carry out analyses by indication and include outcomes, increasing the relevance of these results in daily practice. In addition, this cohort is regularly updated, which makes it possible to monitor the uptake and switching over time in clinical practice in the Netherlands.

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Conflict of interest statement

JO, JK, MB and RH were employees of the PHARMO Institute for Drug Outcomes Research during the conduct of the study. This independent research institute performs financially supported studies for government and related health care authorities and several pharmaceutical companies. BB declares no conflict of interests.

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JO, JK, MB and RH are employees of the PHARMO Institute for Drug Outcomes Research. This independent research institute performs financially supported studies for government and related health care authorities and several pharmaceutical companies. BB declares no conflict of interests.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Requests for sharing study data must be made on specific grounds either with the aim to corroborate the study results in the interest of Public Health or in the context of an audit by a competent authority. Sufficient information needs to be provided to confirm that the request is made for one of the above-mentioned purposes, including a wound justification and, in case of a request with a view to corroborate study results, a protocol on the research for which the data will be used or a plan for quality control checks, as applicable.

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Tables

Table 1. Demographic characteristics at index date of new users of originator and biosimilar infliximab between 2002-2018

	Originator infliximab N = 2,496 n (%)	Biosimilar infliximab N = 777 n (%)
Sex		
Male	1,051 (42)	342 (44)
Female	1,445 (58)	435 (56)
Age, years		
<30	650 (26)	231 (30)
30-39	429 (17)	135 (17)
40-49	445 (18)	152 (20)
50-59	447 (18)	133 (17)
60-69	311 (12)	79 (10)
≥69	214 (9)	47 (6)
mean ± SD	43.8 ± 17.6	41.7 ± 16.8
Index date		
<2015	2,303 (92)	-
2015	127 (5)	81 (10)
2016	25 (1)	230 (30)
2017	13 (1)	180 (23)
2018	28 (1)	286 (37)
Number of dispensings		
Total	40,804	10,425
Median (IQR) per patient	10.0 (3.0-31.0)	4.0 (2.0-9.0)
Prescriber		
Internist	606 (24)	212 (27)
Gastroenterologist	778 (31)	347 (45)
Rheumatologist	404 (16)	122 (16)
Paediatrician	80 (3)	15 (2)
Dermatologist	7 (<0.5)	4 (1)
Others	302 (12)	18 (2)
Unknown	319 (13)	59 (8)

IQR = Interquartile range; SD = standard deviation.

Table 2. Demographic characteristics of (non-)switchers initiating on originator infliximab

	Switchers N = 238 n (%)	Non-switchers N = 466 n (%)
Sex		
Male	95 (40)	208 (45)
Female	143 (60)	258 (55)
Age, years		
<30	55 (23)	161 (35)
30-39	43 (18)	81 (17)
40-49	41 (17)	77 (17)
50-59	50 (21)	79 (17)
60-69	29 (12)	49 (11)
≥69	20 (8)	19 (4)
mean ± SD	45.1 ± 16.7	39.8 ± 17.0
Index date		
<2015	192 (81)	319 (68)
2015	25 (11)	102 (22)
2016	6 (3)	19 (4)
2017	8 (3)	5 (1)
2018	7 (3)	21 (5)
Time to switch		
Median (IQR), years	1.7 (0.6-2.1)	-
Median (IQR), dispensings*	24.0 (9.0-46.0)	-
Prescriber at index date		
Internist	71 (30)	142 (30)
Gastroenterologist	45 (19)	196 (42)
Rheumatologist	99 (42)	45 (10)
Pediatrician	2 (1)	17 (4)
Dermatologist	-	30 (6)
Others	9 (4)	36 (8)
Unknown	12 (5)	142 (30)

IQR = Interquartile range; SD = standard deviation; *median (IQR) number of originator infliximab dispensings during time to switch.

Figure Legends

Figure 1. Monthly number of new infliximab users between 2002-2018

Figure 2. Distribution of new originator vs biosimilar infliximab users over time