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ORIGINAL RESEARCH

Persistence and safety of anti-TNF biosimilars versus originators in immune-mediated inflammatory diseases: an observational study on the French National Health Data System

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ABSTRACT

Objectives Biosimilar-originator equivalence has been demonstrated in phase 3 trials in a few indications of infliximab, etanercept and adalimumab. The objective of our study was to compare the persistence and safety of biosimilars versus originators in all the licensed indications of these molecules.

Methods We used data from the French National Health Data System (SNDS), covering 99% of the French population, to identify infliximab, etanercept and adalimumab initiators from biosimilar launch (January 2015, May 2016 and October 2018, respectively) to 30 June 2021. Patients were then followed for 1 year. Treatment persistence (duration without treatment discontinuation or modification) and safety (including severe infections, all-cause hospitalisation and death) were compared between originator and biosimilar users by Cox regressions weighting the populations on the inverse probability of treatment. Analyses were performed by molecule, by disease and by biosimilar product.

Results From January 2015 to June 2021, 86 776 patients were included in the study: 22 670, 24 442 and 39 664 patients had initiated infliximab, etanercept and adalimumab, respectively; 49 752 (53%) were biosimilar initiators. We did not find any risk of discontinuation (HRs were below or around 1, here all pathologies and products together: infliximab 0.88 (0.80–0.97), etanercept 0.85 (0.81–0.90) and adalimumab 0.96 (0.91–1.00)) or safety event (infection: infliximab 0.97 (0.78–1.21), etanercept 1.04 (0.81–1.33) and adalimumab 0.98 (0.83–1.16); hospitalisation: infliximab 1.08 (0.96–1.23), etanercept 0.99 (0.87–1.11) and adalimumab 0.91 (0.83–0.99)) associated with biosimilar versus originator use.

Conclusions Our study shows reassuring results regarding the persistence and safety of biosimilar tumour necrosis factor-alpha inhibitors compared with originators in all licensed indications.

INTRODUCTION

Tumour necrosis factor-alpha (TNF-alpha) inhibitors are a class of biotherapies that have significantly improved the therapeutic care

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Biosimilar-originator equivalence was proven in phase 3 randomised clinical trials in few indications of infliximab, etanercept and adalimumab, and then extrapolated to all the other indications of these molecules.
- ⇒ We thus aimed to address the persistence and safety of biosimilar products compared with originator products for each brand name product and each licensed indication of each molecule.

WHAT THIS STUDY ADDS

- ⇒ This is the largest cohort of biosimilar or originator infliximab, etanercept and adalimumab initiators from 2015 to 2021.
- ⇒ This is the first observational study to address persistence and safety endpoints by comparing marketed biosimilar products and originator products of the tumour necrosis factor (TNF)-alpha inhibitor family in a systematic approach for each licensed indication and each branded product.
- ⇒ We did not show any difference in persistence or safety between biosimilar products and their originators in any licensed indication.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ This study provides reassuring results regarding the use of anti-TNF alpha biosimilar products in real life.
- ⇒ Marketed biosimilars of TNF-alpha inhibitors can thus be used more broadly in order to limit the financial impact of these molecules on health systems.

of immune-mediated inflammatory diseases. Infliximab (IFX), etanercept (ETA) and adalimumab (ADA), the first three marketed molecules of this class, were used and reimbursed respectively in 2000, 2003 and 2005 in France and indicated, according to the molecule, in rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis in rheumatology,

psoriasis and hidradenitis suppurativa in dermatology, Crohn's disease and ulcerative colitis in gastroenterology and uveitis in ophthalmology.¹ However, these treatments were expensive, leading to an issue of either access for patients or healthcare system sustainability due to the large number of patients treated. TNF-alpha inhibitors patent expiry and biosimilars progressive market approvals partly answered these issues by lowering the cost of treatment.² The active substance of biosimilars is highly similar to the originator's. Biosimilar products are approved provided that the data demonstrating biosimilarity to the originator product include physiochemical, non-clinical (mostly in vitro studies), pharmacokinetics and pharmacodynamics studies and generally one comparative phase 3 clinical trial to demonstrate their bioequivalence.³ The bioequivalence of the biosimilar products is then extrapolated to the other indications of the originator product. Several observational studies assessed the effectiveness of biosimilar products in these remaining indications and showed that there was no difference between originator and biosimilar products. However, they were often small,^{4 5} non-comparative⁶⁻⁸ or pathology-specific,⁹⁻¹² as we already did for inflammatory bowel diseases using the same database from 2015 to 2017.^{13 14}

In Europe, four IFX, four ETA and 12 ADA biosimilars have been approved from 2015, 2016 and 2018, respectively,¹⁵ based on bioequivalence data demonstrated in 1–3 indications. In France, the use of biosimilar products has experienced a significant increase since their market approval.¹⁶

The aim of the present study was to assess and compare the persistence under biosimilar versus originator treatment among initiators for each biosimilar product, taken separately and overall, for each pathology for which the originator products of IFX, ETA and ADA were indicated. In addition, we also compared the safety profiles of biosimilar and originator users in major adverse events.

METHODS

Study design

We built cohorts of IFX, ETA and ADA initiators, exposed to the originator molecule or to a biosimilar molecule, from the date of reimbursement of the first biosimilar product for each molecule (2015, 2016 and 2018, respectively) and followed the patients for 1 year.

Data source

We used data from the French National Health Data System (SNDS). The SNDS covers almost the totality (>99%) of the French population—68 million residents. Each person is identified by a unique and anonymous number. The SNDS records comprehensive outpatient (procedures and pharmacy deliveries of reimbursed drugs) and inpatient (pharmacy deliveries of expensive drugs, procedures performed during hospital stays and discharge diagnoses coded according to the International

Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)) reimbursement information since 2006. The SNDS also contains socio-demographic information on sex, age, place of residence and vital status, among others. Patients' status for 100% reimbursement of care related to a severe and costly long-term disease (LTD) is recorded and LTD diagnosis is coded according to the ICD-10. The SNDS has been extensively used to conduct pharmacoepidemiological studies, especially on the use, safety and effectiveness of health products.¹⁷⁻²¹

Study periods and populations

Inclusion periods differed for each originator molecule, according to the date of reimbursement in France of the first biosimilar for each of the three studied TNF-alpha inhibitor originators: IFX (ATC L04AB02), ETA (ATC L04AB01) and ADA (ATC L04AB04). Inclusions started on 27 January 2015 for IFX users, on 10 May 2016 for ETA users and on 9 October 2018 for ADA users. Every patient initiating treatment, that is, having a first delivery with no delivery of IFX, ETA or ADA within the year before initiation, between the inclusion start date and 30 June 2021, was included in the study.

Patient characteristics

Sociodemographic characteristics (sex, age, affiliation to complementary universal health insurance—CSS, deprivation index and region of residence) were collected at the index date. Comorbidities were assessed within 5 years before the index date. The history of visits to a specialist was assessed within 2 years before the index date. The history of dispensing of corticosteroids, non-steroidal anti-inflammatory drugs, non-biological systemic drugs on the one side and biological and targeted drugs on the other side was assessed within the year before the index date (ATC codes and grouping specified in online supplemental table 1). The pathology treated by the TNF-alpha inhibitor was defined at the index date. ATC codes, ICD-10 codes and the procedure used for pathology definition were presented in a previous study.¹⁶ Patients under 18 or treated with a molecule not indicated for their pathology were excluded.

Exposure, outcome, censoring and safety

The exposure of interest was, within a molecule, originator use versus biosimilar use. Specific exposure to each marketed biosimilar product (CT-P13 and SB2 for IFX; SB4 and GP2015 for ETA; ABP501, MSB11022, FKB327, GP2017 and SB5 for ADA; the other biosimilar products were excluded due to a lack of patients) was assessed as a subgroup analysis. Exposure was defined at the index date and reassessed at each subsequent delivery or non-delivery. The main outcome was persistence in treatment, defined as a period of continued treatment with the same product. Discontinuation, specified as a treatment gap of more than 60 days after the theoretical coverage period of each molecule (56 days for IFX, 28 days for

ETA and ADA), and treatment modification, defined as the delivery of a different biologic molecule, were considered outcome events. Censoring events included intra-molecule switching (at least two consecutive deliveries of a different product from the same molecule), death and the end of the 1-year follow-up period. Safety events included severe infection,²² major adverse cardiovascular events,²³ immunological disorders, cancer, anaphylaxis,²⁴ identified through ICD-10-coded hospitalisation discharges (specified in online supplemental table 2), death and all-cause hospitalisations for at least one night, except pathology-related hospitalisations.

Statistical analysis

Patients' characteristics at inclusion and during the follow-up (follow-up duration and outcome, censoring and safety event rates) were described. To account for the indication bias on exposure groups, a stabilised propensity score of treatment was computed using a logistic regression modelling the probability of initiating a biosimilar compared with the originator adjusted for all the covariates measured at inclusion (year of inclusion, age in categories, sex, affiliation to complementary universal health insurance, deprivation index, region of residence, main comorbidities, number of consultations and hospitalisations linked to the pathology in categories, drug history). Covariate balance was assessed graphically, plotting the standardised mean difference in covariates and the distribution of the propensity score before and after weighting. Inverse probability of treatment weighting (IPTW), truncating the first and 99th percentiles of weights to keep non-extreme weights, was used in Cox proportional hazards regressions comparing the risk of non-persistence for biosimilar users versus originator users. As ponderation was not sufficient to balance the covariates completely (as shown in online supplemental figures 1–3), we further adjusted the model for all the covariates included in the propensity score model. A univariate unweighted Cox proportional hazards regression was also computed. All the analyses were repeated for each pathology and each biosimilar treatment group (all together and each biosimilar taken separately). The proportionality of the hazards hypothesis was confirmed using the test of Schoenfeld residuals. The 0.05 p value threshold was corrected by dividing it by the number of pathologies tested for each molecule (six for IFX, four for ETA and eight for ADA) to follow the Bonferroni correction,²⁵ and two-sided tests were carried out. The p values and p value thresholds were reported in Supplementary tables. The whole method was repeated for three of the safety events, namely severe infections, all-cause hospitalisation and death. Lastly, we only described (effectives and proportions) the other events as they were less frequent and we lacked the power to carry out multivariable analyses.

All extractions from the SNDS were carried out with SAS Enterprise Guide software V.7.15; analyses were

done with R²⁶ V.3.5.2, using multiple packages including *dplyr*,²⁷ *ggplot2*,²⁸ *survival*²⁹ and *cobalt*.³⁰

Sensitivity analyses

Several sensitivity analyses were carried out. First, the biosimilar to originator switch was considered as a treatment discontinuation outcome, as we made the hypothesis that this switch would correspond to a medical switch for lack of efficacy of the biosimilar. Second, the intra-molecule switch was defined as a three-consecutive delivery change of product (and not two), not to misclassify a punctual switch due to stock issues. We also considered the intra-molecule switch at the first delivery to be comprehensive. In addition, we modified the definition of discontinuation, taking a 30-day or 90-day (vs 60-day gap in the main analysis) gap in addition to the theoretical covering period of the molecules. Fourth, we restricted the analyses to at least 6-month persistent patients, to analyse only treatment responders. Fifth, we modified the inclusion criteria, carrying out an additional analysis by changing the definition of TNF initiation to 'no delivery of any of the three TNF-alpha within the past 5 years' to prevent including non-initiating patients. We also restricted the analyses to calendar years with at least 10% of patients included in each group to have a minimal balance for this variable, and we repeated the analyses for each year of inclusion as a subgroup analysis. Additionally, the follow-up was extended to 2 years and also restricted to the pre-COVID-19 time period to exclude pandemic-specific discontinuations and the delay in care for new biologics users in the postlockdown period. Finally, the relative risk (RR) of non-persistence at 1 year was computed using the IPTW Kaplan-Meier survival estimate at 1 year; the CI for this estimate was assessed using the percentiles of the RR estimates on 1000 bootstraps.

RESULTS

Patient characteristics

A total of 86 776 patients were included, of whom 22 670 were IFX users, 24 442 were ETA users and 39 664 were ADA users. Among IFX users, 5292 (23%) initiated treatment with the originator product, 14 678 (65%) with CT-P13 and 2700 (12%) with SB2; 2042 (9%) had rheumatoid arthritis, 4059 (18%) ankylosing spondylitis, 611 (3%) psoriatic arthritis, 9531 (42%) Crohn's disease, 5054 (22%) ulcerative colitis and 1373 (6%) psoriasis. Among ETA users, 13 354 (55%) initiated treatment with the originator product, 8917 (36%) with SB4 and 2171 (9%) with GP2015; 11 265 (46%) had rheumatoid arthritis, 9702 (40%) ankylosing spondylitis, 1556 (6%) psoriatic arthritis and 1919 (8%) psoriasis. Among ADA users, 18 378 (46%) initiated treatment with the originator product, 10 048 (25%) with ABP501, 4189 (11%) with FKB327, 3939 (10%) with SB5, 1870 (5%) with MSB11022 and 1240 (3%) with GP2017; 5111 (13%) had rheumatoid arthritis, 11 091 (28%) ankylosing spondylitis, 1857 (5%) psoriatic arthritis, 11 047 (28%) Crohn's

Table 1 Main patients' characteristics at baseline

	Infliximab		Etanercept		Adalimumab	
	Originator	Biosimilars	Originator	Biosimilars	Originator	Biosimilars
Effective	5292	17 378	13 354	11 088	18 378	21 286
Mean age (SD)	43.2 (15.9)	43.3 (16.2)	50.5 (15.0)	51.8 (15.0)	43.4 (15.3)	45.1 (14.9)
Median age (Q1-Q3)	42 (30–54)	42 (30–55)	50 (39–61)	52 (40–63)	42 (31–54)	45 (33–56)
Male	2486 (47.0)	8415 (48.4)	4805 (36.0)	4143 (37.4)	8232 (44.8)	9492 (44.6)
Pathologies						
Rheumatoid arthritis	472 (8.9)	1570 (9.0)	5640 (42.2)	5625 (50.7)	1607 (8.7)	3504 (16.5)
Ankylosing spondylitis	806 (15.2)	3253 (18.7)	5447 (40.8)	4255 (38.4)	3570 (19.4)	7521 (35.3)
Psoriatic arthritis	155 (2.9)	456 (2.6)	905 (6.8)	651 (5.9)	620 (3.4)	1237 (5.8)
Crohn's disease	2369 (44.8)	7162 (41.2)	0 (0)	0 (0)	6270 (34.1)	4777 (22.4)
Ulcerative colitis	1044 (19.7)	4010 (23.1)	0 (0)	0 (0)	3685 (20.1)	2306 (10.8)
Psoriasis	446 (8.4)	927 (5.3)	1362 (10.2)	557 (5.0)	1929 (10.5)	1722 (8.1)
Hidradenitis suppurativa	0 (0)	0 (0)	0 (0)	0 (0)	188 (1)	43 (0.2)
Uveitis	0 (0)	0 (0)	0 (0)	0 (0)	509 (2.8)	176 (0.8)
Number of consultations linked to the pathology*						
0	880 (16.6)	2613 (15.0)	1291 (9.7)	679 (6.1)	1467 (8.0)	1621 (7.6)
1–2	1321 (25.0)	4339 (25.0)	2419 (18.1)	1934 (17.4)	3704 (20.2)	4530 (21.3)
3–4	1069 (20.2)	3848 (22.1)	3226 (24.2)	2821 (25.4)	4771 (26.0)	6014 (28.3)
5+	2022 (38.2)	6578 (37.9)	6418 (48.1)	5654 (51)	8436 (45.9)	9121 (42.8)
Number of hospitalisations linked to the pathology*						
0	284 (5.4)	667 (3.8)	7713 (57.8)	5838 (52.7)	7878 (42.9)	10 020 (47.1)
1	1379 (26.1)	5246 (30.2)	3400 (25.5)	3422 (30.9)	5995 (32.6)	6800 (31.9)
2	1235 (23.3)	4945 (28.5)	1085 (8.1)	961 (8.7)	2426 (13.2)	2535 (11.9)
3+	2394 (45.2)	6520 (37.5)	1156 (8.7)	867 (7.8)	2079 (11.3)	1931 (9.1)
Drug history*						
Other biologics	726 (13.7)	3344 (19.2)	2491 (18.7)	2055 (18.5)	2149 (11.7)	2738 (12.9)
Other systemic	2953 (55.8)	10 267 (59.1)	6859 (51.4)	6650 (60)	10 209 (55.6)	11 497 (54.0)
Steroids	3598 (68.0)	12 301 (70.8)	9387 (70.3)	8004 (72.2)	13 473 (73.3)	15 007 (70.5)
Non-steroidal anti-inflammatory drug	1932 (36.5)	6881 (39.6)	9472 (70.9)	7698 (69.4)	7710 (42.0)	12 249 (57.5)

Detailed patients' characteristics at inclusion are presented in online supplemental tables 3–5.

*Drug history was assessed within the year before inclusion; the number of consultations linked to the pathology within 2 years before inclusion and the number of hospitalisations within 5 years before inclusion.

Q1-Q3, quarter 1-quarter 3; SD, Standard deviation.

disease, 5991 (15%) ulcerative colitis, 3651 (9%) psoriasis, 231 (1%) hidradenitis suppurative and 685 (1%) uveitis.

Patients' characteristics at inclusion were similar between biosimilar and originator product users within each molecule, as shown in [table 1](#) and online supplemental tables 3–5. The only significant difference came from the year of inclusion, as biosimilar product uptake was progressive throughout the years.

Persistence

All pathologies taken together, patients treated with a biosimilar of IFX were followed on average for 280 days (SD 112 days), slightly more than originator IFX users

(269 (120) days). Both groups had similar discontinuation or molecule switch rates at 1 year (38.9% (n=6761) in the biosimilar group and 38.3% (n=2026) in the originator group).

In ETA users, patient follow-ups in the biosimilar versus originator groups were close (264 (118) days vs 253 (120) days). The biosimilar group experienced fewer events than the originator group (45.7% (n=5064) compared with 52.2% (n=6965)).

Patients treated with a biosimilar of ADA were followed on average for 267 days (SD 117 days), slightly less than originator ADA users (273 (114) days). Event rates at 1 year in both groups were similar (42.8% (n=9104) in the

Table 2 Risk of non-persistence of biosimilar use versus originator use in infliximab-initiating patients, by pathology

Pathology	Reference events	Biosimilars events	Crude HR	P value	IPTW aHR	P value
Rheumatoid arthritis	48% (228/472)	51% (798/1570)	0.95 (0.78 to 1.16)	0.534	0.88 (0.63 to 1.23)	0.300
Ankylosing spondylitis	41% (330/806)	43% (1407/3253)	0.98 (0.84 to 1.16)	0.797	0.84 (0.67 to 1.07)	0.057
Psoriatic arthritis	39% (61/155)	44% (199/456)	1.08 (0.74 to 1.60)	0.580	0.87 (0.45 to 1.69)	0.590
Crohn's disease	35% (829/2369)	32% (2272/7162)	0.85 (0.77 to 0.95)	<0.001	0.83 (0.71 to 0.96)	<0.001
Ulcerative colitis	38% (394/1044)	41% (1626/4010)	1.05 (0.91 to 1.22)	0.375	0.90 (0.74 to 1.11)	0.193
Psoriasis	41% (184/446)	50% (459/927)	1.28 (1.02 to 1.61)	0.005	0.98 (0.70 to 1.36)	0.845

HR are presented in point estimates (CI); bold font denotes significant differences. Bonferroni-corrected p value=0.00833.
IPTW computed through a multivariable logistic regression.
aHR, adjusted HR; IPTW, inverse probability of treatment weighting.

biosimilar group and 43.1% (n=7916) in the originator group).

IPTW aHR (presented in tables 2–4 and online supplemental tables 9–17) of event were close to 1 and CIs covered 1, except for several subgroups: in the IFX cohort, biosimilar use showed a better persistence in Crohn's disease (aHR 0.83 (95% CI 0.71 to 0.96), driven by the CTP13); in the ETA cohort, biosimilar use showed a better persistence in rheumatology (rheumatoid arthritis: aHR 0.85 (95% CI 0.78 to 0.93); ankylosing spondylitis: aHR 0.88 (95% CI 0.80 to 0.96) and psoriasis: aHR 0.80 (95% CI 0.65 to 1.00); in the ADA cohort, biosimilar use showed a better persistence in ankylosing spondylitis (aHR 0.89 (95% CI 0.81 to 0.97). In addition, each biosimilar product subgroup had better or similar persistence than the originator groups (online supplemental tables 9–17). All the sensitivity analyses (shown in online supplemental figure 4) were consistent with the results of the main analysis.

Safety

Across molecules, adverse event rates were mostly similar. The most common adverse events were severe infection, all-cause hospitalisation and death, with 6.0% (n=1370), 2.3% (n=566) and 2.5% (n=982) of IFX, ETA and ADA patients having experienced hospitalisation for severe infection, respectively; 19.5% (n=4424), 10.2% (n=2495)

and 8.8% (n=3505) of IFX, ETA and ADA patients having experienced all-cause hospitalisation, respectively; and 0.8% (n=173), 0.3% (n=71) and 0.2% (n=74) of IFX, ETA and ADA patients having died before the end of the follow-up, respectively. Weighted Cox proportional hazard models showed no difference between biosimilar and originator users regarding these adverse events (figure 1, online supplemental tables 18–20). The description of other safety outcomes for each group is available in online supplemental tables 6–8. All the sensitivity analyses (shown in online supplemental figure 5) were consistent with the results of the main analysis.

DISCUSSION

The marketed biosimilar TNF-alpha inhibitors had been approved based on specific phase 3 randomised controlled trials in 1–3 indications, and their equivalence was then extrapolated in all the other indications of the molecule. In this systematic observational study based on the SNDS gathering all French patients, we showed no difference in terms of persistence or safety between biosimilar TNF-alpha inhibitors and originator products, within each molecule analysed, namely, IFX, ETA and ADA, in all their respective licensed indications.

We have consistent results with the clinical trials that led to the market authorisation of the biosimilar

Table 3 Risk of non-persistence of biosimilar use versus originator use in etanercept-initiating patients, by pathology

Pathology	Reference events	Biosimilars events	Raw HR	P value	IPTW aHR	P value
Rheumatoid arthritis	48% (2731/5640)	42% (2380/5625)	0.84 (0.78 to 0.90)	<0.001	0.85 (0.78 to 0.93)	<0.001
Ankylosing spondylitis	55% (2977/5447)	49% (2078/4255)	0.86 (0.80 to 0.92)	<0.001	0.88 (0.80 to 0.96)	<0.001
Psoriatic arthritis	53% (484/905)	49% (320/651)	0.86 (0.72 to 1.03)	0.033	0.82 (0.65 to 1.03)	0.031
Psoriasis	57% (773/1362)	51% (286/557)	0.90 (0.76 to 1.07)	0.123	0.80 (0.65 to 1.00)	0.011

HRs are presented in point estimates (CI); bold font denotes significant differences. Bonferroni-corrected p value=0.0125.
IPTW computed through a multivariable logistic regression.
aHR, adjusted HR; IPTW, inverse probability of treatment weighting.

Table 4 Risk of non-persistence of biosimilar use versus originator use in adalimumab-initiating patients, by pathology

Pathology	Reference events	Biosimilars events	Raw HR	P value	IPTW aHR	P value
Rheumatoid arthritis	51% (822/1607)	47% (1664/3504)	0.89 (0.79 to 1.00)	0.006	0.99 (0.87 to 1.13)	0.881
Ankylosing spondylitis	51% (1803/3570)	45% (3388/7521)	0.83 (0.76 to 0.90)	<0.001	0.89 (0.81 to 0.97)	<0.001
Psoriatic arthritis	54% (333/620)	48% (592/1237)	0.88 (0.73 to 1.06)	0.061	0.81 (0.65 to 1.01)	0.009
Crohn's disease	34% (2127/6270)	33% (1581/4777)	1.05 (0.96 to 1.15)	0.173	1.01 (0.92 to 1.12)	0.679
Ulcerative colitis	42% (1546/3685)	42% (966/2306)	1.08 (0.97 to 1.21)	0.056	1.07 (0.95 to 1.21)	0.109
Psoriasis	53% (1027/1929)	49% (846/1722)	0.90 (0.80 to 1.02)	0.028	0.95 (0.83 to 1.10)	0.374
Hidradenitis suppurativa	43% (80/188)	33% (14/43)	0.81 (0.36 to 1.78)	0.455	0.85 (0.27 to 2.74)	0.711
Uveitis	35% (178/509)	30% (53/176)	0.97 (0.63 to 1.48)	0.825	0.90 (0.54 to 1.51)	0.581

HRs are presented in point estimates (CI); bold font denotes significant differences. Bonferroni-corrected p value=0.00625. IPTW computed through a multivariable logistic regression. aHR, adjusted HR; IPTW, inverse probability of treatment weighting.

products (as shown in table 5) but also with observational studies in other indications demonstrating either no difference between biosimilars and originators^{9 11 12 14} or a better persistence in biosimilar-treated patients (IFX CT-P13 had already been shown to be slightly beneficial in Crohn's disease in a study carried out on the same database,¹³ and ETA biosimilars had better retention in a French recent study).³¹ For the first time, our study assessed, in a large unselected population, persistence and safety in all the indications and all the anti-TNF-alpha products altogether.

While clinical trials mainly focus on efficacy endpoints, our study intends to assess biosimilar versus originator equivalence in its globality: persistence first, as a proxy of real-world effectiveness, but also safety, through a complete description and advanced statistical comparative analyses.

Biosimilar products share the same amino acid sequence as originator products, but their tri-dimensional structure, exact formulation and excipients may vary from one product to another. Manufacturing processes may alter the composition of biosimilar or originator

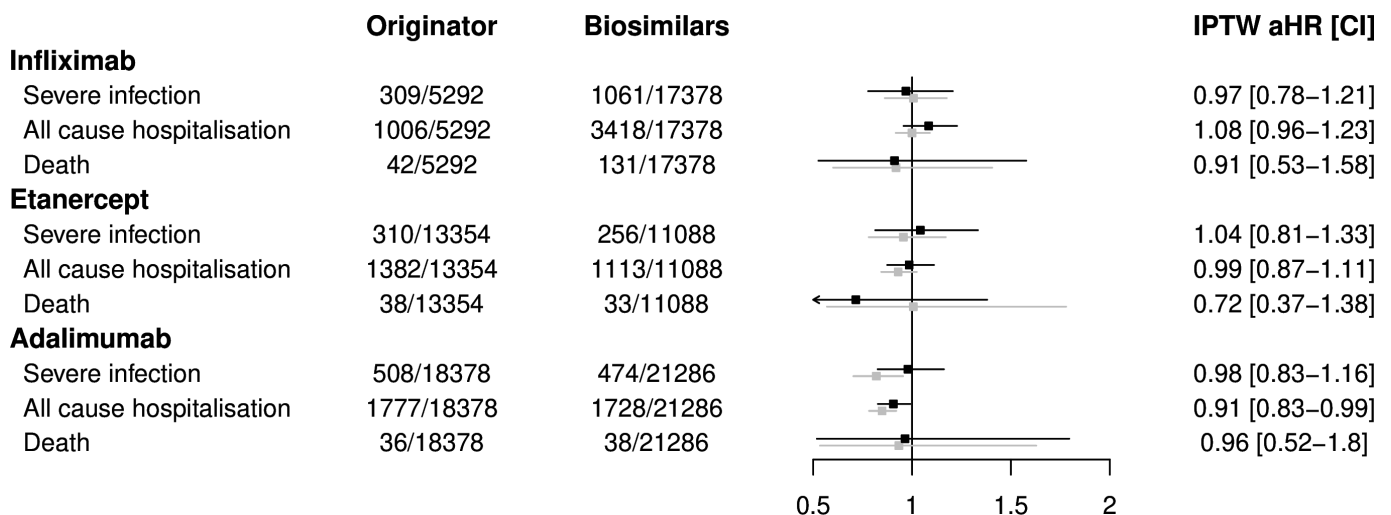


Figure 1 Estimation of the association between product type exposure (biosimilar vs originator, with originator as a reference) and major adverse events in antitumour necrosis factor-alpha-initiating patients, by molecule and adverse event type (crude HRs are presented in grey, whereas IPTW HRs, adjusted on all the covariates, are presented in black). HR values are presented in point estimates (CI) for the IPTW models only. aHR adjusted HR; IPTW, inverse probability of treatment weighting.

Table 5 Results overview filling the randomised controlled trial gaps with subgroup analyses by biosimilar product in all the indicated pathologies

	Rheumatoid arthritis	Ankylosing spondylitis	Psoriatic arthritis	Crohn's disease	Ulcerative colitis	Psoriasis	Hidradenitis suppurativa	Uveitis
Infliximab								
CT-P13	Yoo and colleagues ³⁷	Park and colleagues ³⁸		Ye and colleagues ³⁹				
SB2	Choe and colleagues ⁴⁰							
ALL								
Etanercept								
GP2015	Matucci-Cerinic and colleagues ⁴¹					Griffiths and colleagues ⁴²		
SB4	Emery and colleagues ⁴³							
ALL								
Adalimumab								
ABP501	Cohen and colleagues ⁴⁴					Papp and colleagues ⁴⁵		
FKB327	Genovese and colleagues ⁴⁶							
SB5	Weinblatt and colleagues ⁴⁷							
MSB11022	Edwards and colleagues ⁴⁸					Hercogova and colleagues ⁴⁹		
GP2017	Wiland and colleagues ⁵⁰					Blauvelt and colleagues ⁵¹		
ALL								

Grey box: no persistence difference. Blue box: statistically higher persistence with biosimilar. Brown box: not enough patients to conclude. Blank box: not indicated. Randomised controlled trials are shown, with the authors and reference number of the study in the respective box.

products over time (referred to as molecule drift),³² potentially triggering a divergence between products from the clinical trial lots to the actual packs used in the real world. In addition, the extrapolation paradigm can be questioned by practitioners and patients, even irrationally, and educational efforts had to be made to counter prescription inertia³³ and the nocebo effect.³⁴ The aim of our study was then to break down the remaining barriers to the adoption of biosimilar products.

Our study has several strengths. First, as it was based on a comprehensive database, we were able to include almost every patient living in France and having initiated one of the three studied anti-TNF-alpha, which represented almost 90 000 patients, and to follow them through their contact with health services. It allowed us to use a systematic approach to compare biosimilar and originator products in a real-life setting based on the events of interest in all of the licensed indications of the three TNF-alpha inhibitors at stake and to carry out subgroup analyses on each biosimilar product. Second, we tested the robustness of our results with many sensitivity analyses. The selection of the population could have been a source of bias, in particular as the definition of initiation (no delivery of any of the three TNF-alpha within the past year) allowed multiple initiations for different products. The sensitivity

analysis we carried out with a modified definition (no delivery of any of the three TNF-alpha within the past 5 years) did not differ from the main analysis. We also varied the outcome definition, the follow-up duration and the statistical methods. None of these modifications changed the main results of our study. Third, the indication bias, often argued in observational studies, should be limited in our case, as the originator and biosimilar products are vastly considered interchangeable (as demonstrated by the well-balanced groups at inclusion and the fast adoption of the biosimilar products).¹⁶

Our study has nonetheless several limitations. First, we do not report long-term persistence and safety data, censoring patient follow-ups for 1 year only. We adopted this approach to be comparable with randomised clinical trials on biosimilars, which generally report equivalence data at 52 weeks, and to have similar follow-ups between both exposure groups. As biosimilar uptake was progressive, the biosimilar group would have had a shorter follow-up without our arbitrary right censoring. Second, we included a sufficient number of patients to get enough events for most of our analyses. However, for several pathology subgroups, we did not have enough sample size to show results at the drug level. Moreover, as we took an interest in adverse events in the therapeutic

sequence with limited follow-up, safety was reported only for a few event types and results had to be pulled at the molecule level. Third, we were somewhat limited by the nature of the database we used, as it does not capture most patients and disease characteristics, such as baseline disease activity or autoantibody status. We were not able to use the same clinical outcomes as in clinical trials, such as the American College of Rheumatology criteria, the Psoriasis Area Severity Index and the Crohn's Disease Activity Index. We had thus to identify many covariates (such as pathology) and outcomes (medical discontinuation) with indirect information or proxies, which can be questionable. Specifically regarding intra-molecule switches, we could not distinguish between medical and non-medical switches and thus chose to consider switches as censoring events, which could be an explanation for the beneficial effects found in some biosimilar groups. Also, other factors, such as patient and physician preferences, which are not recorded in the database, could influence drug prescription and continuation. As a consequence, in spite of the fact that our algorithms and methodological choices were validated by a large number of previous studies based on the SNDS and specific to the diseases we studied,^{13 14 22 35 36} residual bias by indication and misclassification error cannot be precluded. Finally, our systematic approach can be disputable, as we used the same outcome criteria and adjustment covariates for each of our analyses. We think this is in fact one of the interests of the study, as our methodology is highly reproducible in time (for data updates with more patients and more follow-up) and space (in other countries and data sources).

To conclude, our study shows reassuring results regarding the persistence and safety of biosimilars compared with the originator anti-TNF-alpha product in all licensed indications of these molecules in a real-world use context. As originator and biosimilar products seem interchangeable, biosimilar products should be used more broadly.

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Contributors Literature search: all; study design: all; data extraction and collection: HJ; statistical analysis: HJ; interpretation of the results: all; drafting of the manuscript: HJ; revision of the manuscript: all; supervision: ES and MZ and guarantor: MZ. HJ and MZ confirm that they had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Patient consent for publication Not applicable.

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