

UC Berkeley

UC Berkeley Previously Published Works

Title

Penetration rate of anti-TNF biosimilars and savings at 5 years after their introduction in French hospitals

Permalink

<https://escholarship.org/uc/item/7jv0q6v0>

Journal

Therapies, 77(4)

ISSN

0040-5957

Authors

Jarrion, Quentin

Azzouz, Brahim

Robinson, James

et al.

Publication Date

2022-07-01

DOI

10.1016/j.therap.2021.10.012

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at <https://creativecommons.org/licenses/by/4.0/>

Peer reviewed



Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com



SOCIAL PHARMACOLOGY

Penetration rate of anti-TNF biosimilars and savings at 5 years after their introduction in French hospitals

Quentin Jarrion^{a,*}, Brahim Azzouz^b,
James Robinson^c, Damien Jolly^d,
Catherine Vallet^e, Thierry Trenque^b

^a Department of Health Information Management, Department of Pharmacovigilance and Pharmacoepidemiology, University Hospitals of Reims, 51092 Reims, France

^b Department of Pharmacovigilance and Pharmacoepidemiology, University Hospitals of Reims, 51092 Reims, France

^c School of Public Health, University of California, 94720-7360 Berkeley, CA, USA

^d Department of Clinical Research, University Hospitals of Reims, 51092 Reims, France

^e Department of Health Information Management, University Hospitals of Reims, 51092 Reims, France

Received 5 October 2021; accepted 29 October 2021

KEYWORDS

Biosimilar
pharmaceuticals;
Tumor necrosis factor
inhibitors;
Commerce;
Cost savings;
Hospitals

Summary

Objective. — Since the expiry of the patents on originator anti-TNF agents in Europe, France has authorized the sale of biosimilars. The penetration rate of anti-TNF agents and their biosimilars, and the cost savings driven by the introduction of biosimilars appears to vary widely. This study aimed to describe the market share of anti-TNFs and their biosimilars, and the cost savings generated by the introduction of biosimilars in French hospitals 5 years ago.

Methods. — The pharmaceutical component of the French national uniform hospital discharge data set database (PMSI) was used to study sales of infliximab, etanercept and adalimumab originators and biosimilars, and to estimate cost savings generated by the introduction of biosimilars onto the market, using the historical tariffs of the originators.

Results. — The penetration rate of anti-TNF biosimilars in France in 76% for infliximab, 74% for etanercept and 77% for adalimumab. In 2020, Inflectra® (41%) was the Remicade® biosimilar with the highest sales volume, while Erelzi® (57%) and Amgevita® (64%) were the most widely

* Corresponding author.

E-mail address: quentinjarrion@yahoo.fr (Q. Jarrion).

<https://doi.org/10.1016/j.therap.2021.10.012>

0040-5957/© 2021 Société française de pharmacologie et de thérapeutique. Published by Elsevier Masson SAS. All rights reserved.

sold biosimilars of Enbrel® and Humira® respectively. In terms of cost savings since the launch of biosimilars, overall, for all biosimilars taken together, over the 5-year period, a total of 824 million Euro was saved, in relation to the historical tariffs of the originators.

Conclusions. – This study shows firstly that the penetration rate of anti-TNF biosimilars in France 5 years after their launch is close to 80%. Secondly, we show that the cost savings generated by the use of biosimilars to anti-TNF agents exceed 820 million Euro over 5 years.

© 2021 Société française de pharmacologie et de thérapeutique. Published by Elsevier Masson SAS. All rights reserved.

Abbreviations

ADA	adalimumab
BS	biosimilars
COVID-19	Coronavirus disease 2019
ETA	etanercept
INF	infliximab
INN	international non-proprietary name
TNF	tumor necrosis factor

Introduction

Biologics are drugs that are developed based on compounds derived from live organisms. They were initially reserved for in-hospital use, but are now widely available in a range of medications in the form of vaccines, hormones, or monoclonal antibodies [1], such as anti-tumor necrosis factor (TNF) agents [2].

When patents expire on originator biologics, competitor pharmaceutical companies are entitled to produce and commercialize copies of the originator, known as biosimilars. However, due to the specific production processes of biologics, biosimilars are not exact replicas of the originator drug, but, as their name suggests, only similar.

Releasing new drugs onto the market usually drives tariffs down, since the monopoly is challenged. This was the case when the first biosimilar for infliximab was released in Europe [3]. In France, infliximab was the first anti-TNF agent for which a biosimilar was released, in December 2014 [4,5], followed by the introduction of biosimilars for etanercept in 2016, and for adalimumab in 2018 [6]. Infliximab is distributed only in hospitals, whereas etanercept and adalimumab are also distributed in hospitals but mainly in the community.

French legislation for the regulation of the healthcare system stipulates that procurement procedures should be optimized with a view to generating a target saving of several billion Euro over the next 2 years [7]. Expanding the market for biosimilars meets this economic objective of containing healthcare spending on drugs. However, evaluating the actual savings on the basis of the penetration rate of each drug is challenging, since penetration depends on a range of factors including local policies in favour of a specific

biosimilar, government incentives, marketing tactics on the part of the pharmaceutical companies, recommendations from scientific societies, and acceptance of these new treatments by healthcare providers and by patients.

This study aimed to describe the current rate of penetration of anti-TNF agents in French hospitals 5 years after they were first introduced on the market. We will also describe the penetration rate of each anti-TNF biosimilars since its launch, and we will estimate the savings generated through tariffs reductions driven by the introduction of biosimilars on the market in France.

Methods

This is a retrospective, observational study using data from the French national uniform hospital discharge data set database (PMSI), specifically its pharmaceutical component [8]. All French healthcare establishments (public and private), including hospital ambulatory clinics as well as inpatient care, having prescribed at least one unit dose of any one or more of the five available anti-TNF agents were included in the analysis. We did not take into account the ambulatory system. The five anti-TNF agents retained for this study, and still available on the French market, are as follows:

- infliximab: originator: Remicade®; and biosimilars: Inflectra®, Remsima®, Flixabi®, Zessly®;
- etanercept: originator: Enbrel®; and biosimilars: Benepali®, Erelzi®;
- adalimumab: originator: Humira®; and biosimilars: Amgevita®, Hulio®, Hyrimoz®, Idacio®, Imraldi®;
- golimumab: originator: Simponi®; no biosimilars available at this time;
- certolizumab-pegol: originator: Cimzia®; no biosimilars available at this time.

We analysed all prescriptions of these drugs from 1 January 2014 to 30 April 2020.

National-level data were obtained from the national database of the French technical agency for healthcare informatics (*Agence technique française de l'information médicale*). This database is compiled by all prescribers and for each patient receiving an anti-TNF agent, the following data were available:

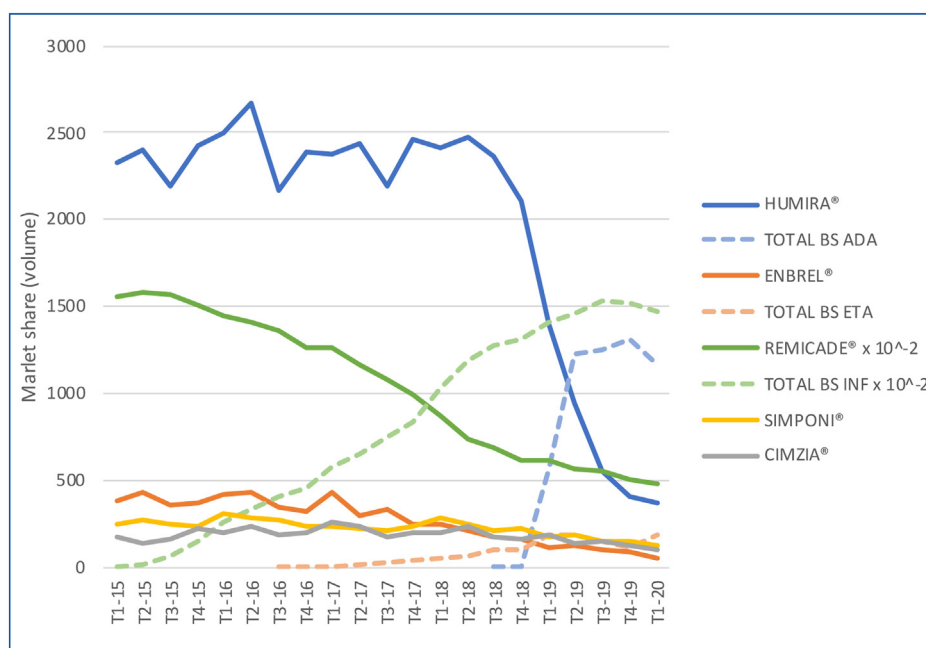


Figure 1. Market share by trimester for all anti-TNF agents by number of boxes sold (Remicade® and biosimilars = 10^{-2}).

- geographical code of the healthcare establishment (from 2017 to 2020);
- the product's identifying code (from 2014 to 2020);
- the month of administration of the drug (from 2014 to 2020);
- the year of administration of the drug (from 2014 to 2020);
- the number of products administered (from 2014 to 2020).
- the actual purchase price paid by each hospital, for each product (from 2014 to 2020)

The data query was for all data from 1 January 2014 to 30 April 2020.

In order to establish the market share of each drug, we analysed the number of unit doses by product name, by year and by trimester. Thus, we were able to calculate the percentage of each product among the total drugs prescribed, for each international non-proprietary name (INN) and for each brand-name. We thus compared each originator versus all its biosimilars grouped together, and categorized by individual INN.

Finally, we estimated the economic savings generated by the introduction of biosimilars on the market. To this end, we calculated the volume of sales at the price negotiated by the hospitals with the manufacturers, and also volume of sales at the national tariff negotiated with the French authorities responsible for the tariff of healthcare products. As the historical tariff, we used the tariff that was in force before the introduction of the first biosimilar. The savings were calculated based on the historical tariff [9]. The tariff history was taken from the French social security system. For the tariff history, we retained the national tariff for Remicade® in force prior to December 2014, the regulatory tariff for Enbrel® in force prior to November 2017, and the regulatory tariff for Humira® in force prior to October 2018; these dates correspond to the dates of first

commercialization at an officially determined tariff of a biosimilar for each anti-TNF drug [10].

To calculate the savings (S) generated over time [11], we calculated the product of sales volume (Q) multiplied by the difference between the historical tariff of the drug (T_{REF}), and the actual final hospital purchase price of the drug (i.e. final price after group procurement, public tenders, or other forms of price negotiation) (P_{ACT}), as follows:

$$S = Q \times (T_{HIS} - P_{ACT}).$$

Even though some anti-TNF agents do not currently have available biosimilars, we chose to analyse the cost savings for all anti-TNFs from 2015 to 2020, in the event that there may be a class effect, whereby the availability of biosimilars for one patented drug might drive down the prices of other originator drugs in the same class.

For infliximab only, to evaluate the market share of all anti-TNF agents, a conversion factor of 10^{-2} was applied to Remicade® and its biosimilars to render the dynamics of the anti-TNF market visually comparable (Fig. 1).

Quantitative variables are expressed as raw values, and qualitative variables as number and percentage.

Results

Volume of market sales — All anti-TNF agents

Our data were derived from hospital prescriptions, and infliximab is dispensed exclusively in-hospital, and thus raw data on infliximab were not comparable to those of adalimumab and etanercept, which are mainly distributed through community pharmacies/doctor's surgeries.

The time required for the biosimilar of Remicade® to reach 50% of the market share after introduction was 3 years; 2 years for the biosimilars of Enbrel® and less than one year for the biosimilars of Humira® (Fig. 1). In parallel,

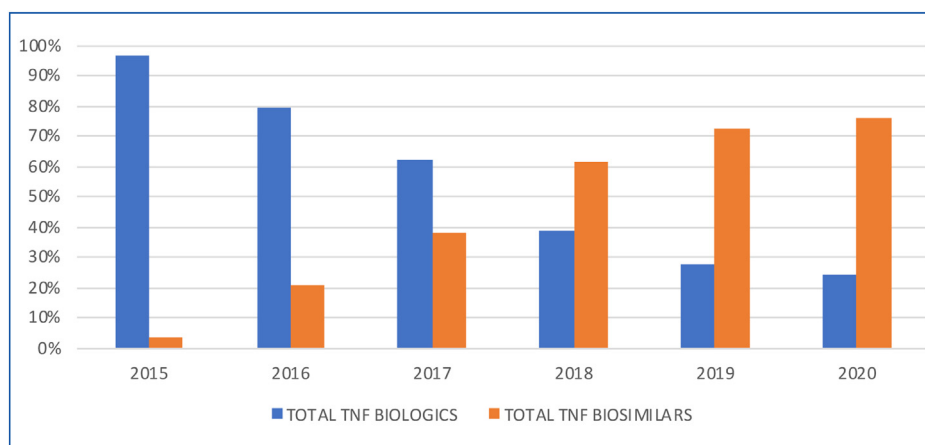


Figure 2. Annual percent market share for all patented anti-TNF biologics and all anti-TNF biosimilars, 2015–2020.

sales of Simponi® decreased from 271 boxes in 2015 to 126 in 2020, while a similar decrease was also observed for sales of Cimzia®, dropping from 173 boxes sole in 2015 to 98 in 2020.

In the hospital setting, originator anti-TNF agents represented 97% of the market sales in 2015, but this market share declined to 24% in 2020, while the market share for biosimilars rose from 3% in 2015 to 76% in 2020 (Fig. 2).

Volume of market sales – Infliximab

Regarding infliximab, and the originator Remicade®, the penetration rate declined from 96% in 2015 to 24% in 2020 (Fig. 3). Regarding the biosimilars, for Inflectra®, the market share increased from 3% to 41% between 2015 and 2020, from 1% to 17% and 0% to 18% over the same period for Remsima® and Flixabi®, respectively. For all biosimilars of infliximab taken together, the market share rose from 4% in 2015 to 76% in 2020. The volume of sales of Remicade® fell from 156,000 boxes in 2015 to 48,000 boxes in 2020 (Fig. 4), while the volume of sales of all biosimilars in 2020 represented a total of 148,000 boxes.

Volume of market sales – Etanercept

Regarding etanercept (originator Enbrel®), the market share dropped from 100% in 2015 to 26% in 2020. For the biosimilar Benepali®, the penetration rate went from 0% in 2015 to 17% in 2020, with a peak at 36% in 2019. Similarly, the market share of Erelzi® went from 0% to 57% over the same period (Fig. 5). In total, for all etanercept biosimilars taken together, their market share rose from 0% in 2015 to 74% in 2020. As shown in Fig. 6, the number of units of the originator Enbrel® sold in the hospital setting declined from 377 in 2015 to 52 in 2020. A total of 192 units of all biosimilars together were sold in 2020.

Volume of market sales – Adalimumab

Finally, for adalimumab (originator Humira®), the penetration rate dropped from 100% in 2015 to 23% in 2020 (Fig. 7). For the biosimilar Amgevita®, the penetration rate rose from 0% in 2015 to 64% in 2020, while the corresponding rates

for Hulio® and Imraldi® rose from 0% to 4% and 0% to 9% respectively between 2015 and 2020. Hyrimoz® and Idacio® are not sold in France in the hospital setting. For all adalimumab biosimilars taken together, market share rose from 0% in 2015 to 77% in 2020. As shown in Fig. 8, the number of standard units of Humira® sold in the hospital setting in 2015 was over 2300, but this number dropped to 367 in 2020, while biosimilars sold a total of 1200 units in 2020.

Cost savings generated by the introduction of biosimilars

Overall, for the French hospital market only, the introduction of biosimilars generated savings of 823,530,360 €, relative to the historical tariff; approximately 499 million Euro saved on the prices of biosimilars, and around 325 million saved on the prices of originators (Tables 1 and 2).

Table 1 details the cost savings generated per year by the introduction of biosimilars, compared to the original historical tariff fixed by the French government. The savings went from 4.4 million Euro saved on the purchase of all infliximab biosimilars in 2015, to a total of 229 million Euro saved in 2019 across biosimilars of all anti-TNFs.

Table 2 describes the amounts saved on the purchase of original anti-TNFs, as compared to the historical tariff, per year. Savings ranged from 27.25 million in 2015, to almost 76 million in 2019.

Overall, for infliximab, total savings amounted to almost 805 million Euro (496 million € from biosimilars, and 309 million € from the originator). For etanercept, hospital savings amounted to 236,158 Euro (99,636 € from biosimilars, and 136,522 € from the originator). It can be noted that by 2019, almost three-quarters of the savings generated were due to the biosimilars. Finally, for adalimumab, hospital savings amounted to 18.7 million € (3.1 million € from biosimilars, and 15.6 million € from the originator). Of note, savings on purchase of the originator Humira® were relatively stable, at around 3.5 million from 2016 to 2018, then dropped dramatically in 2019 after the introduction of biosimilars, with an increase of almost 1.15 million € in overall savings in 2019.

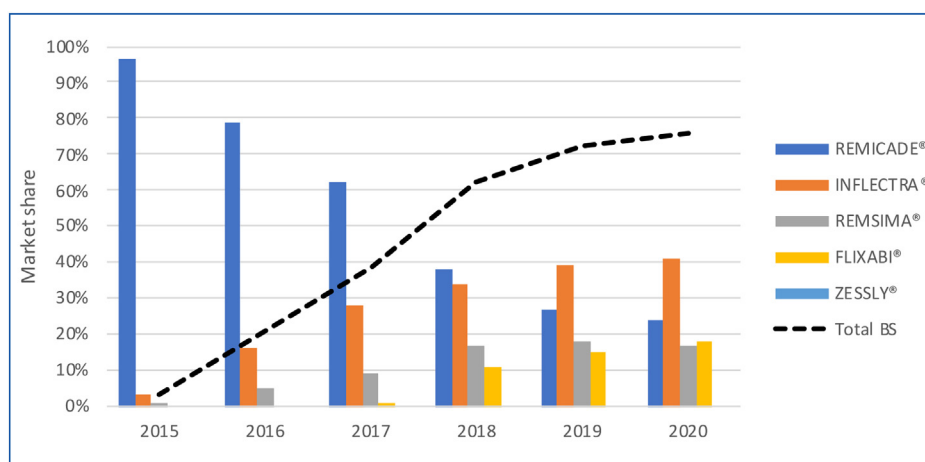


Figure 3. Annual market share of infliximab and biosimilars (percentage of total sales).

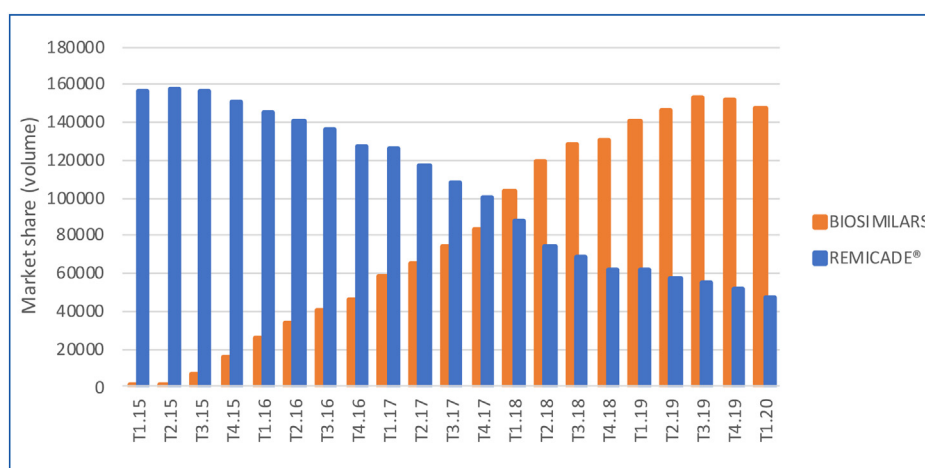


Figure 4. Market share by trimester for all infliximab biosimilars (sales volume in standard units).

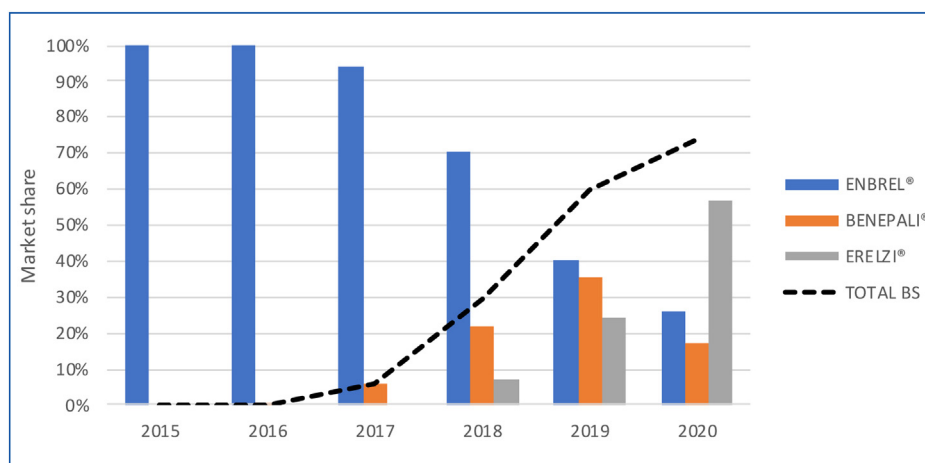


Figure 5. Annual market share of etanercept and biosimilars (percentage of total sales).

Discussion

This study shows that in the five years since biosimilars of anti-TNF agents first appeared on the market in France, the price reductions driven by the hospital market competition

generated total savings of 824 million Euro, compared to the costs that would have ensued if all these drugs had been purchased at the historical tariff fixed by the French government. Of these overall savings, approximately 499 million Euro were saved on the prices of biosimilars, and

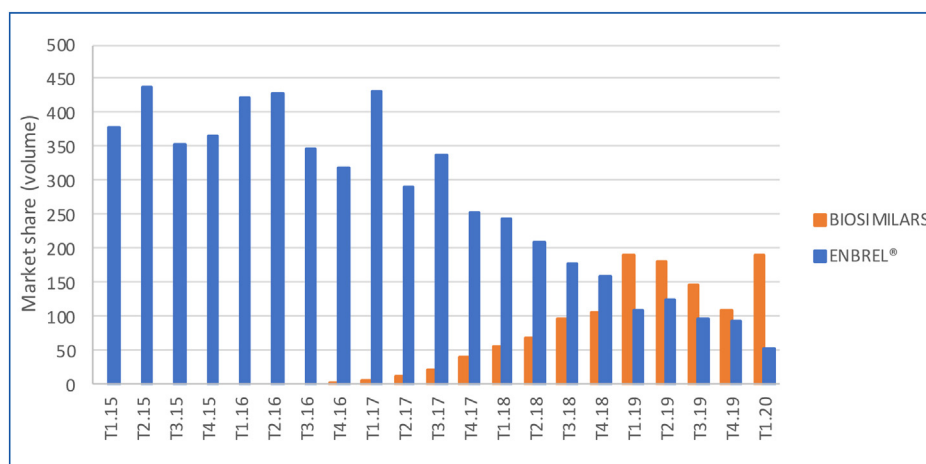


Figure 6. Market share by trimester for all etanercept biosimilars (sales volume in standard units).

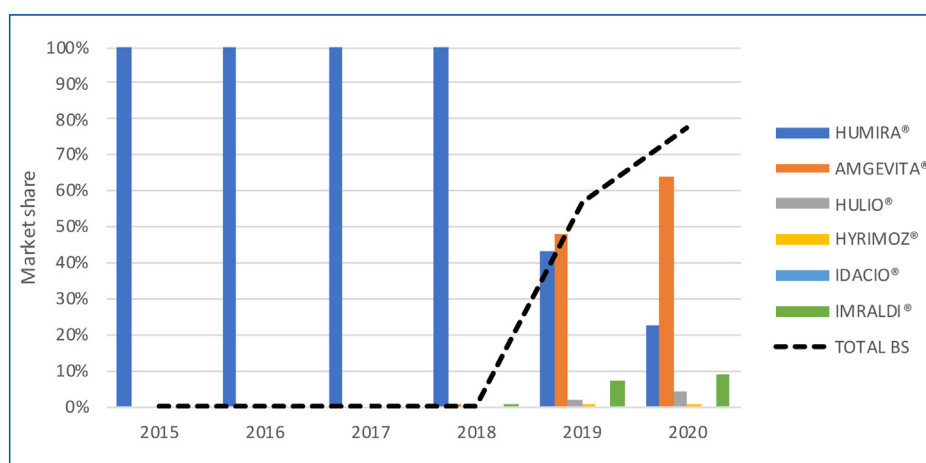


Figure 7. Annual market share of adalimumab and biosimilars (percentage of total sales).

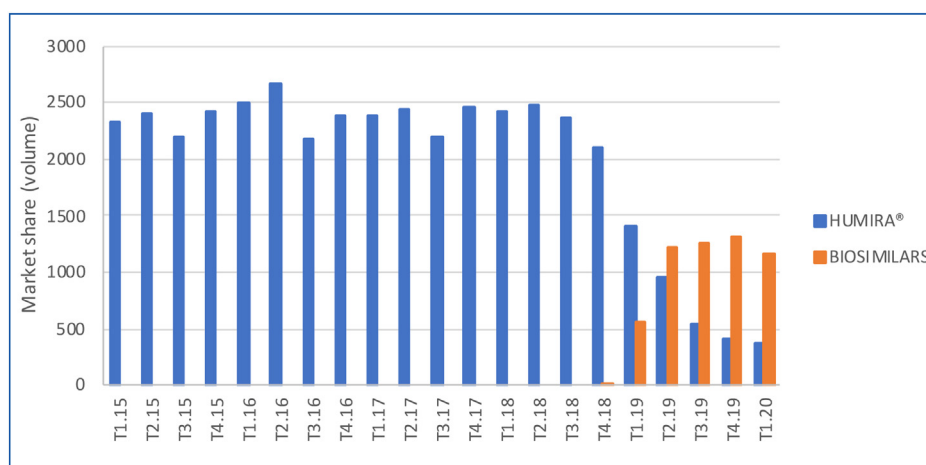


Figure 8. Market share by trimester for all adalimumab biosimilars (sales volume in standard units).

around 325 million on the originators. The calculations in our study were based on the national market of hospital sales for these drugs, as this made it possible to obtain exhaustive and representative information for the whole country regarding sales volumes, and the proportion of

market volume of each drug. In addition, we were able to identify trends in sales over the 5 years period studied. Overall, for all originators, we noted that sales began to decline with the introduction of biosimilars, and levelled off at approximately 25% of sales volumes, while the biosimilars

Table 1 Reduction in the total purchase price of all anti-TNF biosimilars as compared to the historical tariff, per year of sales (€).

	BS for HUMIRA®	BS for ENBREL®	BS for REMICADE®	Total BS
2015	0 €	0 €	4,355,892 €	4,355,892 €
2016	0 €	60 €	30,020,095 €	30,020,156 €
2017	0 €	1373 €	69,290,282 €	69,291,655 €
2018	4385 €	25,857 €	166,179,436 €	166,209,678 €
2019	3,064,347 €	72,346 €	225,820,336 €	228,957,029 €
Total	3,068,732 €	99,636 €	495,666,042 €	498,834,410 €

BS: biosimilars.

Table 2 Reduction in the total purchase price of all anti-TNF originators, as compared to the historical tariff, per year of sales (€).

	HUMIRA®	ENBREL®	REMICADE®	Total originators
2015	3,751,069 €	23,428 €	23,476,774 €	27,248,271 €
2016	3,489,847 €	58,357 €	44,535,027 €	48,083,231 €
2017	3,209,267 €	56,726 €	77,809,241 €	81,075,234 €
2018	3,548,059 €	–25,949 €	88,773,880 €	92,295,990 €
2019	1,634,210 €	24,140 €	74,334,874 €	75,993,224 €
Total	15,632,452 €	136,702 €	308,926,796 €	324,695,950 €

occupied an increasing share of the market, plateauing at around 75 to 80% of sales. We observed that for all anti-TNF agents used in the hospital setting in France, originators accounted for 97% of drugs in 2015, and 24% in 2020, while conversely, biosimilars accounted for 3% in 2015 and 76% in 2020.

Regarding the individual drugs, it can be seen that the rate of penetration of the biosimilars of infliximab has reached the target of 80% set by the French government [12]. Sales of all biosimilars increased, although Inflectra® remains the most common in the French hospitals, with 41% of market sales in 2020. For all infliximab biosimilars taken together, the sales curve intersected that of the originator 3 years after the launch of the first biosimilar, and a slight deceleration can be noted as the market share approaches the national target value (Fig. 2). This stabilisation raises questions, such as the incentives to prescribe biosimilars becoming less attractive, or perhaps it is a natural stability in the marketplace. Infliximab was the first anti-TNF agent for which a biosimilar was launched in France [13], and we can clearly see the expected drop in sales as the competitor biosimilars took over a part of the market share [14,15]. It should be noted that in our study, we only included drugs purchased for use in the hospital setting. Indeed, it is for use exclusively in the hospital setting due to its route of administration (by injection) [16]. This monopoly on the distributed makes it easier to have a comprehensive overview of the market, since there is no competition with private practice or community-based care settings, thus yielding a true and exhaustive picture of the penetration rate of infliximab. The other drugs included in our study are in large part administered in doctors' offices and distributed through community pharmacies, which is a limitation of this analysis. We noted

that the drop in sales of Remicade® intensified from 2017 onwards, while biosimilars for etanercept first appeared on the market in 2016 and those of adalimumab in 2018 [17,18]. This suggests that infliximab sales may be affected by the launch of biosimilars of other anti-TNF drugs.

Regarding etanercept, since the launch of the first biosimilars in 2016, sales of the original Enbrel® have declined steadily in the hospital setting, even accelerating from around mid-2017. The rate of penetration of etanercept biosimilars is also close to the national target of 80%, mainly drive by sales of Erelzi®, which increased dramatically from 2017 to 2020. Sales of Benepali® rose steadily until 2019, then dropped again, a trend that may be explained by the contemporaneous increase in sales of Erelzi®, which in 2020 accounted for 57% of market sales, versus only 36% in 2019 and 27% in 2020 for Benepali®. Taken together, total sales of all etanercept biosimilars remain lower than the total volume of sales of the originator Enbrel® in 2016, before the biosimilars were launched. The sales curves intercept around 2 years after the introduction of the biosimilars. However, it should be noted that the erratic sales pattern is illustrative of market instability. As previously seen for infliximab, the drop in hospital market share of Enbrel® is significant, and visible as early as one year after the introduction of the first biosimilar. The artificial slowing of sales in 2020 is likely due to a drop in hospital activity due to the COVID epidemic [19], particularly in medical and surgical specialties [20]. In parallel, there was an estimated 35% less economic activity (compared to normal, non-COVID conditions) in France for the same period [21]. During this time, many patients chose not to visit the hospital, including hospital ambulatory clinics, with the result that fewer physicians initiated anti-TNF treatment,

resulting in an overall drop in sales of both biosimilars and originators in 2020.

Finally, regarding adalimumab, as for the other anti-TNF agents, sales of the originator dropped markedly as soon as the biosimilars were introduced. However, it is noteworthy that that increasing market share accounted for by the biosimilars is driven mainly by only one biosimilar, namely Amgevita®. Although all biosimilars of adalimumab entered the market in late 2018, sales of Hulio® and Imraldi® have progressed very slowly, to plateau out at around 10%. Amgevita® alone accounted for almost 64% of sales in 2020. However, since 2019, there has been a clear deceleration of hospital sales of biosimilars. During the first few months when adalimumab biosimilars were available, there was a marked decrease in sales of the originator, while in parallel, biosimilar sales rose to reach 77% of the market share (again, close to the national target of 80%). We can see that the penetration rate rose quicker for adalimumab biosimilars than for previous anti-TNF biosimilars, as if the market was already familiar with the reaction prompted by the introduction of competitors. Indeed, it took 3 years for the sales curve of infliximab biosimilars to intercept the sales curve of the originator, where for etanercept, the interception occurred after 2 years, and for adalimumab, in less than one year. Both prescribers and patients appears to have become accustomed to the availability of biosimilars and the consequences this has on the market [22], i.e. the drug is more rapidly available for prescription, more rapidly recommended with confidence by physicians, and more rapidly accepted by patients.

We observed that Simponi® and Cimzia®, two anti-TNFs for which there are currently no biosimilars, have both shown declining sales since 2017. This suggests that there may be some effect of competition between categories of anti-TNF agents, even though there are limited possibilities for interchangeability between these drugs in the French healthcare system for regulatory and medical reasons [23,24].

To evaluate the financial gains, from the point of view of the national insurer, generated by the introduction of biosimilars on the market in France, it is challenging to choose the correct price to use for the calculations. Indeed, group procurement and/or tender negotiations mean that the final purchase price of drugs may differ from the original price advertised. We chose to use the historical tariff for the originator fixed by the French authorities prior to the introduction of competitor biosimilars, as recommended by Le Pen et al. [25]. As a reminder, our study only shows savings in the hospital sector; we did not study the ambulatory system. As etanercept and adalimumab are mainly sold in the community, the savings are minimized here. For infliximab, there was an increase in the savings due to the likely lower price of the biosimilars coupled with increasing sales. Interestingly, for etanercept, the pattern of savings was somewhat erratic, and in 2018, there was even a net loss, with the price paid for etanercept actually exceeding the regulatory tariff. Savings derived from adalimumab biosimilars increased rapidly, exceeding more than 3 million Euro within a year. Clearly, our study shows that overall, the introduction of biosimilars drove overall prices and tariffs down, generating substantial savings for healthcare establishments procuring this category of drugs. These

results are comparable to previous reports from Europe [26,27].

Conclusion

Since the launch of the first anti-TNF biosimilars in France, the penetration rate of biosimilars has increased steadily, from less than 5% in 2015 (for all anti-TNF biosimilars) to over 75% in 2020 in the hospitals. This study shows that the hospital market share of the originators has stabilised at around 25%. Biosimilars of infliximab, which were the first to be introduced, took three years to achieve the same hospital market share as the originator, whereas for the biosimilars of etanercept and adalimumab, released later, they achieved a similar market share more quickly. This suggests that the market had begun to adapt to the presence of biosimilars, with more rapid availability for prescription, greater consumer trust, and/or acceptance by providers and patients. Our study also shows that sales the two originator drugs that have no available biosimilars are declining. Therefore, there appears to be some competition among the anti-TNF agents themselves, with reduced sales of those for which biosimilars are not available, in favour of those with available biosimilars.

The cost savings generated by this market competition amount to over 820 million Euro over the last 5 years in the hospital setting. The biosimilar market depends greatly on the involvement of prescribers, consumers, suppliers and purchasers. The public powers also play a key mediating role in the market competition, via legal regulation of regulations regarding interchangeability of drugs, substitution of originators with biosimilars, financial incentives, and prescription indications. Anti-TNF agents are also increasingly prescribed outside the hospital setting, and therefore, close collaboration between hospitals and community-based distributors is essential to ensure optimal marketing conditions. Improved penetration of these expensive drugs will be to the benefit of our patients.

Disclosure of interest

The authors declare that they have no competing interest.

References

- [1] Farhat F, Torres A, Park W, Lopes G, de L, Mudar R, et al. The concept of biosimilars: from characterization to evolution – a narrative review. *Oncologist* 2018;23:346–52.
- [2] Lis K, Kuzawińska O, Bałkowiec-Iskra E. Tumor necrosis factor inhibitors—state of knowledge. *Arch Med Sci* 2014;10:1175–85.
- [3] McKeage K. A review of CT-P13: an infliximab biosimilar. *Bio-Drugs* 2014;28:313–21.
- [4] Blackstone EA, Joseph PF. The economics of biosimilars. *Am Health Drug Benefits* 2013;6:469–78.
- [5] GaBi. Patent expiry dates for best-selling biologicals. *Generics Biosimilars Initiat J* 2015;4:178–9, <http://dx.doi.org/10.5639/gabij.2015.0404.040>.
- [6] Kim Y, Kwon HY, Godman B, Moorkens E, Simoens S, Bae S. Uptake of biosimilar infliximab in the UK, France, Japan, and

- Korea: budget savings or market expansion across countries? *Front Pharmacol* 2020;11:970.
- [7] Ministère des Solidarités et de la Santé. In: Le programme PHARE. Internet; 2021 [Accessed 10 December 2021] <https://solidarites-sante.gouv.fr/professionnels/gerer-un-etablissement-de-sante-medico-social/performance-des-etablissements-de-sante/phare-11061/article/le-programme-phare>.
- [8] Boudemaghe T, Belhadj I. Data resource profile: the French National Uniform Hospital Discharge Data Set Database (PMSI). *Int J Epidemiol* 2017;46 [392–392d].
- [9] MSD. In: Etude Remicade. Internet; 2017 [Accessed 10 December 2021 (11 pp.)] <https://www.apmnews.com/documents/201702071023100.MSD.EtudeRemicade1.pdf>.
- [10] BdM.IT. Recherche par code. Internet; 2021 [Accessed 10 December 2021] http://www.codage.ext.cnamts.fr/codif/bdm.it/index.php?p_site=AMELI.
- [11] Berreur B, Guerin F, Christophe B, Limido G, Paubel P. Évaluation de l'impact économique des biosimilaires d'étanercept et d'adalimumab à l'échelle des établissements adhérents au groupement de commandes PharmAlp'Ain. *Ann Pharm Fr* 2018;76:57–63.
- [12] Ministère des Solidarité et de la Santé. In: Dossier SNS. Internet; 2017 [Accessed 10 December 2021 [53 pp.]] https://solidarites-sante.gouv.fr/IMG/pdf/dossier_sns_2017_vdef.pdf.
- [13] Park SH, Park JC, Lukas M, Kolar M, Loftus EV. Biosimilars: concept, current status, and future perspectives in inflammatory bowel diseases. *Intest Res* 2020;18:34–44.
- [14] Rumore MM, Randy Vogenberg F. Biosimilars: still not quite ready for prime time. *Pharm Ther* 2016;41:366–75.
- [15] Kabir ER, Moreino SS, Sharif Siam MK. The breakthrough of biosimilars: a twist in the narrative of biological therapy. *Biomolecules* 2019;9:410 [Accessed 10 December 2021] <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6770099/>.
- [16] EMA. European Medicines Agency. In: EPAR remicade. summary for the public. Internet; 2020 [Accessed 10 december 2021 (65 pp.)] https://www.ema.europa.eu/documents/product-information/remicade-epar-product-information_fr.pdf.
- [17] Moorkens E, Vulto AG, Huys I, Dylst P, Godman B, Keuerleber S, et al. Policies for biosimilar uptake in Europe: an overview. *PLoS One* 2017;12:e0190147.
- [18] Tyer D. In: Fourth Humira biosimilar set for EU approval. Internet; 2018 [Accessed 10 December 2021] <https://pharmaphorum.com/news/humira-biosimilar-eu-sandoz-chmp/>.
- [19] Barro K, Malone A, Mokede A, Chevance C. Gestion de l'épidémie de la COVID-19 par les établissements publics de santé – analyse de la Fédération hospitalière de France. *J Chir Viscerale* 2020;157:S20–4.
- [20] Le Quotidien du Médecin. In: Chute des passages aux urgences, soins «non Covid» en Berne : les recos de l'AP-HP pour baliser la reprise d'activité. Internet; 2020 [Accessed 10 December 2021] <https://www.lequotidiendumedecin.fr/hopital/politique-hospitaliere/chute-des-passages-aux-urgences-soins-non-covid-en-berne-les-recos-de-lap-hp-pour-baliser-la-reprise>.
- [21] INSEE. In: Point de conjoncture du 26 mars 2020. Internet; 2020 [Accessed 10 December 2021] <https://www.insee.fr/fr/statistiques/4473294?sommaire=4473296>.
- [22] Kaida-Yip F, Deshpande K, Saran T, Vyas D. Biosimilars: review of current applications, obstacles, and their future in medicine. *World J Clin Cases* 2018;6:161–6.
- [23] Biosimilar automatic substitution in the EU5: current state & future outlook. Internet; 2019 [Accessed 10 December 2021] <https://www.biosimilardevelopment.com/doc/biosimilar-automatic-substitution-in-the-eu-current-state-future-outlook-0001>.
- [24] Gabay M. Biosimilar substitution laws. *Hosp Pharm* 2017;52:544–5.
- [25] APMnews. In: L'arrivée des biosimilaires de l'infliximab a entraîné une économie de 65 millions d'euros (étude MSD). Internet; 2017 [Accessed 10 December 2021] <https://www.apmnews.com/freestory/0/299019/l-arrivee-des-biosimilaires-de-l-infliximab-a-entraîne-une-economie-de-65-millions-d-euros-%28etude-msd%29>.
- [26] ProBiosimilars. In: Biosimilars in Zahlen. Internet; 2019 [Accessed 10 December 2021] <https://probiosimilars.de/>.
- [27] IQVIA. In: Advancing biosimilar sustainability in Europe. Internet; 2018 [Accessed 10 December 2021 (42 pp.)] https://www.biosimilars-nederland.nl/wp-content/uploads/2018/10/okt_2018_IQVIA_Pfizer_Advancing-Biosimilar-Sustainability-in-Europe.pdf.