

Funding Innovation Thanks to Anti-TNF- α Biosimilars Uptake: The Economic Impact in Italy

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ABSTRACT

INTRODUCTION: Anti-TNF- α biosimilars (ATB) hold the promise of reducing costs leading in improving access to biological therapies. There is limited insight into how the savings generated by biosimilars may translate into patient benefit in other disease areas.

AIMS: To assess the economic savings for Italian National Health System (NHS) due to the expansion of ATB market, together with a reduction in their price and to illustrate how this potential savings can be used by NHS to fund orphan drugs.

METHODS: Trend of IMS Health monthly sell-in units (August 2016-December 2019) were used to estimate the current biologic and biosimilar market for rheumatic and inflammatory bowel disease in Italy and its evolution up to 2022. The scenario for 2019-2020 was compared with the future evolution (2021-2022) assuming an increasing uptake of biosimilars in the Italian market. Finally, it was estimated how these savings can potentially fund the treatment of orphan drugs, without increasing the Italian NHS budget.

RESULTS: Italian biologic and biosimilar market remains stable in the next years (about 4 million units both in the current scenario and in the future evolution market) with a slight decreasing of less than 2%. However, according to our assumptions, ATB market is expected to increase of about 33% in the next two years, covering 67% of the total Italian market, mostly due to biosimilar etanercept. Total savings due to biosimilars increases from € 96 million in 2019 to € 161 million in 2022 corresponding to a mean annual savings of about € 130 million. Such savings would permit funding 17.4% of the actual orphan drugs market corresponding to 2,600-4,800 new patients.

CONCLUSIONS: The introduction of biosimilars in a range of rheumatic, dermatological and inflammatory bowel disease can be an opportunity to increase patient access to innovative treatments. Potential savings due to biosimilars uptake could lead to a re-allocation of economic resources to fund innovative therapies.

Keywords

Anti-TNF- α ; Biosimilar; Savings; Funding innovation; Orphan drugs

INTRODUCTION

According to the European Medicines Agency (EMA), a biosimilar drug is a version of an already registered original product, the reference product (RP), whose qualitative characteristics, biological activity, and safety and efficacy profiles have been shown to be similar to those of the RP by means of comparability studies [1]. The first-generation biologics were launched in the early 1980s, and this innovative class of drugs is now one of the fastest growing sectors of the pharmaceutical industry [2].

Biosimilars and reference drugs cannot be considered to be totally equivalent since, even after patent expiration, the reference agent manufacturer is not obliged to reveal details of its production practice [3]. Furthermore, biologicals are produced using living cells that have inherent variability, hence they are complex mixtures of closely related molecules that cannot be copied exactly. Similarity to the RP is demonstrated in a comprehensive biosimilarity exercise including comparative physicochemical characterization, biological activity assessment, pharmacokinetic studies and clinical trials. A biosimilar may be approved by the EMA based on clinical data in a sensitive indication; efficacy and safety data may be extrapolated to other indications approved for the RP, meaning that a biosimilar agent may not have been clinically tested in each indication [1,4].

The EMA's assessment of biosimilar medicines is done exclusively for the purpose of marketing authorization; Any decision to transition a patient from RP to biosimilar should

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be made by qualified healthcare personnel on the basis of national or local guidelines [5]. The Italian Medicines Agency (*Agenzia Italiana del Farmaco*, AIFA) considers biosimilars and RP as interchangeable products (i.e. they are assumed to have the same effectiveness and they can be used for the same disease), both for naïve patients and for patients already under treatment, but recommends that the decision to prescribe a biosimilar drug be made exclusively by the specialist managing the specific disease [6]. Clinicians must thus be aware of the availability of a biosimilar and they must be free to make informed treatment choices with their patients.

As of the end of 2019, there are ten approved anti-TNF- α biosimilar (ATB) medicines that are available on the Italian market. Three biosimilar versions of infliximab, one of which is available under two brand names, Inflectra[®] and Remsima[®] (manufactured by Celltrion Inc.), one under the brand name Flixabi[®] (manufactured by Biogen), and one under the brand name Zessly[®] (manufactured by Sandoz). All biosimilars are approved for use in rheumatoid arthritis (RA), adult and pediatric Crohn's disease (CD), adult and pediatric ulcerative colitis (UC), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and psoriasis [7-9]. Two etanercept biosimilars are available under the brand name Benepali[®] (manufactured by Biogen) and Erelzi[®] (manufactured by Sandoz). Both biosimilars are approved for the treatment of adults with RA, PsA, axial spondyloarthritis (AS and non-radiographic axial spondyloarthritis), juvenile idiopathic arthritis (JIA), and plaque psoriasis including pediatric in patients weighing >62.5 kg [10,11]. Finally, five adalimumab biosimilars have been approved in Europe for use in mostly the same indications as reference adalimumab including rheumatology, gastroenterology and dermatology: Amgevita[®] (Amgen), Imraldi[®] (Biogen), Hyrimoz[®] (Sandoz), Hulio[®] (Mylan) and Idacio[®] (Fresenius Kabi). Amgevita[®] and Imraldi[®] are reimbursed in Italy since the end of 2018, Hyrimoz and Hulio during 2019, while Idacio has not yet been reimbursed [12-16].

Switching between a RP and a ATB is relevant for clinical practice, but also for pharmacoeconomic considerations; the arrival of ATB is expected to provide cost savings and expand access to other medicinal products [17]. While there is continued debate about interchangeability of biosimilars, recent systematic reviews concluded that there was no increased risk of immunogenicity or adverse events, and no significant loss of efficacy or effectiveness was observed [18-21]. According to another comprehensive systematic review of published evidence summarizing all of the available studies (up to September 2015) on biosimilars across multiple therapeutic areas and at all stages of development [22], both Inflectra[®] and Flixabi[®] are reported to have shown evidence of similarity with their originator, based on results of clinical studies as well as a large number of patients described in real-world studies.

The NOR-SWITCH study [23], involved 481 adult patients with a diagnosis of RA, AS, PsA, CD, UC or plaque psoriasis, on stable treatment with the originator infliximab (Remicade[®]) for at least 6 months prior to randomization; patients were randomized to continue RP, or switch to CT-P13 (Inflectra[®]/Remsima[®]) and followed for 52 weeks, clinical outcomes were comparable between the two arms. Furthermore real-world studies [24,25] and results from PLANETAS and PLANETRA extension studies [26,27], showed analogous results for infliximab biosimilars for patients with RA and AS.

In an open-label extension to the phase III, 52-week randomized study that compared etanercept biosimilar SB4 (Benepali[®]) with reference etanercept (Enbrel[®]) for the treatment of RA, 126 patients continued to receive ATB and 119 patients switched from reference etanercept to SB4 for a further 48 weeks [28]. At the end of this open-label treatment period, the efficacy, safety and immunogenicity profiles were comparable for both groups. A real-world study, evaluating the safety and effectiveness of switching from Enbrel[®] to Benepali[®] in patients with RA, PsA or axial spondyloarthritis [29] reported no clinically relevant difference in disease activity at 3 months post-switch, nor in that observed in the 3 months prior to switch.

Inotai et al. [30] conducted a systematic literature review to assess the clinical consequences of switching from originator biologics to biosimilar. The analysis identified 58 papers: 41 non-empirical papers (15 not disease specific, 9 on IBD, 5 on RA, 5 on chronic kidney disease and anemia, and 3 focused on malignancies), 5 systematic reviews (3 on infliximab and related ATB in inflammatory diseases, and 2 no drug-specific) and 12 original clinical studies (4 on IBD, 4 on chronic kidney disease and anemia, 2 on RA, and 1 on AS). None of the 5 systematic reviews concluded that there were safety or efficacy concerns in switching from the original biologics to biosimilars, and 3 of them also explicitly stated that switching from an original biologic to a biosimilar drug was not associated with increased safety risk, while effectiveness was maintained. Also, two trials explicitly reported no adverse events or loss of efficacy related to switching, whereas 10 trials concluded that, overall, there was no increased

risk of immunogenicity or adverse events, while no statistically significant loss of efficacy was observed. In conclusion, the opinion of the authors of this review is that the fear against switching to biosimilars is not supported by empirical evidence.

The last position paper on ATB published in Italy by AIFA [6], confirmed this statement and highlighted the importance of ATB in improving the accessibility to biological therapies due to high cost of RP. Use of biosimilars in the EU5 countries alone stands to offer savings of more than € 10 billion between 2016 and 2020 [31]. Expanding ATB market could finance other therapeutic area, partially or completely.

Aims of this paper are

- To assess the economic savings for Italian National Health System (NHS) due to the expansion of ATB market, together with a reduction in their price,
- To illustrate how this potential savings can be used by NHS to fund orphan drugs.

METHODS

The anti-TNF- α market evolution in Italy was estimated using monthly sell-in units between January to December 2019 [32], applying an annual increasing rate estimated from August 2018 to December 2019 and supposed constant up to 2022 (Table I). Only formulations available both as RP and ATB were considered in the analysis, e.g. Enbrel[®] (etanercept) 10 mg is excluded from the analysis since not available as biosimilar. Annual ATB uptake was assumed almost linear from 2019 to 2022 for all treatments considered in the analysis according to Biogen internal analysis (Figure 1). Current market was defined as biennium 2019-2020, future market as biennium 2021-2022.

Only drug acquisition cost was considered in the analysis since, as described in the introduction, no evidence of lower efficacy or increased toxicity with or after switching to an ATB were detected in clinical trials or real-world studies. The ex-factory reimbursement price [33] charged to NHS, net of price reductions stipulated by law and by tender procedures [34] was considered for all available products (Table II).

RP/ATB	Actual Market (2019 sell-in units)	Annual increasing (2020-2022)
Adalimumab (40 mg syringes/pens)	734,853	+7.1%
Etanercept (25 mg syringes/pens)	114,687	-4.3%
Etanercept (50 mg syringes/pens)	812,085	-9.1%
Infliximab (100 mg vials)	277,489	-2.5%

Table I. Italian biologic and ATB market for 2019 (number of unit sold between January and December) and 2020-2022 evolution
ATB = anti-TNF- α biosimilars; RP = reference products

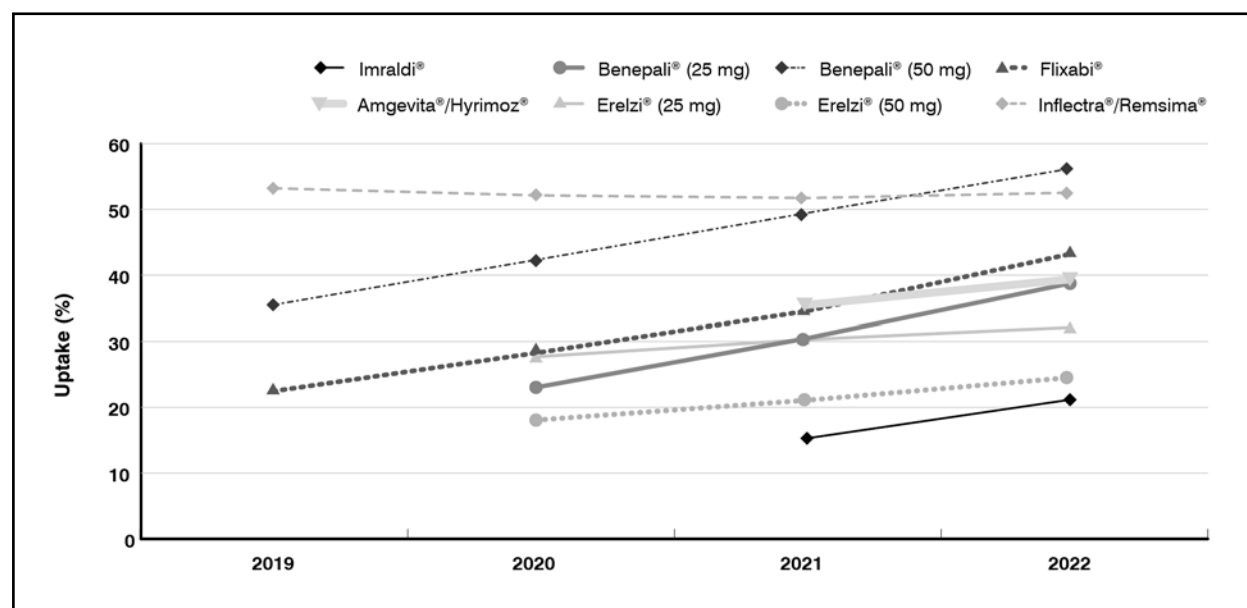


Figure 1. Italian anti-TNF- α biosimilars uptake for 2019-2022

Drug	Branded	Pharmaceutical form	Ex-factory price (€)
Adalimumab	Humira®	40 mg solution for injection in pre-filled syringe	482.19
	Imraldi®		342,35
	Amgevita®		342,35
	Hyrimoz®		342,35
Etanercept	Enbrel®	25 mg solution for injection in pre-filled syringe	115.13
		50 mg solution for injection in pre-filled syringe	230.26
	Benepali®	25 mg solution for injection in pre-filled syringe	78.52
		50 mg solution for injection in pre-filled syringe	157.25
	Erelzi®	25 mg solution for injection in pre-filled syringe	74.84
		50 mg solution for injection in pre-filled syringe	149.67
Infliximab	Remicade®	100 mg powder for concentrate for solution for infusion	463.53
	Flixabi®		386.28
	Inflectra®		386.28
	Remsima®		386.28
	Zessly®		386.28

Table II. Ex-factory prices in Italy

The savings generated by all ATB available in the Italian market was calculated as the difference between the actual market (Table I) and the hypothetical market with all ATB replaced by the corresponding RP. Finally, a simulation estimated how these savings can potentially fund innovative treatments for orphan diseases.

The current model of attribution of the degree of innovation defined by AIFA [35] is based on three domains: the therapeutic need (TN), the added therapeutic value (ATV), and the quality of the evidence (QE) carried to support the drug. The first two factors are graded in five levels (maximum, important, moderate, poor, absent), the third factor is evaluated as high, moderate, low, very low. A drug is declared innovative if QE is “high” and both TN and ATV are valued “maximum” or “important”. For rare diseases, a greater difficulty in conducting clinical trials is acknowledged, which is why it is possible to consider innovative a drug with low QE, provided TN and ATV are high [35].

All orphan drugs, that were granted the innovative status up to end of January 2019 [36] were included in the analysis (Table III).

The economic impact of each drug was calculated by estimating the annual number of new patients that should be treated with each drug and the cost of the first year of treatment [37-49]. According to the savings produced by ATB uptake, a percentage of this impact could be funded, i.e. a fraction of patients could be treated without increasing the NHS budget. Two potential allocation algorithms, depending on the policy preferred by the decision-makers, were considered:

- Cost allocation proportional to number of potential new patients; i.e. the higher the disease incidence, the higher the fraction of resources dedicated to that disease;
- Optimal allocation calculated in order to globally maximize the fraction of patients (across diseases) potentially treated without increasing NHS expenditures.

RESULTS

Evolution of the Italian biologic and biosimilar market due to increasing use of ATB is illustrated in Figure 2. Italian market remains basically stable in the next years: 3.85 million units in the current market (2019-2020) compared with 3.80 million in the future evolution market (2021-2022), corresponding to a slight decreasing of about 1.4% (Table IV). However, according to our assumptions, ATB market is expected to increase of 33% up to 2022, covering 67% of the total Italian market, mostly due to adalimumab (38%) and etanercept (44%) biosimilars uptake.

The economic impact of ATB uptake in Italy is detailed in Table V. Total savings due to ATB increases from € 96.2 million in 2019 to € 161.5 million in 2022 (mean annual savings € 128.8 million). Comparing 2019-2020 market with future evolution in the total savings amount to about € 84 million.

The number of new patients potentially treated for selected orphan diseases ranges between 15 for autologous CD34+ cells to almost 9,700 for cenegermin in Italy (Table VI).

Drug	Therapeutic indication	Pharmaceutical form	Ex-factory price ^a (€)	Posology	Unit per year ^b	Annual incidence	Note
Daratumumab (Darzalex [®])	In combination with dexamethasone plus either lenalidomide or bortezomib for the treatment of multiple myeloma in patients who have received at least one treatment previously	20 mg/ml concentrate for solution for infusion (20 ml vial)	1,700.37	Dose 16 mg/kg In combination with lenalidomide: weeks 1-8 (weekly), weeks 9-24 (every 2 weeks), week 25 until progression (every 4 weeks) In combination with bortezomib: weeks 1-9 (weekly), weeks 10-24 (every 3 weeks), week 25 until progression (every 4 weeks)	60.16 vials (with lenalidomide), 49.20 vials (with bortezomib) ^c	8.61 every 100,000 inhabitants [37]	Treatment persistence was calculated according to PFS at one year from POLLUX [38] and CASTOR [39] trials, in combination with lenalidomide and bortezomib, respectively [41]
Cenegeim (Oxervate [®])	Treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) neurotrophic keratitis in adults	20 mcg/ml eye drops (weekly carton)	2,125	1 drop 6 times a day at 2 hourly intervals for 8 weeks	8 cartons	16 every 100,000 inhabitants [40]	
Letermovir (Prevymis [®])	Prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients of an allogeneic hematopoietic stem cell transplant (HSCT)	480 mg, 28 film-coated tablets	8,400	1 tablet every day through 100 days post-transplant	3.57 cartons	301-400 allogeneic HSCT every 10 million inhabitants [42] of which 27% with CMV reactivation [43]	
Dinutuximab beta (Qarziba [®])	Treatment of high-risk neuroblastoma in patients aged 12 months and above, previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation	20 mg concentrate for infusion	8,600	100 mg/m ² per 5 cycles (each cycle comprising 35 days)	17.39 vials	130-140 [44] new cases every year	Mean BSA 0.719 for pediatric population between 1-10 years [45]. Treatment persistence was calculated according to 5-years survival [46]
Midostaurina (Rydapt [®])	In combination with daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, for adult patients with newly diagnosed acute myeloid leukemia FLT3 mutation-positive	25 mg, 112 soft capsules	13,348	50 mg twice daily on days 8-21 of induction and maximum 4 consolidation chemotherapy cycles (28-day cycles). If there was definitive evidence of clinically significant residual leukemia, a second cycle of induction therapy was administered	1.61 cartons	4.79 every 100,000 inhabitants [47] of which 8% candidate to chemotherapy [48]	Treatment persistence calculated according to RATIFY trial [48]
Nusinersen (Spinraza [®])	Treatment of 5q Spinal Muscular Atrophy	12 mg solution for injection	70,000	4 loading doses on days 1, 15, 29 and 64 followed by maintenance doses every 4 months (days 183 and 302)	4.32 vials ^d	1/6,000 born alive every year [49]	
Autologous cd34+ cells (Strimvelis [®])	Treatment of ADA-SCID	Dispersion for infusion bag	594,000	1 bag <i>una tantum</i>	1 bag	15 ^e	

Table III. Innovative treatments for rare disease

ADA-SCID = severe combined immunodeficiency due to adenosine deaminase deficiency; BSA = body surface area; PFS = progression free survival

^a Ex-factory prices fixed by law as the 66.65% of retail price, at net of VAT 10%; mandatory discount (5% + 5% reduction) were also applied for daratumumab, latermovir, dinutuximab beta (not required for the other drugs)

^b In case of posology related to disease progression (e.g. oncology drugs), results from most recent clinical trials were used to estimate annual treatment cost

^c Assuming 70 kg mean weight

^d Based on European agreements all ADA-SCID cases will be treated at IRCCS San Raffaele Hospital, Milan (Italy) [GSK communication, available at <http://www.telethon.it/news-video/news/via-libera-in-europa-a-stirmvelis-per-il-trattamento-della-malattia-genetica-rara-ada-scid>]

^e Biogen data on file

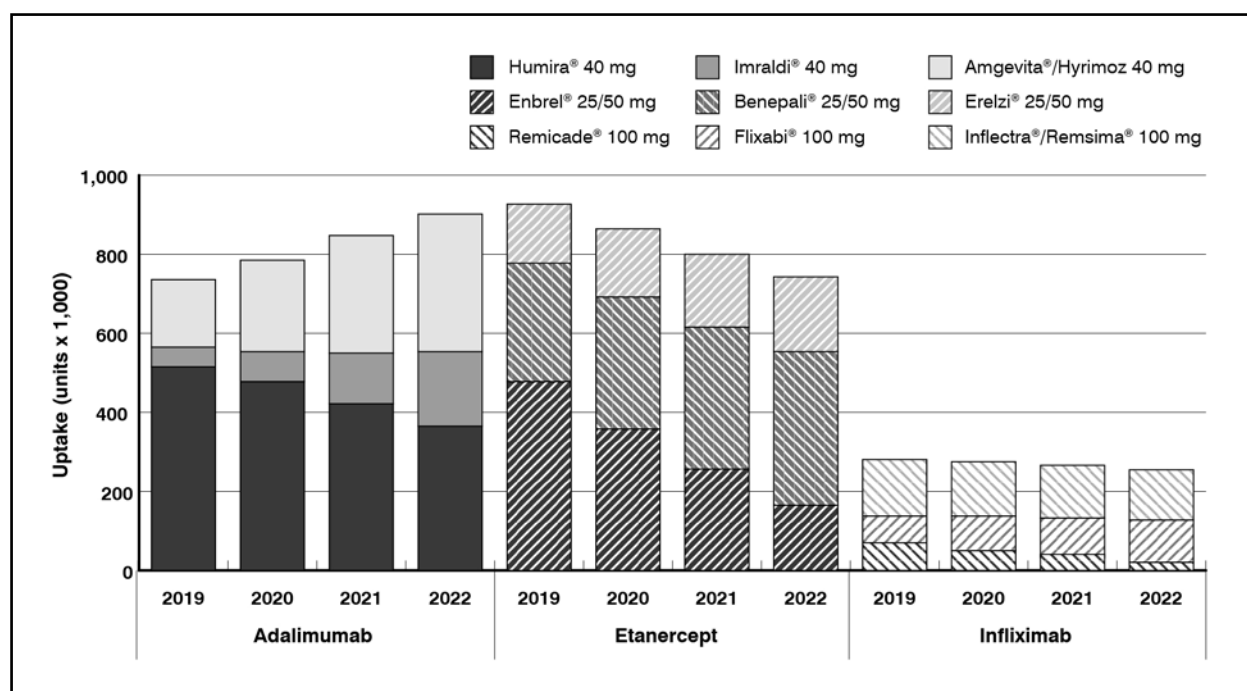


Figure 2. Resulting Italian market for 2019-2022

	2019-2020	2021-2022
Italian market (total biologic and biosimilar sell-in units)	3,854,311	3,801,377
ATB market, units (%)	1,914,379 (50%)	2,554,607 (67%)
Adalimumab, units (%)	535,192 (28%)	962,521 (38%)
Etanercept, units (%)	954,678 (50%)	1,123,802 (44%)
Infliximab, units (%)	424,509 (22%)	468,284 (18%)

Table IV. Comparison between 2019-2020 Italian market and evolution estimated for 2021-2022

 ATB = anti-TNF- α biosimilars

	Current market		Future market evolution	
	2019	2020	2021	2022
Annual drug cost – market without ATB (€)	612,683,002	617,038,368	624,426,997	634,832,963
Annual drug cost – market with ATB (€)	516,465,296	497,648,431	486,202,672	473,365,303
Savings due to ATB (€)	96,217,706	119,389,937	138,224,325	161,467,660
Mean annual saving due to ATB (€)		128,824,907		
Increase in total savings due to ATB – future vs current market (€)		84,084,342		

Table V. Economic impact of ATB market increasing in Italy

 ATB: anti-TNF- α biosimilars

Different allocation strategies gave different consequences on the number of patients treated without impacting NHS expenditures: with strategy 1 (cost allocation proportional to disease incidence), 4,837 new patients can be funded by ATB saving where the proportions of patients treated for each disease result very different (Table VI and Figure 3); with strategy 2 (optimal allocation) instead, the fraction of patients treated without impacting NHS results around 14-18%, but the total number of patients decreases down to 2,640 (Table VI and Figure 3).

DISCUSSION

In this analysis we estimated the total pharmaceutical impact of ATB in the 2019 Italian market and its evolution in the next three years due to increasing ATB. Biosimilars market

Drug	New patients (n/year)	Therapy cost (€/year)	Strategy 1: Cost allocation proportional to disease incidence		Strategy 2: Optimal allocation ^a	
			Savings allocation (%)	New patients potentially treated (n)	Savings allocation (%)	New patients potentially treated (n)
Daratumumab (Darzalex [®])	5,197	92,982	32.7	453	69.2	959
Cenegermim (Oxervate [®])	9,658	18,957	60.8	4,132	22.5	1,532
Letermovir (Prevymis [®])	574	30,000	3.6	155	1.9	83
Dinutuximab beta (Qarziba [®])	135	149,515	0.8	7	2.3	20
Midostaurina (Rydapt [®])	231	21,485	1.5	87	0.6	33
Nusinersen (Spinraza [®])	73	302,400	0.5	2	2.5	11
Autologous cd34+ cells (Strimvelis [®])	15	594,000	0.1	<1	1.0	2
Total	15,883	739,677,228	100	4,837	100	2,640
Mean annual savings due to ATB (€/year)				128,824,907		

Table VI. New patients potentially treated without impact on NHS due to ATB savings^a Optimal allocation was defined as the resources allocation that permits to fund the maximal percentage of patients globally (i.e. for all diseases considered in the analysis)

ATB = anti-TNF- α biosimilars

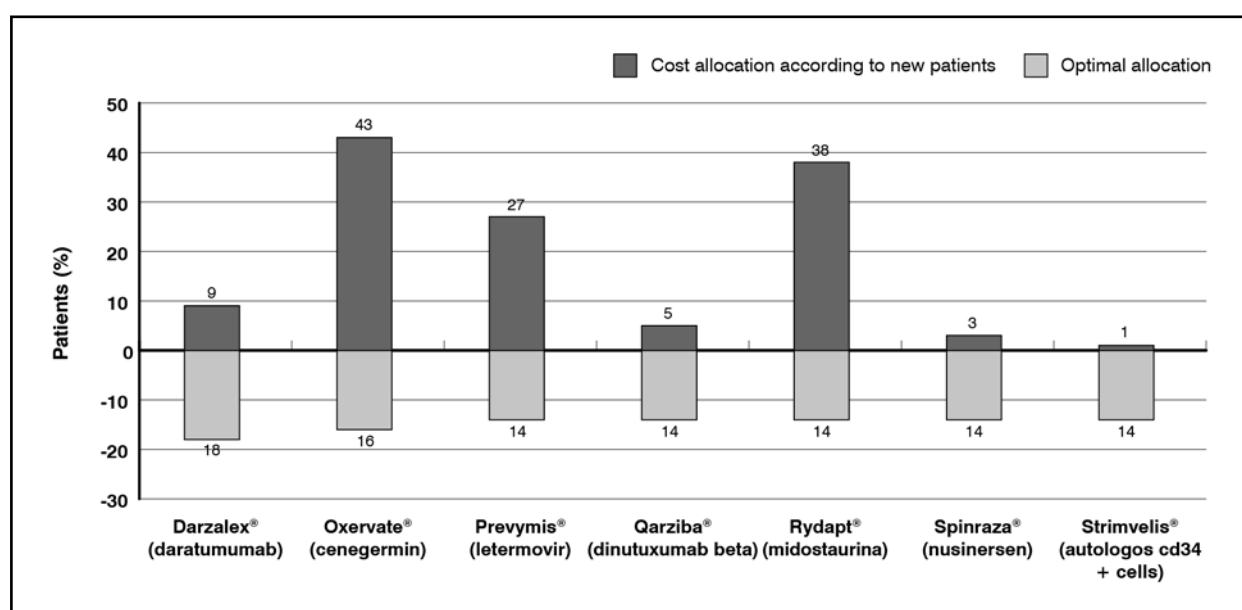


Figure 3. Percentage of new patients potentially treated without impact on NHS due to ATB savings (comparison between allocation proportional to patients and optimal allocation)

grows, from 50% (current market 2019-2020) to 67% (future market 2021-2022), produces an increasing trend in the annual savings from about € 96 million in 2019 up to € 161 million in 2022. In line with the AIFA position, this favorable impact on NHS expenditures could be directed to fund innovation, in particular to fund more expensive therapeutic areas, such as orphan drugs gained innovative status.

Our estimate may be too conservative since the biosimilar market is rapidly evolving, both due to increase in biosimilars price discounting and biosimilars uptake; this evolution could lead to greater savings.

The cost analysis by Mulcahy et al. [50] for US estimated that the total biosimilar market (including all available biologic classes) is expected to save approximately \$ 44 billion from 2014 to 2024; this savings is due mainly to ATB that account for 21% of the estimated savings.

Jha et al. [51] estimated the impact of Remsima[®] for the treatment of autoimmune diseases in five European Countries (Germany, UK, Italy, The Netherlands and Belgium). Under the assumption that the list price of Remsima[®] might be between 10% and 30% lower than the current list price of Remicade[®], ATB uptake resulted to be associated with considerable drug

cost savings for the healthcare payer for all countries; in Italy the savings ranged between € 4.6 to € 13.8 Million during the first year after launch.

ATB savings could be used to fund other therapeutic areas. In this analysis, such savings was converted in new patients potentially treated without impact on NHS. Orphan drugs were chosen since the correspondent disease costs are significantly high; according to epidemiology and drugs posology, this impact is estimated in about 740 million per year (Table VI). The annual savings due to ATB uptake could finance 17.4% of this cost; depending on the decision of the policy makers, favoring equal access across diseases, or rather assigning freed resources proportionally to their incidence in the population, this corresponds to about 2,600-4,800 new patients affected by orphan diseases treated with innovative drugs, without increasing overall NHS expenditures.

CONCLUSION

The introduction of biosimilars in a range of rheumatic, dermatological and inflammatory bowel disease can be an opportunity to increase patient access to innovative treatments. Potential savings due to biosimilars uptake could lead to a re-allocation of economic resources to fund innovative therapies.

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Conflicts of interest

LP is co-owner and employee of AdRes, which has received project funding from Biogen SRL Italy. MP is employee of AdRes. This study and the article were funded by Biogen Italy.

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