Article

Budget impact analysis of rituximab biosimilar in Italy from the hospital and payer perspectives

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Carla Rognoni[1], Arianna Bertolani[1] and Claudio Jommi[1,2]

Abstract

Introduction: This article aims at investigating the 5-year budget impact of rituximab biosimilars in Italy.

Methods: A budget impact analysis model was developed in accordance with the International Society For Pharmacoeconomics and Outcomes Research recommendations. Drug acquisition and drug administration costs were considered since the risk/benefit profile of biosimilars and the originator was assumed to be overlapping. The perspectives of hospitals and payers were used. Input data were retrieved from the literature and validated/integrated by an expert panel of seven clinicians from various Italian regions. A dynamic incidence-based approach was used.

Results: From the hospital perspective, adopting a rituximab biosimilar would produce savings of €79.2 and €153.6 million over 3 and 5 years, respectively. The results are very similar if the payer perspective is considered, with a cumulated savings of about €153.4 million in 5 years. Lymphoma and chronic lymphocytic leukaemia would account for the most significant savings.

Discussion: Despite its limitations, this study provides the first Italian evaluation of the financial impact of rituximab biosimilars and also incorporates the effects of biosimilars on the pricing strategies of the originator (dynamic impact). This dynamic effect is more relevant than the impact of the treatment shift from the originator to biosimilars. Our hope is that these savings will be used to cover new cost-effective drugs and not just for cost-cutting policies.

Keywords

Rituximab, biosimilar, budget impact analysis, economic evaluation

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Introduction

Biosimilars may represent an important opportunity to enhance allocative efficiency in the market for biological products. Savings from price-competition could be invested in new cost-effective drugs and/or to broaden patient access to existing therapies. The availability of biosimilars is expected to be associated with allocative efficiency and decreased spending on medications, being one of the driving forces in budgetary savings.[1]

At present, 44 biosimilar products have been approved by the European Medicines Agency (EMA) for 14 molecules,[2] and 16 are under evaluation.[3] In Italy, 32 biosimilars have been approved so far and, in the first 9 months of 2017, they had reached an 18% market share over total volumes (number of counting units) for the relevant markets (molecules with at least one available biosimilar). The biosimilar market share shows huge variations across regions in Italy, ranging from 62.6% in Piedmont to 6.5% in Puglia.[4] Regional variations can be

[1]Centre for Research on Health and Social Care Management (CERGAS), SDA Bocconi University, Milan, Italy
[2]Department of Pharmaceutical Sciences, Università del Piemonte Orientale, Novara, Italy

Corresponding author:
Carla Rognoni, Centre for Research on Health and Social Care Management (CERGAS), SDA Bocconi University, Via Roentgen 1, Milan 20136, Italy.
Email: carla.rognoni@unibocconi.it

ascribed to divergent procurement policies and actions on prescribing behaviour.[5] However, these differences could diminish in the future. A new regulation (Law 232/2016) only allows prescribing physicians to switch from the originator to the biosimilar (or from one biosimilar to another biosimilar). According to the same law, procurement should rely on a framework agreement if there are more than three available products for an off-patent biological molecule (originator and biosimilars).

Rituximab was the first monoclonal antibody approved for cancer in 1997, and is also approved for rheumatoid arthritis. It can be administered by both the intravenous (IV) and the more recently approved subcutaneous (SC) route as a monotherapy or in combination with chemotherapy regimens.

Rituximab is a chimeric monoclonal antibody targeting the CD20 antigen, which is present on the surface of B-lymphocytes. In 2016, rituximab was the third-largest selling hospital drug in Italy (€156 million), according to the Italian Medicines Agency (Agenzia Italiana del Farmaco – AIFA).[6]

Since the patent for rituximab IV expired, EMA has approved two biosimilars so far: Truxima and Rixathon on 17 February 2017 and 23 June 2017, respectively.[2] The rituximab biosimilars were approved for the treatment of all indications approved for the reference biological (non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis). AIFA subsequently also approved the use of biosimilar rituximab for the off-label indications previously identified for the originator (Determina AIFA 2107/2017) and included in the 648 List (i.e. the off-label use list covered by the Italian National Health Service – INHS).

Our study aims at investigating the financial impact of the introduction of rituximab biosimilars in clinical practice in Italy through a Budget Impact Analysis (BIA). In the present analysis, BIA of rituximab biosimilars is evaluated, including both approved and off-label indications, with a split per indication and adopting both the hospital and third-party payer point of view.

To the best of our knowledge, the budget impact of rituximab biosimilars has been investigated by only one study so far.[7] Although this article provided a general overview of the budget impact in European countries from the third-party payer perspective, it lacked information regarding the number of patients per approved indication and did not distinguish between specific off-label uses.

Methods

A BIA model was developed in accordance with the ISPOR Principles of Good Practice for BIA.[8]

The model considers for both the rituximab originator and biosimilar as follows:

- The approved clinical indications: follicular lymphoma (FL) III–IV stage (induction, associated with chemotherapy scheme CVP – cyclophosphamide, vincristine, prednisolone), recurrent/refractory FL III–IV stage (induction, associated with chemotherapy scheme CHOP – cyclophosphamide, hydroxydaunorubicin, oncovin, prednisolone), untreated or recurrent/refractory FL (maintenance therapy), recurrent/refractory FL III–IV stage (induction, mono-therapy), non-Hodgkin lymphoma (NHL) CD20+ large B cells in combination with chemotherapy CHOP, untreated or recurrent/refractory chronic lymphocytic leukaemia (CLL) in combination with chemotherapy, severe rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis.
- The off-label use for the following indications: non-Hodgkin lymphoma CD20+ large B cells in combination with polychemotherapy for first-line or salvage treatment, CLL B cells in combination with polychemotherapy for first-line or salvage treatment, post-transplant lymphoproliferative disorder, acute or chronic graft versus host disease (GVHD), FL in patients not eligible for polychemotherapy (mono-chemotherapy), lymphocyte-predominant Hodgkin lymphoma, warm antibody autoimmune haemolytic anaemia, relapsing or refractory thrombotic thrombocytopenic purpura resistant to plasma exchange, immune thrombocytopenic purpura resistant to standard treatments, resistant acquired haemophilia.

The model was developed in MS Excel according to the following process:

- Collection and analysis of epidemiological data (prevalence and incidence) relating to patients in Italy for whom treatment with rituximab is indicated (including off-label use);
- Definition of the current scenario, that is, the number of prevalent and incident patients treated with the rituximab originator;
- Definition of future scenarios (i.e. the penetration rate of the biosimilar) for the different indications;
- Cost estimates for current and future scenarios.

Since biosimilars are approved through a comparability exercise, we assumed an overlapping risk/benefit profile between the originator and the biosimilars, the only difference being the actual unit price of the drug and the administration route (IV vs SC).

Two perspectives were used: (1) the hospital perspective, that is, the acquisition cost of the drug and the administration cost and (2) the payer perspective, that is, rituximab is

administered either in 'day hospital' or in an outpatient setting, and hospitals are paid in principle on a fee-per-episode basis that should cover the full treatment cost but, in reality, hospitals are paid the drug acquisition cost and a 'discounted' fee[9] (Regional Laws).

Input data were validated and integrated by an expert panel of seven clinicians. Considering the large variability in biosimilar penetration rates across Italian regions, clinicians from different regions were invited to join the panel. A Delphi-driven approach was applied in the early stage of the data collection, since experts were asked to answer a questionnaire independently.[10] Afterwards, data gathered were discussed with the experts through a group meeting (11 October 2017). Hence, we have adopted a mixed method, integrating a Delphi approach with an experts' panel approach. The panel was asked to: (1) validate the epidemiological data for each indication and the relevant proportion of patients treated with rituximab, (2) validate the therapeutic schemes per indication, (3) estimate the yearly and 5-year market share for the originator and the biosimilars per indication and (4) estimate time dedicated by healthcare professionals to patient care when the drug is being administered.

Market shares were applied to new, incident cohorts (naïve treatment) for almost all the indications, since the treatment lasts less than 1 year. The prevalent population was used only for maintenance therapy for FL (patients are treated every 2–3 months until progression, for a maximum of 2 years). We assumed that half of the prevalent patients are in the first year of treatment and half are in the second year of treatment. The expert panel reached a consensus of 12 cycles of therapy over 2 years for patients with untreated FL and 8 cycles of therapy distributed over 2 years for patients with relapsed or refractory FL. Survival curves for the different indications were consulted to obtain the percentages of patients still alive and treated at different times. As the focus was on the expected budget at each point in time, the financial streams were presented as undiscounted costs.[8]

Clinicians expressed the opinion that biosimilars will be used only for drug-naïve patients (i.e. there will not be patients switching from the originator to the biosimilars) and that biosimilars will mostly substitute the IV rituximab originator. This assumption minimizes the impact of biosimilar market penetration on drug administration costs.

The unit cost of the rituximab originator was calculated as the ex-factory price net of the compulsory 5% + 5% discount and an additional discount, according to the agreement negotiated by AIFA and the company holding the marketing authorization in July 2017.[11] The unit cost of biosimilars was calculated as the ex-factory price of Rixathon net of the 5% + 5% discount. For future scenarios, we have adopted a dynamic approach looking at further discounts for the rituximab originator due to price-competition (5%, 10% and 15% for year 1, year 2 and years 3–5, respectively). Biosimilars are expected to be discounted to 30%, 35% and 45% on average for year 1, year 2 and years 3–5, respectively. These discounts were estimated on the basis of the most recent experience for infliximab (*data on file*).

As mentioned above, rituximab is administered in day hospital or in an outpatient setting. For both settings fees for drug administration are determined by the regional governments (payers). However, regions usually pay to the hospital the acquisition costs of the drugs and a 'discounted' fee. In the hospital perspective case, drug administration costs were estimated based on the consensus reached by the expert panel on time dedicated by nurses and physicians, that is, 50 and 20 minutes for an IV infusion, respectively, and 25 minutes spent by nurses on SC administration. The unit cost per minute for healthcare personnel was estimated using the gross annual salaries[12] of €32,518 for nurse and €73,050 for physician. These values correspond to a cost per hour of €19.64 and €44.11, respectively, considering 46 working weeks per year (36 working hours per week) and translate into €0.33 and €0.74 per minute, for nurse and physician, respectively.

Table 1 summarizes all unit costs used in the model.

The BIA model has been designed to allow for additional analyses. For example, a scenario analysis has been performed considering 7% savings if vial sharing is applied.[13]

Results

Table 2 illustrates the target population per indication. According to the expert panel, use of rituximab in patients with granulomatosis, polyangiitis and microscopic polyangiitis is very rare in Italy, and these three indications were excluded from the model.

Current (year 0) and future scenarios (years 1–5) of market shares are presented in Table 3. As mentioned before, clinicians agreed that biosimilars will erode market share of the IV rituximab originator without large variations in the trend for the SC formulation and that regional policies (some more hostile to SC administration, others more favourable) will not change for the considered time horizon.

From the hospital perspective, rituximab would cost €123.8 million under the current scenario. Savings due to biosimilars would reach €16.9, €26.0, €36.2, €36.8 and €37.6 million in the 1st, 2nd, 3rd, 4th and 5th years, respectively, with cumulated savings of €153.6 million in the next 5 years (Figure 1). Results are very similar using the payer perspective, with a cumulated savings of about €153.4 million over the next 5 years. Detailed results are presented in Table 4.

Table 1. BIA model input data.

	Data	References
Epidemiological data	See Table 2	See Table 2
Market share data	See Table 3	See Table 3
Rituximab originator ex-factory price	Two vials 100 mg/10 mL (IV): €455.96 One vial 500 mg/50 mL (IV): €1139.7 One vial 1400 mg/11.7 mL (SC): €1450.29	Determina AIFA 1348/2017 net of 5%+ 5% discount and 9% discount[a]
Rituximab biosimilar ex-factory price	One vial 500 mg/50 mL (IV): €1110.17	Determina AIFA 1286/2017
Personnel unit cost per minute	Nurse: €0.33 Physician: €0.74	«Conto Annuale»–Dipartimento della Ragioneria Generale dello Stato[b]
Personnel time for drugs administration	Nurse (IV): 50 min Physician (IV): 20 min Nurse (SC): 25 min	Expert panel
Full tariffs (weighted average)	IV: €170.55 SC: €153.24	Regional laws + Assobiomedica[c]
Discounted tariffs (weighted average)	IV: €19.84 SC: €18.11	

BIA: budget impact analysis.
[a]http://www.aobrotzu.it/documenti/9_383_20170727121539.pdf.
[b]http://www.contoannuale.tesoro.it/cognos1022/cgi-bin/cognosisapi.dll?b_action=xts.run&CAMUsername=cog_usr&CAMPassword=cog_usr&h_CAM_action=logonAs&CAMNamespace=ADS&m=portal/cc.xts&m_tab=w&b_action=cognosViewer&ui.action=run&ui.object=%2fcontent%2fpackage%5b%40name%3d%27Sico%20Sito%27%5d%2freport%5b%40name%3d%27Home%20Page%27%5d&ui.name=Home%20Page&run.outputFormat=HTML&run.prompt=true&cv.header=false&cv.toolbar=false.
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Table 2. Number of patients considered for the different clinical indications each year.

Indication	Treatment type	Incidence/prevalence		No. of patients considered	Reference
Approved indications					
Untreated follicular lymphoma III–IV stage	Induction, associated to chemotherapy CVP	Total FL patients (incidence)	1213	134	14–16
		III–IV stage	75%		
		Untreated	15%		
		Induction + chemotherapy	98%		
		Treated with rituximab	100%		
Recurrent/refractory follicular lymphoma III–IV stage	Induction, associated to chemotherapy CHOP	Total FL patients (incidence)	1213	164	14–16
		III–IV stage	75%		
		Recurrent/refract	20%		
		Induction + chemotherapy	90%		
		Treated with rituximab	100%		
Untreated follicular lymphoma	Maintenance	Total FL patients (prevalence)	9525	2858	14,15
		Untreated	30%		
		Maintenance	100%		
		Treated with rituximab	100%		
Recurrent/refractory follicular lymphoma	Maintenance	Total FL patients (prevalence)	9525	2858	14,15
		Recurrent/refractory	30%		
		Maintenance	100%		
		Treated with rituximab	100%		
Recurrent/refractory follicular lymphoma III–IV stage	Induction, monotherapy	Total FL patients (incidence)	1213	18	14–16
		III–IV stage	75%		
		Recurrent/refractory	20%		
		Induction	10%		
		Treated with rituximab	100%		
Non-Hodgkin lymphoma CD20+, large B cells	In combination with chemotherapy CHOP	Total NHL B-cell CD20+ patients (incidence)	2912	1791	15,17
		In combination with chemotherapy	62%		
		Treated with rituximab	100%		

(Continued)

Table 2. (Continued)

Indication	Treatment type	Incidence/prevalence		No. of patients considered	Reference
Untreated chronic lymphocytic leukaemia	In combination with chemotherapy	Total CLL patients (incidence)	2750	1422	14,18
		Untreated	55%		
		Treated with rituximab	94%		
Recurrent/refractory chronic lymphocytic leukaemia	In combination with chemotherapy	Total CLL patients (incidence)	2750	578	14,18
		Recurrent/refractory	25%		
		Treated with rituximab	84%		
Severe rheumatoid arthritis	–	Total severe rheumatoid arthritis patients (prevalence)	5000	1100	19
		Treated with rituximab	22%		
Off-label indications					
Non-Hodgkin lymphoma CD20+, large B cells	In combination with polychemotherapy or as first-line or salvage	Total NHL B-cell CD20+ patients (incidence)	2912	371	15,17
		In combination with chemotherapy	13%		
		First-line or salvage	98%		
		Treated with rituximab	100%		
Chronic lymphocytic leukaemia B cells	In combination with polychemotherapy or as first-line or salvage	Total CLL patients (incidence)	2750	470	14,20
		B cells	95%		
		First-line or salvage	20%		
		Associated with chemotherapy first-line or salvage	90%		
		Treated with rituximab	100%		
Post-transplant lymphoproliferative disorder	–	Total post-transplant lymphoproliferative disorder patients (incidence)	23	23	21–23
		Treated with rituximab	100%		
Acute or chronic graft-versus-host disease (GVHD) (steroid resistant)	–	Total acute or chronic GVHD patients (steroid resistant; incidence)	1700	340	24,25
		Treated with rituximab	20%		
Follicular lymphoma–monochemotherapy (patients not eligible for polychemotherapy)	Induction + treatment	Total FL patients (incidence)	1213	61	14
		Not eligible to polychemotherapy	5%		
		Treated with rituximab	100%		
Lymphocyte-predominant Hodgkin lymphoma	–	Total Hodgkin lymphoma patients (incidence)	1820	91	26,27
		Lymphocyte predominant	5%		
		Treated with rituximab	100%		
Warm antibody autoimmune haemolytic anaemia	–	Total warm antibody autoimmune haemolytic anaemia patients (incidence)	480	336	28
		Treated with rituximab	70%		
Relapsing or refractory thrombotic thrombocytopenic purpura resistant to plasma exchange	–	Total relapsing or refractory thrombotic thrombocytopenic purpura resistant to plasma exchange patients (incidence)	30	30	29
		Treated with rituximab	100%		
Immune thrombocytopenic purpura resistant to standard treatments	–	Total immune thrombocytopenic purpura resistant to standard treatments patients (incidence)	971	486	29
		Treated with rituximab	50%		
Resistant acquired haemophilia	–	Total resistant acquired haemophilia patients (incidence)	30	24	29
		Treated with rituximab	80%		

Figure 2 shows that the most important savings derive from the use of rituximab biosimilars for lymphoma (including follicular and non-Hodgkin lymphoma CD20+, large B cells) and chronic lymphocytic leukaemia.

Table 3. Market shares for current (year 0) and future scenarios (years 1–5) for the different clinical indications.

Indication	Treatment type	Therapies	Year 0 (%)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)
Approved indications								
Untreated follicular lymphoma III–IV stage	Induction, associated to chemotherapy CVP	Rituximab originator IV	43.3	26.7	16.7	10.0	8.3	6.7
		Rituximab biosimilar IV	0.0	13.3	20.0	23.3	25.0	26.7
		Rituximab SC	56.7	60.0	63.3	66.7	66.7	66.7
		Total	100.0	100.0	100.0	100.0	100.0	100.0
Recurrent/refractory follicular lymphoma III–IV stage	Induction, associated with chemotherapy CHOP	Rituximab originator IV	43.3	26.7	16.7	10.0	8.3	6.7
		Rituximab biosimilar IV	0.0	13.3	20.0	23.3	25.0	26.7
		Rituximab SC	56.7	60.0	63.3	66.7	66.7	66.7
		Total	100.0	100.0	100.0	100.0	100.0	100.0
Untreated follicular lymphoma	Maintenance	Rituximab originator IV	43.3	26.7	16.7	10.0	8.3	6.7
		Rituximab biosimilar IV	0.0	13.3	20.0	23.3	25.0	26.7
		Rituximab SC	56.7	60.0	63.3	66.7	66.7	66.7
		Total	100.0	100.0	100.0	100.0	100.0	100.0
Recurrent/refractory follicular lymphoma	Maintenance	Rituximab originator IV	43.3	26.7	16.7	10.0	8.3	6.7
		Rituximab biosimilar IV	0.0	13.3	20.0	23.3	25.0	26.7
		Rituximab SC	56.7	60.0	63.3	66.7	66.7	66.7
		Total	100.0	100.0	100.0	100.0	100.0	100.0
Recurrent/refractory follicular lymphoma III–IV stage	Induction, monotherapy	Rituximab originator IV	100.0	66.7	45.5	30.0	25.0	20.0
		Rituximab biosimilar IV	0.0	33.3	54.5	70.0	75.0	80.0
		Total	100.0	100.0	100.0	100.0	100.0	100.0
Non-Hodgkin lymphoma CD20+, large B cells	In combination with chemotherapy CHOP	Rituximab originator IV	63.3	50.0	36.7	30.0	28.3	26.7
		Rituximab biosimilar IV	0.0	10.0	20.0	23.3	25.0	26.7
		Rituximab SC	36.7	40.0	43.3	46.7	46.7	46.7
		Total	100.0	100.0	100.0	100.0	100.0	100.0
Untreated chronic lymphocytic leukaemia	In combination with chemotherapy	Rituximab originator IV	100.0	40.0	23.3	10.0	10.0	10.0
		Rituximab biosimilar IV	0.0	60.0	76.7	90.0	90.0	90.0
		Total	100.0	100.0	100.0	100.0	100.0	100.0
Recurrent/refractory chronic lymphocytic leukaemia	In combination with chemotherapy	Rituximab originator IV	100.0	40.0	23.3	10.0	10.0	10.0
		Rituximab biosimilar IV	0.0	60.0	76.7	90.0	90.0	90.0
		Total	100.0	100.0	100.0	100.0	100.0	100.0
Severe rheumatoid arthritis	–	Rituximab originator IV	100.0	70.0	50.0	10.0	10.0	0.0
		Rituximab biosimilar IV	0.0	30.0	50.0	90.0	90.0	100.0
		Total	100.0	100.0	100.0	100.0	100.0	100.0
Off-label indications								
Non-Hodgkin lymphoma CD20+, large B cells	In combination with polychemotherapy first-line or salvage	Rituximab originator IV	100.0	25.0	7.5	5.0	2.5	2.5
		Rituximab biosimilar IV	0	75.0	92.5	95.0	97.5	97.5
		Total	100.0	100.0	100.0	100.0	100.0	100.0
Chronic lymphocytic leukaemia B cells	In combination with polychemotherapy first-line or salvage	Rituximab originator IV	100.0	40.0	22.5	15.0	12.5	12.5
		Rituximab biosimilar IV	0	60.0	77.5	85.0	87.5	87.5
		Total	100.0	100.0	100.0	100.0	100.0	100.0
Post-transplant lymphoproliferative disorder	–	Rituximab originator IV	100.0	42.5	25.0	16.3	12.5	12.5
		Rituximab biosimilar IV	0	57.5	75.0	83.8	87.5	87.5
		Total	100.0	100.0	100.0	100.0	100.0	100.0
Acute or chronic graft-versus-host disease (GVHD; steroid resistant)	–	Rituximab originator IV	100.0	42.5	22.5	15.0	12.5	12.5
		Rituximab biosimilar IV	0	57.5	77.5	85.0	87.5	87.5
		Total	100.0	100.0	100.0	100.0	100.0	100.0
Follicular lymphoma monochem. (patients not eligible for polychem.)	Induction + treatment	Rituximab originator IV	100.0	25.0	7.5	5.0	2.5	2.5
		Rituximab biosimilar IV	0	75.0	92.5	95.0	97.5	97.5
		Total	100.0	100.0	100.0	100.0	100.0	100.0
Lymphocyte-predominant Hodgkin lymphoma	–	Rituximab originator IV	100.0	15.0	7.5	5.0	2.5	2.5
		Rituximab biosimilar IV	0	85.0	92.5	95.0	97.5	97.5
		Total	100.0	100.0	100.0	100.0	100.0	100.0

(Continued)

Table 3. (Continued)

Indication	Treatment type	Therapies	Year 0 (%)	Year 1 (%)	Year 2 (%)	Year 3 (%)	Year 4 (%)	Year 5 (%)
Warm antibody autoimmune haemolytic anaemia	–	Rituximab originator IV	100.0	15.0	7.5	5.0	2.5	2.5
		Rituximab biosimilar IV	0	85.0	92.5	95.0	97.5	97.5
		Total	100.0	100.0	100.0	100.0	100.0	100.0
Relapsing or refractory thrombotic thrombocytopenic purpura resistant to plasma exchange	–	Rituximab originator IV	100.0	15.0	7.5	5.0	2.5	2.5
		Rituximab biosimilar IV	0	85.0	92.5	95.0	97.5	97.5
		Total	100.0	100.0	100.0	100.0	100.0	100.0
Immune thrombocytopenic purpura resistant to standard treatments	–	Rituximab originator IV	100.0	15.0	7.5	5.0	2.5	2.5
		Rituximab biosimilar IV	0	85.0	92.5	95.0	97.5	97.5
		Total	100.0	100.0	100.0	100.0	100.0	100.0
Resistant acquired haemophilia	–	Rituximab originator IV	100.0	16.7	10.0	6.7	3.3	3.3
		Rituximab biosimilar IV	0	83.3	90.0	93.3	96.7	96.7
		Total	100.0	100.0	100.0	100.0	100.0	100.0

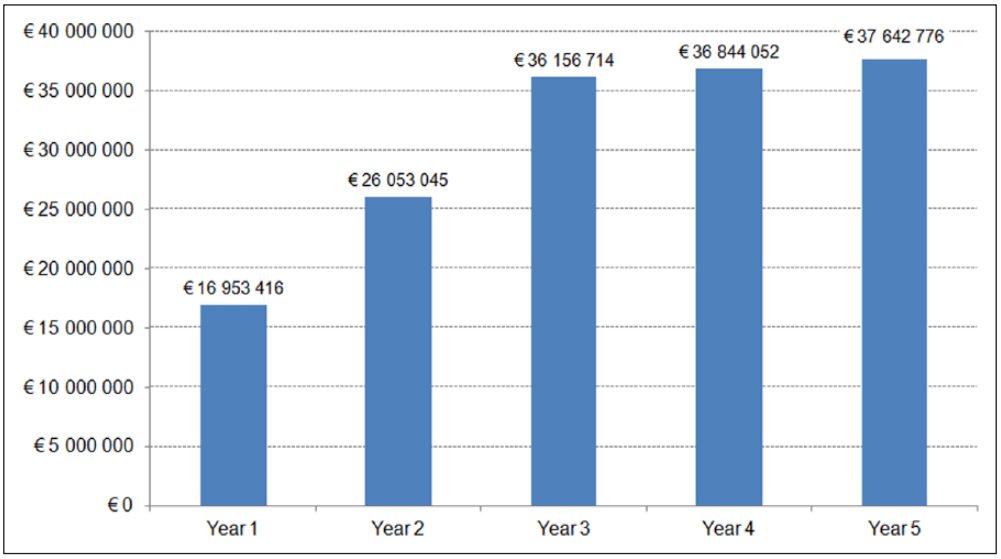

Figure 1. Savings in the future scenario compared to current scenario from the hospital perspective.

The scenario analysis assuming a 7% discount for vial sharing showed a total savings of €142.7 million for the period considered.

Discussion

This study, to the best of our knowledge, is the first BIA of rituximab biosimilars for all indications in Italy (both approved and off-label covered by the INHS). The BIA model was developed and populated with data retrieved from the literature and integrated and validated through expert opinions.

The model estimated a total savings in a 5-year time horizon of about €153.6 million if the perspective of hospital is used and very similar savings could be reached using the payer perspective.

Since we have adopted a dynamic approach, we were able to estimate savings derived from price competition on originators (67% of total savings) together with savings caused by the biosimilars uptake (33% of total savings). Hence, dynamic effects (i.e. price-competition induced by the biosimilar) seem to be more relevant than reallocation of market shares from the originator to biosimilars. However, since the penetration rate of biosimilars has been derived from expert opinions, it is worth to highlight that the reported values might be not fully representative of the real market shares and the consequent potential total savings.

Table 4. BIA according to the different clinical indications and perspectives considered.

Indication	Therapies	Hospital perspective						Payer perspective					
		Year 0 (€)	Year 1 (€)	Year 2 (€)	Year 3 (€)	Year 4 (€)	Year 5 (€)	Year 0 (€)	Year 1 (€)	Year 2 (€)	Year 3 (€)	Year 4 (€)	Year 5 (€)
Approved indications													
Untreated follicular lymphoma III–IV stage	Rituximab originator IV	537 846	314 749	186 572	105 856	88 213	70 571	534 134	312 465	185 145	105 000	87 500	70 000
	Rituximab biosimilar IV	0	102 513	143 066	141 937	152 075	162 214	0	87 391	122 222	121 907	130 615	139 322
	Rituximab SC	741 129	784 725	828 320	871 916	871 916	871 916	744 485	788 278	832 072	875 865	875 865	875 865
	Total	1 278 974	1 201 986	1 157 959	1 119 709	1 112 205	1 104 701	1 278 619	1 188 134	1 139 438	1 102 771	1 093 979	1 085 187
Recurrent/refractory follicular lymphoma III–IV stage	Rituximab originator IV	657 701	384 889	228 149	129 445	107 871	86 297	653 163	382 096	226 403	128 398	106 998	85 599
	Rituximab biosimilar IV	0	126 021	175 943	174 728	187 209	199 689	0	124 625	173 849	172 284	184 590	196 897
	Rituximab SC	906 071	959 370	1 012 668	1 065 966	1 065 966	1 065 966	910 171	963 711	1 017 250	1 070 790	1 070 790	1 070 790
	Total	1 563 773	1 470 279	1 416 760	1 370 140	1 361 046	1 351 953	1 563 334	1 470 431	1 417 502	1 371 472	1 362 379	1 353 285
Untreated follicular lymphoma	Rituximab originator IV	12 085 801	8 914 483	5 240 530	3 039 407	2 147 407	1 750 963	12 002 404	8 849 797	5 200 436	3 014 816	2 130 033	1 736 796
	Rituximab biosimilar IV	0	1 350 848	2 784 062	3 019 657	3 344 557	3 573 898	0	1 335 879	2 750 917	2 977 424	3 297 780	3 523 914
	Rituximab SC	14 305 788	14 800 012	15 641 529	16 483 046	16 830 339	16 830 339	14 385 139	14 881 667	15 727 851	16 574 036	16 923 693	16 923 693
	Total	26 391 589	25 065 343	23 666 121	22 542 110	22 322 303	22 155 200	26 387 543	25 067 343	23 679 204	22 566 276	22 351 506	22 184 403
Recurrent/ refractory follicular lymphoma	Rituximab originator IV	8 057 201	5 820 200	3 423 813	1 982 222	1 420 592	1 156 296	8 001 603	5 777 966	3 397 618	1 966 184	1 409 099	1 146 941
	Rituximab biosimilar IV	0	964 891	1 885 977	2 025 846	2 236 075	2 388 970	0	954 200	1 863 524	1 997 512	2 204 802	2 355 557
	Rituximab SC	9 582 608	9 937 915	10 501 598	11 065 280	11 273 656	11 273 656	9 629 799	9 986 464	10 552 922	11 119 381	11 329 176	11 329 176
	Total	17 639 809	16 723 006	15 811 388	15 073 349	14 930 324	14 818 922	17 631 402	16 718 630	15 814 065	15 083 078	14 943 076	14 831 674
Recurrent/ refractory follicular lymphoma III-IV stage	Rituximab originator IV	118 394	75 058	48 536	30 292	25 243	20 195	117 577	74 513	48 165	30 047	25 039	20 031
	Rituximab biosimilar IV	0	24 576	37 430	40 889	43 810	46 730	0	24 303	36 985	40 317	43 197	46 077
	Total	118 394	99 634	85 967	71 181	69 053	66 925	117 577	98 817	85 150	70 364	68 236	66 108
Non-Hodgkin lymphoma CD20 +, large B cells	Rituximab originator IV	14 157 304	10 628 651	7 392 354	5 719 389	5 401 645	5 083 901	14 059 613	10 551 526	7 335 796	5 673 114	5 357 941	5 042 768
	Rituximab biosimilar IV	0	1 392 021	2 591 281	2 573 385	2 757 198	2 941 011	0	1 376 596	2 560 431	2 537 393	2 718 636	2 899 878
	Rituximab SC	8 328 743	9 085 901	9 843 060	10 600 218	10 600 218	10 600 218	8 370 808	9 131 791	9 892 774	10 653 756	10 653 756	10 653 756
	Total	22 486 047	21 106 573	19 826 695	18 892 992	18 759 061	18 625 131	22 430 421	21 059 913	19 789 001	18 864 263	18 730 333	18 596 402
Untreated chronic lymphocytic leukaemia	Rituximab originator IV	18 093 984	6 880 841	3 805 719	1 541 834	1 541 834	1 541 834	18 001 354	6 843 789	3 784 105	1 532 571	1 532 571	1 532 571
	Rituximab biosimilar IV	0	6 739 983	8 011 083	7 992 996	7 992 996	7 992 996	0	6 684 405	7 940 067	7 909 628	7 909 628	7 909 628
	Total	18 093 984	13 620 825	11 816 802	9 534 830	9 534 830	9 534 830	18 001 354	13 528 195	11 724 172	9 442 200	9 442 200	9 442 200
Recurrent/refractory chronic lymphocytic leukaemia	Rituximab originator IV	7 175 756	2 728 823	1 509 284	611 466	611 466	611 466	7 138 975	2 714 111	1 500 702	607 788	607 788	607 788
	Rituximab biosimilar IV	0	2 672 988	3 177 096	3 169 940	3 169 940	3 169 940	0	2 650 919	3 148 898	3 136 837	3 136 837	3 136 837
	Total	7 175 756	5 401 811	4 686 380	3 781 406	3 781 406	3 781 406	7 138 975	5 365 030	4 649 599	3 744 625	3 744 625	3 744 625
Severe rheumatoid arthritis	Rituximab originator IV	10 166 057	6 765 212	4 581 561	866 165	866 165	0	10 116 667	6 730 639	4 556 865	861 226	861 226	0
	Rituximab biosimilar IV	0	1 892 574	2 933 865	4 487 430	4 487 430	4 986 033	0	1 877 756	2 909 170	4 442 978	4 442 978	4 936 642
	Total	10 166 057	8 657 786	7 515 426	5 353 595	5 353 595	4 986 033	10 116 667	8 608 395	7 466 035	5 304 204	5 304 204	4 936 642
Off-label indications													
Non-Hodgkin lymphoma CD20 +, large B cells	Rituximab originator IV	3 620 995	860 851	244 936	154 411	77 205	77 205	3 596 008	854 604	243 062	153 162	76 581	76 581
	Rituximab biosimilar IV	0	1 691 168	1 941 359	1 697 193	1 741 856	1 741 856	0	1 672 428	1 918 247	1 673 456	1 717 494	1 717 494
	Total	3 620 995	2 552 019	2 186 295	1 851 604	1 819 062	1 819 062	3 596 008	2 527 033	2 161 309	1 826 618	1 794 075	1 794 075

(Continued)

Table 4. (Continued)

Indication	Therapies	Hospital perspective						Payer perspective					
		Year 0 (€)	Year 1 (€)	Year 2 (€)	Year 3 (€)	Year 4 (€)	Year 5 (€)	Year 0 (€)	Year 1 (€)	Year 2 (€)	Year 3 (€)	Year 4 (€)	Year 5 (€)
Chronic lymphocytic leukaemia B cells	Rituximab originator IV	6 073 727	2 309 736	1 231 865	776 335	646 946	646 946	6 042 656	2 297 308	1 224 874	771 674	643 062	643 062
	Rituximab biosimilar IV	0	2 262 440	2 718 341	2 533 974	2 608 503	2 608 503	0	2 243 797	2 694 262	2 507 564	2 581 316	2 581 316
	Total	6 073 727	4 572 176	3 950 206	3 310 309	3 255 449	3 255 449	6 042 656	4 541 105	3 919 135	3 279 239	3 224 378	3 224 378
Post-transplant lymphoproliferative disorder	Rituximab originator IV	149 659	60 486	33 745	20 741	15 955	15 955	148 627	60 047	33 487	20 574	15 826	15 826
	Rituximab biosimilar IV	0	53 588	65 058	61 840	64 609	64 609	0	52 994	64 284	60 975	63 705	63 705
	Total	149 659	114 074	98 803	82 581	80 564	80 564	148 627	113 041	97 770	81 548	79 531	79 531
Acute or chronic graft-versus-host disease (steroid resistant)	Rituximab originator IV	2 049 216	828 203	415 847	262 156	218 463	218 463	2 035 076	822 193	412 665	260 035	216 695	216 695
	Rituximab biosimilar IV	0	733 759	920 504	859 382	884 658	884 658	0	725 628	909 545	847 363	872 285	872 285
	Total	2 049 216	1 561 961	1 336 351	1 121 538	1 103 121	1 103 121	2 035 076	1 547 821	1 322 211	1 107 398	1 088 981	1 088 981
Follicular lymphoma – monochem. (patients not eligible to polychem.)	Rituximab originator IV	781 621	185 821	52 871	33 331	16 665	16 665	776 227	184 473	52 467	33 061	16 531	16 531
	Rituximab biosimilar IV	0	365 052	419 058	366 353	375 993	375 993	0	361 007	414 069	361 229	370 735	370 735
	Total	781 621	550 874	471 929	399 683	392 659	392 659	776 227	545 480	466 536	394 290	387 265	387 265
Lymphocyte-predominant Hodgkin lymphoma	Rituximab originator IV	592 130	84 463	40 054	25 250	12 625	12 625	588 044	83 850	39 747	25 046	12 523	12 523
	Rituximab biosimilar IV	0	313 425	317 465	277 537	284 840	284 840	0	309 952	313 685	273 655	280 857	280 857
	Total	592 130	397 888	357 518	302 787	297 466	297 466	588 044	393 803	353 432	298 701	293 380	293 380
Warm antibody autoimmune haemolytic anaemia	Rituximab originator IV	2 186 327	311 865	147 890	93 232	46 616	46 616	2 171 240	309 602	146 759	92 478	46 239	46 239
	Rituximab biosimilar IV	0	1 157 262	1 172 177	1 024 751	1 051 718	1 051 718	0	1 144 438	1 158 222	1 010 419	1 037 009	1 037 009
	Total	2 186 327	1 469 127	1 320 067	1 117 983	1 098 334	1 098 334	2 171 240	1 454 040	1 304 981	1 102 897	1 083 248	1 083 248
Relapsing or refractory thrombotic thrombocytopenic purpura resistant to plasma exchange	Rituximab originator IV	195 208	27 845	13 204	8 324	4 162	4 162	193 861	27 643	13 103	8 257	4 128	4 128
	Rituximab biosimilar IV	0	103 327	104 659	91 496	93 903	93 903	0	102 182	103 413	90 216	92 590	92 590
	Total	195 208	131 172	117 863	99 820	98 066	98 066	193 861	129 825	116 516	98 473	96 719	96 719
Immune thrombocytopenic purpura resistant to standard treatments	Rituximab originator IV	3 159 112	450 626	213 693	134 715	67 357	67 357	3 137 313	447 356	212 058	133 625	66 812	66 812
	Rituximab biosimilar IV	0	1 672 175	1 693 726	1 480 705	1 519 671	1 519 671	0	1 653 645	1 673 562	1 459 995	1 498 416	1 498 416
	Total	3 159 112	2 122 801	1 907 419	1 615 419	1 587 028	1 587 028	3 137 313	2 101 002	1 885 619	1 593 620	1 565 229	1 565 229
Resistant acquired haemophilia	Rituximab originator IV	156 166	24 751	14 085	8 879	4 440	4 440	155 089	24 572	13 977	8 807	4 404	4 404
	Rituximab biosimilar IV	0	81 041	81 464	71 912	74 481	74 481	0	80 143	80 494	70 907	73 439	73 439
	Total	156 166	105 792	95 549	80 792	78 920	78 920	155 089	104 714	94 471	79 714	77 843	77 843

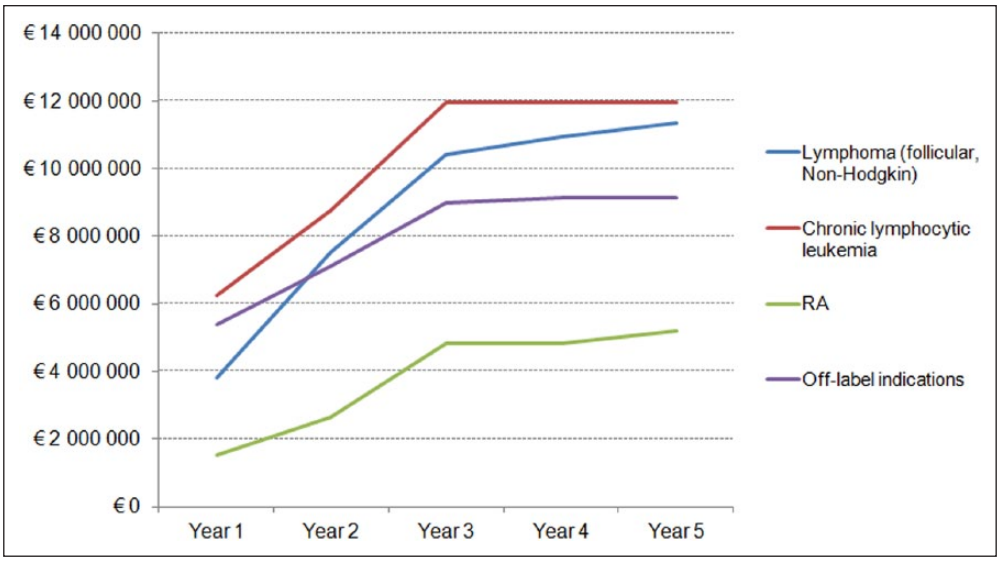

Figure 2. Savings in the future scenario compared to current scenario from the hospital perspective for different indications.

Savings on drug costs will not be counterbalanced by an increase in drug administration costs, since, according to expert panel opinion, IV biosimilars are expected to gain market share at the expense of the IV rituximab originator and not the SC formulation, which is still under patent protection.

The study has some limitations. First, we relied on the opinions of clinical experts gathered initially through a Delphi approach and then through a collective discussion. We are aware that these 'key informants' do not necessarily represent the whole clinical community. However, since the clinicians' home regions have adopted different policies on biosimilar drugs, our expectation is that they adequately represent the current situation across the country.

Second, we are aware that the Delphi method and experts' panel approach could foment a propensity to eliminate extreme positions and force a 'mean' consensus.[30] Nonetheless, this method is very useful when the problem is not confined to precise analytical techniques, but can benefit from subjective judgements on a collective basis, considering diverse backgrounds with different experience and expertise.

Third, the total dimension of the current market for rituximab per indication was estimated on the basis of epidemiological data, for a total of about €124 million, which is lower than the 2016 INHS spending for rituximab (€156.3 million), according to AIFA.[3] However, we could not rely on the actual expenditure for rituximab since the split per indication is not provided.

Fourth, the BIA model does not incorporate the possible impact of new drugs launched for the same indications as rituximab. The longer the time horizon, the higher the level of uncertainty on our savings estimation. A more prudent 3-year time horizon would imply a €79.2 million savings in the hospital scenario.

Despite these limitations, the study provides for an Italian estimate of potential savings from rituximab biosimilars since it could rely on a per-indication analysis and a panel that represents the diverse policies of regional payers on line-extensions (SC vs IV) and biosimilars versus originators.

The main question is how the savings will be used. Savings can be used just to contain public pharmaceutical expenditure or to fund innovative and cost-effective drugs or can be allocated to fund other healthcare technologies and services. Our hope is that savings re-investment will be the option chosen by the healthcare system.

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ORCID iD

Carla Rognoni https://orcid.org/0000-0002-6330-0591

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