AN ECONOMIC PRICE ANALYSIS OF CONVENTIONAL REMISSION THERAPY VS BIOLOGICAL THERAPY FOR RHEUMATOID ARTHRITIS TREATMENT

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Abstract:
Rheumatoid arthritis represents the most common inflammatory rheumatism, affecting about 1% of the general population. Inappropriately untreated usually has a progressively aggressive perspective, generating pain and joint inflammation and functional disability. The severity of the disease results from the fact that more than 50% of patients cease their professional activity in the first 5 years of the disease and 10% of cases show severe disability in the first two years of evolution. The aim of the study is to conduct a comparative price analysis between a conventional remission therapy and a biological therapy for rheumatoid arthritis in Romania. Biologics are huge financial burden due to their high price, large number of patients and the considerable budget impact. The data was obtained from the official pages of National Health Insurance House in Romania up to date December 2018, and also the algorithm treatment for rheumatoid arthritis is followed. Conventional remission therapy is 30-100 times cheaper than biological therapy. The results show that two out of eight INNs (International non-proprietary name or a generic name) have authorized biosimilars (similar biological medicinal product) in Romania, despite of bigger number of authorized biosimilars in EMA (European Medicines Agency) for rheumatoid arthritis. Biosimilars' prices have a 19.66-29.68% reduction in the price of biologics. Introduction of biosimilars on the Romanian market will lead to significant decrease in reimbursed prices paid by public funds and thus increase the patients' access to biological therapy.

Keywords: biological therapy, access, analysis, conventional remission, rheumatoid arthritis

1. Introduction

Rheumatoid arthritis is a systematic autoimmune disease with chronic and variable evolution, with an incomplete pathogenic mechanism elucidated. A complex of factors participates in the initiations and perpetuation of the autoimmune process. Rheumatoid arthritis is a disease that combines HLA and non-HLA genes, which interfere with the susceptibility or resistance.

Rheumatoid arthritis is the result of cytokine overproduction that leads to the destruction of joint tissue by macrophages, neutrophils and T cells. Interferon-gamma (IFN-gamma), the cytokine produced by T-cells, induces class II HLA antigens, molecules essential for antigen presentation.

The mechanism of recurrence for the disease is not fully known. The causal antigen is considered to be trigger only in a individual with high genetic susceptibility. The process begins with an inflammatory synovitis that progress to a proliferative and infiltrative form.

The quality of life of patients with RA(rheumatoid arthritis) is significantly reduced by symptoms such as pain, fatigue and loss of function. Treatment for rheumatoid arthritis consists of NSAIDs (nonsteroidal anti-inflammatory drugs) and low-dose glucocorticoids followed by sequential immunotherapy with anti-rheumatic disease-modifying drugs (DMARDs). So it is important to determine whether immunosuppressive therapy stops the development of polyarthritic lesions and maintains joint function.

More recently, the early initiation of DMARD therapies (alone or in combination) or biological agents such as tumor necrosis factor (TNF) antagonists have been introduced into treatment regimens of specialized physicians because they appear to be more effective than previous therapies. Biological drugs are complex, protein-based drugs used not only in inflammatory diseases, but also in diabetes (insulin) or cancers. The biological drugs are as well expensive, but after their patent has expired, a biosimilar (similar biological medicinal product) product with high similarity to the original biological product will be released by pharmaceutical companies at a lower price. But this is not a certainty for lower reimbursement values because the expenditures could increase as the biosimilars are becoming more accessible to patients.

In patients with already established disease where conventional treatments have not worked, these new strategies can have great benefits, and the higher costs caused by these more aggressive therapeutic strategies can be justified by an increase in quality of life, but also of saving the hospital therapeutic units in terms of patient productivity.

Since the resources for health care can be limited, the necessary expenditures that need to be made for early aggressive treatment must be considered from the point of view of efficacy, but also from the benefits it brings to the patient.

For example, from an existing rheumatology budget (assuming there is no additional funding), decision makers can be divided between a choice of budget spending available for early RA on a relatively cheap conventional DMARD therapy for all patients with RA versus costly biological therapy only for some RA patients diagnosed selectively with an aggressive disease. Economists and decision-makers tend to assess such decisions by comparing all the costs and benefits of the new strategy with that of the existing one. Substitution and interchangeability of

the biosimilar drugs are at the discretion of the physician after a clinical assessment. But, the patient is not disadvantaged because the reimbursement rate of biologics and biosimilar drugs are amounted to 100%. On the other hand, the original drugs used in the conventional therapies may not be reimbursed 100% if they have generics drugs that are reimbursed in Romania and the patient ultimately will pay a difference.

It is very common that economists are only interested in direct health spending because the ultimate goal is to determine to what extent a particular type of treatment is beneficial but also how much it costs. This can then be used to better inform patients and health-care providers, and last but not least, to allocate the funds needed to achieve the best medical service for patients with limited resources.

The aim of the study is to conduct a comparative price analysis between a conventional remission therapy and a biological therapy for rheumatoid arthritis in Romania. The data was obtained from the official pages of National Health Insurance House in Romania, and also the algorithm treatment for rheumatoid arthritis is followed.

The main questions were:

How big are the expenditures on reimbursement of biosimilar drugs compared to biological drugs?

What are the differences in costs between conventional therapy and biological therapy?

What are the differences at national level?

2. Material and methods

2.1 Research objectives

In our analysis, we included all currently approved drugs used for the treatment of rheumatoid arthritis in Romania. We selected the current medication and split it into conventional remission therapy VS biological therapy from CaNaMed 21.04.2018 (The National Book of prices for human use, medicine issued with medical prescription).

2.2 Data collection

The data was collected for biologic drugs, both original products and biosimilar ones. The selection of products is for the therapy of rheumatoid arthritis. The assessment was made for all trade names and dosage forms available in Romania.

The manufacturing prices and retail prices were compared by INN (International non-proprietary name or a generic name). All the products that we assessed were approved by EMA (European Medicines Agency) and the National Agency for Medicines and Medical Devices.

All the prices compared in the study were taken from CaNaMed 21.04.2018 (The National Book of prices for human use, medicine issued with medical prescription). The proposed producer price for CaNaMed should be less than or equal to the lowest price of the same drug in the list of 12 countries comparing (Austria, Belgium, Bulgaria, Czechia, Germany, Greece, Hungary, Italy, Lithuania, Poland, Slovenia, Spain) (Ministry of Health Order no. 407/2018).

For the biological therapy that we studied, eight INNs with therapeutic indication for rheumatoid arthritis were selected: infliximab, etanercept, adalimumab,

certolizumab, golimumab, abatacept, tocilizumab and rituximab). They have different pharmaceutical presentations, based on strength, dosage forms and pack size in the price lists. Authorized biosimilar drugs were identified and the comparison between the manufacturing price and the retail price was done.

In terms of conventional therapy, four INNs with therapeutic indication RA were selected for study: sulfasalazinum, leflunomidum, ciclosporinum and azathioprinum. They also have different dosage forms and pack size in the price lists. The generics and the innovative drugs were identified from the list. The comparation between their prices (manufacturing and retail prices) was done.

The prices of equivalent pack sizes were compared. The drug prices were expressed in RON (Romanian currency).

3. Results

The results show that two out of eight INNs have biosimilars in Romania for RA. We examined all concentration for both biological and original drugs. The retail and manufacturing prices for both biosimilar and original drugs are shown in Figure 1 and Figure 2, respectively.

On average, the lowest manufacturer/retail price was shown for tocilizumab 50 and the highest for rituximab 1400 (see Table1). Two INNs authorized biosimilar drgus were identified: infliximab and etanercept. For etanerceptum, only the 50mg dosage has biosimilar drug and it was available after the infliximab biosimilar has been placed on the Romanian market.

Table 1

Drugs pricing in biologic treatment

INN	Dosage form	Manufacturer price (in RON)	Retail price (in RON)	Decreasing Generic drug price versus Original drug	Type
Infliximabum	100	1446.26	1600.25	29.68%	Biosimilar
	100	1445.26	1647.27	27.61%	Biosimilar
	100	1470.84	1674.07	26.44%	Biosimilar
	100	2066.09	2275.66		Innovative
Etanerceptum	50	2962.40	3299.87	19.66%	Biosimilar
	50	3703.01	4107.13		Innovative
	25	1849.69	2087.01		Innovative
	25	1850.98	2088.42		Innovative
Adalimumabum	40	3712.65	4117.64		Innovative
	40	3662.60	4063.08		Innovative
	40	3656.32	4056.24		Innovative

Certolizumab	200	3120.03	3471.68	Innovative
Golimumab	50	3785.49	4197.03	Innovative
Abataceptum	125	3731.13	4137.78	Innovative
	250	1317.25	1506.65	Innovative
Tocilizumabum	162	3988.45	4418.26	Innovative
	80	558.40	679.51	Innovative
	200	1389.61	1585.52	Innovative
	400	2741.51	3059.10	Innovative
Rituximabum	200	1926.93	2171.20	Innovative
	1400	6844.93	7531.82	Innovative
	500	4847.98	5355.15	Innovative

Figure 1. Differences in retail prices of drugs in biologic treatment.

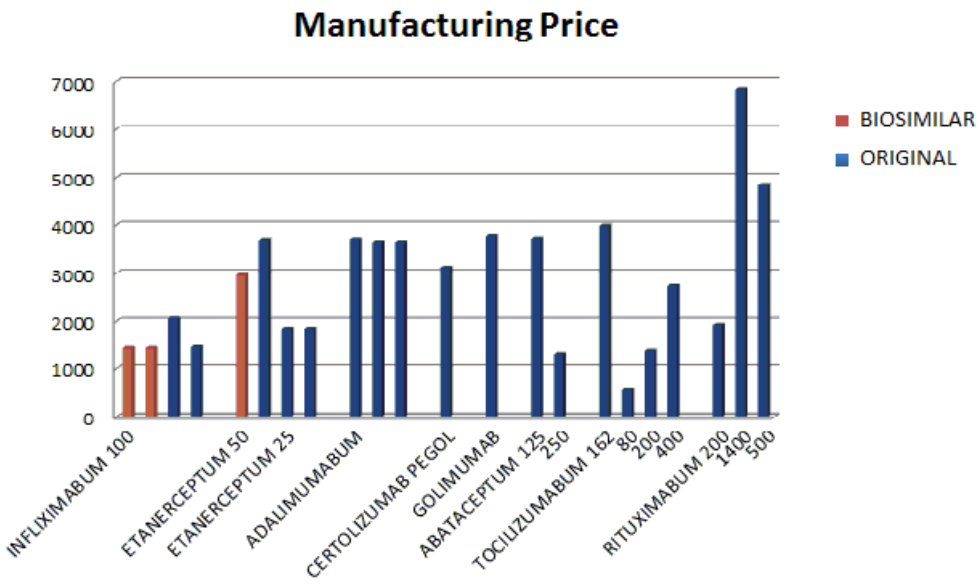

Figure 2. Differences in manufacturing prices of drugs in biologic treatment.

The differences between manufacturing price and retail price are between 10.04% and 21.69%. Two of them are generics drugs and two are innovative drugs. We can observe that the amount of original drugs used for the biological treatment are many more that the biosimilar ones. This can be explained by the complexity of placing a biological medicine on the market.

Table 2

Prices of drugs in conventional treatment

INN	Dosage form	Manufacturer price (in RON)	Retail price (in RON)	Type
Sulfasalazinum	500	19.97	30.77	Generic
Leflunomidum	10	40.25	60.02	Generic
	20	70.27	99.51	Generic
	20	80.51	114.01	Generic
Ciclosporinum	25	87.70	124.19	Innovative
	50	150.14	201.62	Innovative
Azathioprinum	50	51.31	72.66	Innovative

Figure 3. Differences in retail prices of drugs in conventional treatment.

Figure 4. Differences in manufacturing prices of drugs in conventional treatment.

We can observe that annual direct costs per patient treated with biologic therapy could be 20-80 times bigger than treated with conventional disease-modifying antirheumatic drugs.

We can observe in the Tabel 3 and 4 that each INN from the conventional treatment has a usual dosage per day. We calculated the cost-volume treatment

per each month considering the retail price (in RON), the number of pills per box and the usual dosage for treatment per day, according to the medical guides. The retail prices and the manufacturer prices are available from CaNaMed 21.04.2018.

Table 3

Cost-volume of drugs in conventional treatment

INN	Usual dosage for treatment/day	Cost-volume treatment/month (RON)
Sulfasalazinum 500 mg	2000mg/day	74 (120cpr*30,77/50)
Azathioprinum 50 mg	50-150 mg/day	65 (90cpr*72,66/100)
Ciclosporinum 25 mg	2,5-5 mg/kg/day	74,51 (30cpr*124,19/50)
Leflunomidum 20 mg	10-20 mg/day, oral	99,51 (30cpr*99,51/30)

Table 4

Cost-volume of drugs biological treatment

INN	Usual dosage for treatment/day	Cost-volume treatment/month (RON)
Infliximabum	3 mg/kgc	1647,27
Etanerceptum	25 mg/ twice per week	4107,13
Adalimumabum	40 mg once every two weeks	4117,64
Golimumab	50 mg/month	4197,03
Certolizumab	200 mg/once every two weeks	3471,68
Abataceptum	1 injection/month	4137,78
Rituximab	1 injection/month	5355,15

Biosimilar drugs of infliximab have a 26.44-29.68% reduction in the price of biologic drug and the biosimilar of etanercept has a 19.66% reduction in the price of biologic drug.

In the case of conventional therapy we couldn't analyze any reduction of prices because we could not found both generic drugs and innovative drugs for the same INN.

4. Discussion

Biologic drugs have proved highly effective for the treatment of RA. Romania's list of reimbursed drugs has a lot of inovative drugs for RA treatment. The results show that two out of eight INNs have biosimilars in Romania for RA. Manova et al assessed in only six biologic INNs and four authorized biosimilars in EMA in December 2017. Manufacturers' prices differ between 26 and 75%, while retail prices differ between 40 and 92% for biosimilars among eighteen EU countries. Spain and France have the higher number of biosimilar prices.

These drugs are cost-effective for RA patients not responding adequately to conventional therapy, but they have high costs. Prices control and biosimilar policy

are crucial for the decrease in the reimbursed cost. Gulacsi et al. pointed out the estimated savings from the introduction of biosimilars in RA that may lead to an increase in the number of patients with access to treatment.

The first biologic drug was rituximab in 1998. Then infliximab had issued marketing authorization in 1999, etanercept in 2000, adalimumab in 2003. Despite their existing authorizations in Europe, biosimilar adalimumab and rituximab aren't present in Romania - biosimilar rituximab is present in eight EU countries and etanercept in nine (Manova et al., 2018).

The first biosimilar approved by the EMA in 2013 was CT-P13 – a biosimilar version of the TNF inhibitor infliximab with a highly comparable safety, pharmacokinetics and pharmacodynamics in patients with RA (Yoo DH et al., 2013). The result of introduction the CT-P13 from 2014 in Central and Eastern European was a 20-25% reduction in the price of infliximab (Rencz F et al., 2015).

In Romania, biosimilars of infliximab have a bigger reduction than initial one, a 26.44-29.68% reduction in the price of biologic drug. The biosimilar of etanercept is new to the market and has a smaller reduction of 19.66% in the price of biologic drug. It has been estimated that Germany, France and the UK each stand to save between 2.3 billion and 11.7 billion between 2007 and 2020 in response to the introduction of biosimilars drugs (Haustein R et al., 2012).

In Romania each evaluation criterion had its own number of points, and the criteria were as follows: health technology assessment (HTA) based on therapeutic benefit (max. 15 points), HTA based on number of EU countries with a positive reimbursement status (max. 25 points), Positive Assessment Report issued by the National Agency for Medicines and Medical Devices (max. 45 points), and therapy costs—direct costs (max. 30 points). The maximum was 145 points and conditional reimbursement is for 60–79 points (Ministry of Health in Romania, 2013). The criteria for new drugs' reimbursement will change in Romania in the next couple of years; more pharmacoeconomic studies must be done and it is required that cost-effectiveness or cost-utility analysis to be in the procedures of assessment of a new drugs therapy.

There are specific price discounts for the first or subsequent biosimilars (or both) submitted for reimbursement in all countries. The discount ranged from 5 to 30% of the price of the original drug. For example, in Hungary, the first biosimilar entering the market has to offer a price reduction of 30% in relation to the ex-factory price of the original product (ESzCsM Decree 2017), the second—an additional 10% reduction of the ex-factory price of the first biosimilar product, and the third—a further 10% reduction of the ex-factory price of the second biosimilar product. Any additional product has to enter the market with a lower ex-factory price than the cheapest reimbursed product. In Romania, the first biosimilar of etanercept is at a price reduction of 19.66% of the original product.

Studies (Brodszky, V et al., 2016, McCarthy G et al., 2013) were done since 2014, after the first biosimilar was introduced, about cost savings (a price difference of 25% was assumed for biosimilar infliximab compared to the original) and based on these calculations, the introduction of biosimilar drugs will lead to substantial cost savings and increase the number of patients with access to biologic therapy. Dynamic competition through the pharmaceutical market entry of next-generation biologics is an important step in analyzing the impact of biosimilars and their potential savings to the health-care system in Romania.

Studies have shown that only six molecules were available in 2017 on the market (Manova et al., 2018), after in 2018 another two appear in CaNaMed 21.04.2018 (The National Book of prices for human use, medicine issued with medical prescription). Abataceptum and certolizumab pegol are used as well for the treatment of rheumatoid arthritis in Romania.

5. Conclusions

It has been demonstrated that a simple cost saving is not enough to change patients therapy from conventional treatment for rheumatoid arthritis to biosimilar drugs, there must also be a global gain in the quality of life of the patient. Currently, specialists are willing to pass patients on biosimilar treatment if there is a cost saving. On the other hand, if a biosimilar drug does not have a clinically significant difference compared to the efficacy of the reference product, cost savings may be the best reason to promote such therapy.

The introduction of biosimilar drugs on the Romanian national market has, as we discussed above, led to smaller prices reimbursed by the health insurance systems, and also led to a better access for patients to therapy. The drop in prices of biological drugs was achieved with the entry of new biosimilar drugs. However, this has not led specialist in the field to give up the conventional treatment used until now.

From recent studies, we noticed that the reduction in the therapy prices used for rheumatoid arthritis is not very well highlighted in the early years of the treatment. More detailed analyzes are needed to assess whether biosimilar drugs are more often used that biological ones, and whether the prices of these treatments decrease with the change in therapy.

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