Formulário de acesso a dados do Registo Nacional de Doentes Reumáticos (Reuma.pt) da SPR

1. Title

Impact of the implementation of biosimilars in the treatment of different rheumatic diseases perceived by the patients and by society (repercussion in Patient Reported Outcomes and economic costs)

2. Introduction

2.1.Literature review

Biosimilar drugs are a valuable mean of reducing the high costs of biotechnological therapies, particularly in the field of inflammatory rheumatic diseases.

The European Medicines Agency (EMA) has published normative and informative documents on the use of biosimilars in its member states and since the approval of the first biosimilar CT-P13 in 2013, the volume of evidence regarding the infliximab switch of reference for its biosimilar CT-P13 has been increasing.

It is already possible to assert with confidence that this switch does not imply changes in efficacy or safety or increased immunogenicity, based on randomized and double-blind studies and observational studies with robust numbers (1,2), in addition to smaller and open label extensions approval clinical trials.

There is a high potential for savings with the introduction of these drugs, not only because they have a lower price - in Portugal they have to cost at least 20% less than the original - but because they also introduce competition and adjustments in the market.

Decree-Law 115/2017 was published in Diário da República and defined the rules of the National Technology Assessment System (SiNATS) (3).

The decree-law also clarifies the rules for pricing medicines and medical devices. Of particular note is the reduction in the price of biosimilars, which, in order to be financed in the NHS, will have to cost 30% less than the original biologics when biosimilars of the same active substance already exist on the market.

If Portugal is already one of the countries with the largest market shares in some areas, there is still substantial potential for savings that can be achieved in other areas without jeopardizing the quality of treatment and at the same time translating savings investment in innovation and greater access to treatment for patients.

Norway and Denmark are two good examples of the use of these medicines, which are mostly used for rheumatic and cancer diseases.

In Norway, a country that has decided that there would be only one drug bought centrally for all hospitals, the contests have been generating great gains for the system. Steiner Madsen, medical director at the Norwegian Medicines Agency, who names biosimilars for "biogenerics", has advanced examples of annual treatments such as infliximab, used for diseases such as rheumatoid arthritis. The cost per patient obtained in the contest fell by 69%, and that of filgrastim exceeded 80% (4).

In Portugal, for example, filgrastim, a biosimilar used in the treatment of neutropenia already has a market share of 100%. The increase in its use has reduced expenditure by 77%, from € 7.5 million to less than € 2 million (4).

In the coming years, more biosimilars are expected to come in, which will contribute to greater patient access to these drugs, potentially generating savings that can be reversed in access to more innovative medicines. It is fully expected that, once the exclusivity rights of some drugs expire, they too will face direct competition from biosimilars.

There are four approved biosimilars (2 infliximab, 1 etanercept and 1 rituximab) used in Rheumatology in Europe and adalimumab will come soon. The National Register of Rheumatic Patients (Reuma.pt), developed by the Portuguese Society of Rheumatology (SPR), currently has around 400 patients undergoing biosimilar therapy (5).

In 2015, only with eight molecules of originators were spent 47 billion euros in the five largest countries in Europe. In 2015, in Portugal, biological medicines were worth 350 million euros and represented about 34% of the hospital charges of the National Health Service (SNS). From 2008 to 2015, the savings generated by biosimilars in Portugal, with three molecules, was 26 million euros. The behavior of the market from 2017 to 2020, with a healthy and sustainable competitive environment, has the potential to generate more than € 120 million in savings from biosimilars (6).

In addition to this contribution of containment and reduction of the expenses of the State and patients with medicines, and for the sustainability and preservation of the NHS, the value of biosimilars is much more comprehensive: they allow to release resources to finance innovative treatments of high cost, due to reduced treatment costs, make it possible for more patients to be reached for biological treatments at an early stage of their diseases; and, last but not least, reduce the inequalities of the population in relation to healthcare with biological drugs. But if the decrease of costs and

increase of access were the main driver for the fast acceptance of biosimilars, other advantages came such as the better knowledge about originators and biosimilars' production, increase of quality control, awareness about pharmacovigilance and traceability of packages and medications.

However several questions remain. Clinical trials were done in a small number of patients, not for all indications, extrapolation, permutability and automatic switch are sources of controversy and real world data is still very scarce.

2.2.Previous work

Rencz F *et al* are the first to compare the cost-effectiveness of treatment sequences for luminal Crohn's disease in Europe and concluded that infliximab biossimilar can be recommended as a first-line treatment in patients unresponsive to convencional treatments (7).

Several other studies have analyzed the cost-effectiveness of switching from original infliximab to infliximab biossimilar. One systematic review (8) including six budget impact analysis studies of which two studies were published as full text articles and four studies as conference abstracts was identified. Two budget impact analyses were also identified (9, 10). All studies considered cost-savings. The systematic review (8) of budget impact analysis studies included patients with CD, UC, RA, AS and PA. One budget impact analysis study targeted CD patients, (9) while the other included both CD and UC patients.

To our knowledge, data on the cost-effectiveness of the other 2 biosimilars (etanercept and rituximab) used in rheumatology are not published.

PROMs (patient reported outcome measures) are being increasingly used worldwide to assess the quality of services provided and encourage systematic quality improvement. In particular, they "have been used to compare and reward the performance of healthcare providers in England, the USA, Australia and Sweden, and their potential to improve quality has also been recognised in Canada and the Netherlands" (11).

A study in the UK was developed to investigate ankylosing spondylitis and rheumatoid arthritis patients' knowledge and attitudes towards infliximab and etanercept biosimilars in the UK. A self-administered web survey was conducted among the members of the National Rheumatoid Arthritis Society and the National Ankylosing Spondylitis Society in the UK between 2 March 2017 and 2 June 2017. Survey participants had a good knowledge and understanding of biosimilars. Participants on biosimilars were confident and positive about biosimilars' safety, efficacy and switching, whereas participants on the originator bio- logics were more reluctant to switch to biosimilars. Those patients who expressed concerns felt that more clinical trials on switching biosimilars, better communication

and reassurance by healthcare professional teams and further involvement in decision making would in- crease their acceptance of biosimilars (12).

Reuma.pt included since the beginning, PROMs such as visual analogue scales of pain and disease activity, EQ5D, SF36 and HAQ. These instruments can be a fundamental tool in different rheumatic diseases to capture self-reported quality of life and disability in addition to validated and worldwide adopted measures such as diseases activity score (DAS 28), BASDAI or ASDAS.

2.3.Hypothesis

The objective of the current study is to calculate the cost-effectiveness of biosimilars and determine the change in PROMs for patients with different rheumatic diseases between baseline (starting the first biosimilar drug) and follow-up at 6 months, 1 and 2 years on different health dimensions (EQ-5D / SF-36).

The following diseases will be studied: rheumatoid arthritis, spondylarthritis, psoriatic arthritis, juvenile idiopathic arthritis (JIA), SLE, scleroderma, Sjogren's syndrome and vasculitis.

These diseases were chosen because they are the ones for which are prescribed biosimilars according to the Reuma.pt.

Furthermore, the clinical measure of Disease Activity Score (DAS), ASDAS or BASDAI, SLEDAI and SLICC, ESSDAI will be also considered in order to corroborate the conclusions provided by PROMs, ultimately increasing the confidence in the results.

To conclude, understanding the saving potential with the introduction of these drugs in Portugal will be very important for organisations and ultimately motivating quality improvement at the practice level.

In the end we also want to know the relation between PROMs and disease activity scores in patients under biossimilars.

2.4. Innovation and significance

For the reasons mentioned above, it is relevant to analyze the impact of the implementation of biosimilars in the treatment of different rheumatic diseases not only in the classic dimensions related with the disease (effectiveness and safety) but also perceived by the patients (patient reported outcomes – pain, Qol, fatigue, satisfaction) and by society (cost effectiveness and savings).

The National Register of Rheumatic Patients (Reuma.pt) includes patients with several rheumatic diseases and the final objective is to register all patients in Portugal that are treated with biological medicines, ensuring the monitoring of the indication and effectiveness of the treatment and its safety.

Starting from the data available at Reuma.pt, this study intends to measure the effectiveness and safety of biosimilars - assessment of the impact on the disease; calculate costs and savings with the new biosimilars - assessment of the impact on society and the health system; characterize the PROMs with analysis of data on functional capacity and self-reported quality of life by patients - impact on the patient; evaluate the device for administering the drug in terms of usability, preference, satisfaction, pain at the injection site by the needle and excipient bite, product volume; and finally, determine drug persistence / retention - overall measure of all previous points.

To the best of our knowledge, this is the first study that systematically explore the economic gains with the introduction of biosimilars in Rheumatology and their repercussion on PROMS.

Publishing these results could be seen as a step towards a more transparent and open approach to health care.

3. Specific aims

3.1.Primary aim

- Measure the effectiveness and safety of biosimilars approved in rheumatology in comparison with the original drugs
- Calculate costs and savings with the new biosimilars
- Characterize the PROMs and determine the change in PROMs for patients between baseline (drug start) and follow-up at 6 months (1 and 2 years) on different health dimensions (EQ-5D / SF-36)
- Evaluate the device for administering the drug in terms of usability, preference, satisfaction, pain at the injection site by the needle and excipient bite and product volume
- Determine drug persistence/retention

3.2.Secondary aim

- Explore potential reasons for variation in PROMs

4. Methods

4.1.Study design

This will be an observational comparative longitudinal study including all adult patients followed on Reuma.pt starting biosimilar therapy.

Inclusion criteria: all adult patients (>18 years old) starting biosimilar therapies; including biologically naive (therefore biosimilar being the first biological) or biological switch (original switch to biosimilar, keeping the same drug or making switch to biosimilar being another drug or another class).

Patients that do not fulfil the inclusion criteria will be excluded from the study.

The control group will include patients with the same diagnosis, for each of the diseases, with similar characteristics (in terms of activity, duration of disease and demographic characteristics) under original biological therapy.

In the Reuma.pt JIA protocol there is a field asking the physician to check if the adult JIA patient fulfills classification criteria for any of the following adult rheumatic diseases: Rheumatoid Arthritis; Spondyloarthritis; Psoriatic Arthritis; adult Still disease (ASD); non-classifiable. The comparator group will be constituted by patients with adult onset rheumatic diseases (RA, SpA, PsA, ASD) registered in Reuma.pt, matched for sex and disease duration. Disease activity will be assessed through disease specific activity indexes according to the adult rheumatic disease.

To evaluate the device for administering the drug we will have to make a prospective assessment. One possibility is to add the question in the Reuma.pt protocol. If this is not possible, we will ask the collaboration centers to introduce this small questionnaire during the consultations.

In addition to the direct costs- the actual prices paid by the hospitals with the original and biosimilar drug- an economic evaluation will be done in terms of Quality Adjusted Life Year (QALY). Economic evaluation, conducted in terms of cost per QALY, strongly influences pricing and reimbursement decisions for new health technologies in many countries across the world. The calculation of QALYs requires patient outcome measures of a particular type. They must be preference-based, with the EuroQoL EQ-5D being the most widely used example.

The EQ-5D allows the achievement of two essential components of any measure of health-related quality of life to be used in cost-utility economic evaluations: a profile describing the health status in terms of domains or dimensions and a numeric value associated with the health status described.

Patient-reported outcomes measures (PROMs) have recently been used in health care systems around the world to represent the patients' views of their health status. PROMs explore different

health dimensions and can provide a score of the patient's health-related quality of life. Patients are often the best judges of how they feel, and the introduction of PROMs reflects a growing recognition that the perspective of the patient is highly relevant to efforts to improve the quality and effectiveness of health care. The potential of PROMs in conjunction with more traditional clinical measures is enormous: measure the effectiveness and risks of interventions, assess the performance of clinicians and organisations, promote practice improvement and establish value-based payments, among others.

4.2.Variables description and analysis plan

The key variables are listed below. These variables need to be collected for every patient for all centers included:

- Patient-reported outcomes (measured by EQ-5D or SF-36 questionnaires) at baseline and after treatment being initiated
- Disease Activity Score (DAS), ASDAS or BASDAI, SLEDAI and SLICC, ESSDAI at baseline and after treatment being initiated
- Disease duration
- Sex
- Age
- HAQ
- Level of education
- Profissional situation
- Comorbidities
- Biologic therapy and start date
- Biosimilar therapy and start date
- Co medication – corticosteroids, DMARD – Metothrexate, leflunomide, sulphasalazine

Other variables (if available) will allow for controlling for other parameters in regression (better case-mix adjustment)

- Socio-economic status

- Adverse event
- Mortality

4.3. Sample size

There is no specific power calculation for this type of study. The higher the number of patients, the more robust the model will be, provided there is a good control of potential sources of bias.

4.4 Statistical analysis

Descriptive analysis of continuous variables will be reported as mean and standard deviation, or median and quartiles in case of non-normal distribution, according to the biologic treatment.

Descriptive analysis of categorical variables will be displayed as frequency or proportions, according to the biologic treatment.

Data will be compared using the T tests, chi-square or Pearson's correlation according to the classification of the variables in the univariate analyzes.

Logistic and linear multivariate models (depending on outcome variable) will be constructed to determine associations of the drug (independent variable of interest or explanatory) with response and disease activity (dependent variable), adjusted for potential confounders (age, gender, duration of disease, functional capacity, etc.).

The variables of special interest for the study objectives will be included in the multivariate analyzes, regardless of the results of the univariate analyzes. Other potentially confounding variables of the relationship between these dependent variables of special interest and the independent variable will be included in the multivariate analyzes if in the univariate analysis their significance is at least 0.1.

Multivariate models will also be constructed to determine drug associations of interest, with the PROMs as an outcome.

For safety, adverse effects will be assessed by calculating the cumulative adverse events in the end of the follow-up period.

P value will be considered significant at <0.05.

The SPSS v23 will be used to analyse the data collected from this study.

5. Limitations

Depending on the number of missing data, in particular, affecting the key variable of the model “PROMs”, the model might not be robust.

6. Timeline

Access to Reuma.pt data base after scientific approval from *as soon as possible.*

7. Research team and institutions

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Contribution: Study design, protocol writing and revision, processing of the database, statistical analysis, oral/poster presentation and article conception and revision.

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Contribution: Study design, protocol writing and revision, processing of the database, statistical analysis, oral/poster presentation and article conception and revision.

8. Funding and conflicts of interest

We declare no conflicts of interest. The project has no funding.

9. Co-authory

All clinicians who actively work on the project will be co-authors with a maximum of 3 co- authors per participating institution.

10. Ethical considerations

This study will be submitted for validation and approval to the Ethics Committee.

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