Universidade de Lisboa

Faculdade de Farmácia

Biosimilar Switch in Oncology: Opportunities and Challenges

Mariana da Silva Baptista Godinho

Monografia orientada pelo Professor Doutor João Manuel Braz Gonçalves, Professor Catedrático

Mestrado Integrado em Ciências Farmacêuticas

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Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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Abstract

Biologic medicines have shifted the paradigm in oncology treatment, allowing for longer survivals and better quality of life. On the other hand, biosimilars in oncology have the possibility to decrease the price of these therapies, increasing the access to patients.

In the last years, regulatory agencies have developed multiple guidelines and protocols in order to ease the process of evaluation and authorization of biosimilars, with 3 reference products in oncology having already more than one biosimilar approved. With the regulatory and authorization processes that now exist, the proof of biosimilarity allows for extrapolation for all indications of the reference product, assuring faster access to the market.

However, in a clinical perspective, regulation about biosimilar switch is still scarce , with the European Medicines Agency leaving to each state member the decision if the reference product can be switched by a biosimilar and in which conditions. Consequently, during the approval process of biosimilars switch clinical trials are not performed and the same trend is observed in post-marketing studies. This leads to a lack of robust scientific evidence that supports the process of switching. In spite of this, the two switch trials performed in oncology reflect that there is no clinically difference when a patient is switched from the reference product to a biosimilar.

The decision on whether a patient is kept in treatment with a reference product or is switched to a biosimilar is influenced by multiple factors. Since biosimilars have lower acquisition costs, economic, political and market competition factors come into play when choosing a therapeutic. In addition, doctors and patients still have some misconceptions about biosimilars that can lead to a lack of prescription or bad adherence to therapy.

The following years will be stage for authorization of more biosimilars in the oncology area, leading to scenarios such as multiple switching. It is important to develop evidence to support switching processes, assuring more access to these valuable therapies.

Keywords: Biosimilar, oncology, Switch, Clinical trials, Bevacizumab, Trastuzumab, Rituximab.

Resumo

Os medicamentos biológicos mudaram o paradigma no tratamento do cancro, permitindo uma maior esperança e qualidade de vida. Por outro lado, os biossimilares têm a capacidade de reduzir o preço destas terapêuticas, aumentando o acesso.

Nos últimos anos, as agências reguladoras desenvolveram múltiplos protocolos e documentos com o objetivo de facilitar o processo de avaliação e autorização de medicamentos biossimilares. com 3 medicamentos de referência usados em oncologia já com mais de um biossimilar aprovado. Com os processos regulamentares agora em vigor, o conjunto de evidência para provar que o medicamento é biossimilar, garante a sua aprovação para todas as indicações do medicamento de referência, garantindo um acesso mais rápido ao mercado.

No entanto, numa perspetiva clínica, regulamentação sobre a troca de um produto de referência por um biossimilar ainda é limitada, com a Agência Europeia do Medicamento a deixar à consideração de cada estado-membro sobre a troca de biossimilares e em que condições. Consequentemente, durante o processo de aprovação de um biossimilar não são realizados estudos de "switch" e o mesmo acontece nos estudos pós-aprovação. Isto leva a que exista pouca evidência científica robusta sobre este processo. No entanto, os dois estudos de "switch" produzidos na área de oncologia, concluíram que não existe diferença clínica após a troca do medicamento de referência pelo biossimilar.

A decisão se um determinado doente é mantido numa terapêutica com o produto de referência ou trocado por um biossimilar é influenciada por múltiplos fatores. Uma vez que os biossimilares têm custos de aquisição mais baixo, o seu uso é influenciado por fatores políticos, económicos e pela competitividade de mercado. Para além disso, médicos e doentes têm ainda conceções erradas sobre biossimilares, resultando numa reduzida prescrição ou má adesão à terapêutica.

Durante os próximos anos múltiplos biossimilares vão ser aprovados, podendo levar a situações de "switches" múltiplos. É importante desenvolver evidência para suportar estes processos, assegurando o acesso a estas terapêuticas tão valiosas.

Palavras-chave: Biossimilar, oncologia, *Switch*, Ensaios Clínicos, Bevacizumab, Trastuzumab, Rituximab.

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Abbreviations

ADAs- Anti-drug Antibodies

ADCC- Antibody dependent Cellular Cytotoxicity

AE- Adverse Events

AUC- Area Under the Curve

CDC- Complement dependent cytotoxicity

CHF- Congestive Heart Failure

CHO- Chinese Hamster Ovary

CLL- Chronic Lymphocytic leukemia

Cmax- Maximum Concentration

DFS- Disease Free Survival

EGFR- Epidermal Growth Factor Receptor

EMA- European Medicines Agency

Fab- Fragment antigen binding

Fc- Fragment crystallizable

FDA- Food and Drug Administration

HER- Human Epidermal Growth Factor

HIF- Hypoxia Inducible Factor

Ig- Immunoglobulin

INF-α- Interferon alpha

IV- Intravenous

LVEF- Left Ventricular Ejection Fraction

mAbs- Monoclonal Antibodies

MCID- Minimally clinically important difference

NK- Natural Killer

NSCLC- Non-small Cells Lung Cancer

ORR- Objective Response Rate

OS- Overall survival

PcR- Pathological Complete Response

PD- Pharmacodynamic

PFS- Long Term tumor response despite failure in progression free survival

PK- Pharmacokinetic

QoL- Quality of Life

TNF- Tumor Necrosis Factor

USA- United States of America

VEGF- Vascular Endothelial Growth Factor

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1 Introduction

1.1 Biosimilar: Definition and Characteristics

A biosimilar is defined as a biological medicine that is similar with another biological drug, already approved. The drug firstly approved is also referred as the reference product. They are similar in their structure, biological activity, efficacy, safety and immunogenicity profile. In order to be approved, these new drugs need to be evaluated with high standards about quality, efficacy and safety. [1]

When referring to biological drugs it is mandatory to classify them as similar, not the same. They are not the same since the producing mechanisms are complex involving cells or bacteria. Since these are living organisms, the final molecules will have some differences in amino acid structure and glycosylation patterns, for example.The molecules themselves are also very complex, leading to batch variability. The variability present in the biosimilar can be the same observed between batches of the reference medicine, assuring however that there is no significative clinical difference. This justifies why these medicines cannot be classified as generics and are rather called similar. Since the molecules are more complex and difficult to characterize, biosimilar medicines need to have not only full data requirements but also quality studies comparing the structure and biological activity.[1,2]

A biosimilar drug needs to have the same posology and route of administration of the reference medicine. Other things such as excipients, presentation and device for administration can be different if they do not translate in clinically relevant differences.[1]

1.2 Biologics and biosimilars in oncology

In an aging population, cancer has become the disease with more incidence and second highest mortality in the world. Even with better techniques in diagnosis and treatment an increase in the number of cancer cases in the last years has been observed. In spite of this higher incidence, the global cancer mortality decreased due to the advances in treatment in the 21st century. In spite of this, some kinds of cancers are not showing a positive evolution in this field, with the mortality values being stable in the last 40 years. The first effective treatment was discovered in the 1800's with the knowledge about X-ray technology, with the use of modern radiotherapy appearing only in the 1920's.At this

time, surgical interventions were also used, but proved to be ineffective. However, the big evolution in oncology happened after World War II, with the use of cytotoxic antitumor drugs and the birth of chemotherapy. Even though these therapies had good results and are still used until today, there are some problems with these interventions such as toxicity to normal tissues and the relevant adverse effects and also the development of tumor resistance to the treatment. As a response to these problems, and with more knowledge about the tumor mechanisms, in the last 20 years, new therapies have been developed. The most relevant ones are biotechnology products that can be classified as a biological drug.[3]

Taking into account the definition of biologic drug, it is possible to say that these medicines have been around since the 18th century with the development of the small-pox vaccine. However, when talking about biologics in oncology the first ones were interferon-alpha (IFN-α) variants which were only approved at 1985. In the following years, other molecules such as growth factors- granulocyte colony-stimulating factor-cytokines and blood coagulation factors were developed with an important role in minimizing adverse effects of chemotherapy. These were classified as first-generation biologics since they are smaller and less complex molecules.[4]

Following this trend of new drugs for oncology, in 1997 the first second-generation biologic was approved. This medicine was Rituximab which was indicated in the treatment of non-Hodgkin lymphoma and lymphocytic leukemia. This monoclonal antibody lead as an example to multiple others which had different molecular targets: molecular receptors in immunological cells such as CD20 and CD52, growth factors, cell adhesion molecules, pro-survival factors and tumor cell receptors. In 2010, a new mAb was approved, with a different action mechanism. Drugs such as ipilimumab, nivolumab, pembrolizumab and atezolizumab act as checkpoint-inhibitors. They act by inhibiting the negative regulation promoted by tumor cells on the immunological system, keeping it activated and able to destroy neoplastic cells. [4]

In oncology, only a few of these second-generation biologics have biosimilars-rituximab, bevacizumab and trastuzumab. However, the development of biosimilars is an opportunity for better treatment options to an increased number of patients, a concept that aligns with the epidemiological characteristics of cancer.

2 Biosimilar: From the molecule to the market

2.1 Regulations and approval processes

In a similar way of what happens with other biological drugs, these medicines need to be approved by a centralized procedure by the European Medicines Agency (EMA), since they are produced with biotechnology. In order to be approved, all drugs need to show a benefit- risk positive balance. To biosimilars, this evaluation is possible with the biosimilarity demonstration. Because of this, the data requirements needed for the approval process are slightly different and consequently, the clinical, non-clinical and quality studies are all comparative. [1]

The first evaluation that is performed is the functional testing and molecular analysis. Non-clinical trials or animal experimentation are not always required in these cases. Since most of the drugs that are used in cancer treatment are monoclonal antibodies, the use of animal models to test safety, does not always allow extrapolation to humans, therefore, is not recommended. After the analytical testing two different clinical trials must be performed: A trial to evaluate pharmacokinetics and dynamics, when suitable, that is performed in healthy volunteers. It is also mandatory that a comparative clinical trial is performed in the therapy target population. These trials must be performed for at least one of the indications that the reference product has approval.[5,6]

Even though these new medicines need to show comparative clinical studies, just like what happens for other biological drugs, they have pharmacovigilance plans that are able to evaluate drug safety in "real world" patients. With is pharmacovigilance plans and the batch numbers, it is possible to define dynamic quality profiles for the drug. [2]

EMA approved the first biosimilar in 2006 while the Food and Drug administration (FDA) only approved the first biosimilar in 2015. Due to multiple factors, the procedures and evidence required are very different between the two agencies. [2]

In the approval process of a biosimilar product, it is relevant to define a range of differences between the reference medicine and the biosimilar that are acceptable. This range is defined by analyzing multiple batches of the reference product, since even the same product has subtle differences between batches. If the biosimilar has the same level of differences that is found in multiple batches of the reference product, it can be approved. [5]

2.2 Clinical Trials: how to prove similarity

The approval process of a biosimilar is based on the totality of evidence but also on the supposition that the new drug is similar to the originator. In order to prove that similarity, a pharmacokinetic (PK), pharmacodynamic (PD) and immunogenicity evaluation is needed. In addition, a phase III clinical trial is also necessary. In the PD and PK evaluation, a range of 80-125% difference is accepted and the values need to have a 90% confidence value. Depending on the drug that is being evaluated, the PD and PK markers are different since they must reflect the action mechanism of the drug. When choosing a PD marker time of onset, variability on exposure and sensibility must be considered. For PK evaluation, usually peak and lowest concentrations as well as the exposure are used.[7,8]

The trials that evaluate PD and PK are usually phase I trials which have healthy individuals as the study population. This can lead to a difference in immunogenicity due to a different immune status and also different metabolization and elimination rates in cases were the target patients have lesions in the kidneys or the liver. Therefore, the values obtained in phase I trials need to be adjusted to obtain the safest dose to administer to patients. [7,8]

In phase III clinical trials, the main goal for biosimilars is to prove that the activity is not higher or lower than the one of the reference product. To accomplish this, the values measured need to be within a predefined clinical equivalence margin. The study can have a non-superiority design, however, most of the times, a equivalence study is used in detriment of a non-inferiority study. In a similar way to PK and PD evaluation, in these trials there is also a predefined equivalence margin. The difference between the reference drug and the biosimilar is calculated with a 90 or 95% confidence interval and then it's analyzed if it falls within the margin predefined. A non-inferiority trial is usually used in cases when the reference drug is used at the maximum of its clinical effect and allows a smaller study population. [7,8]

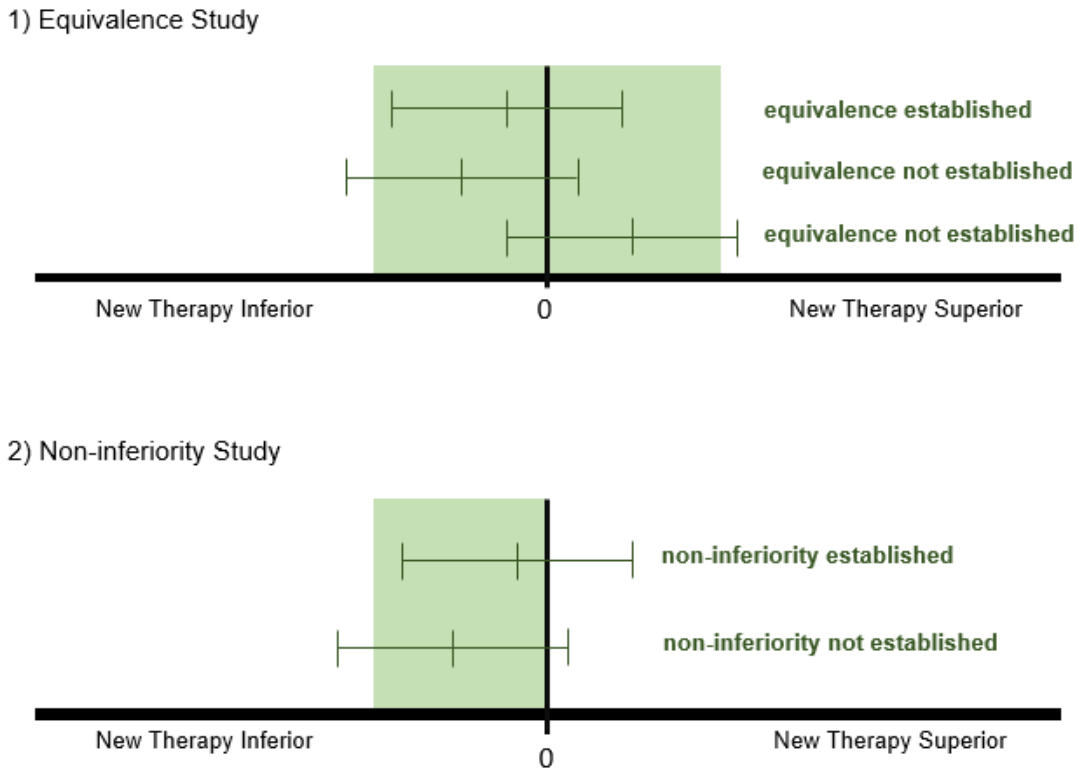

Fig. 1. Representation of the analysis of treatment difference in order to establish equivalence or non-inferiority. The green shading represents the predefined clinical equivalence margin and the results of treatment difference have a confidence interval applied. If the value of difference with the confidence interval is within the margin, equivalence or non-inferiority is established.

Adapted from Walker E, Nowacki AS. Understanding equivalence and noninferiority testing. J Gen Intern Med. 2011 Feb;26(2):192-6. doi: 10.1007/s11606-010-1513-8. Epub 2010 Sep 21

2.3 Interchangeability, substitution and switching

When it comes to biosimilar use, a relevant point to discuss is the possibility of use in patients that were already being treated with the reference drug. To give response to this topic, it is essential to evaluate if these new medicines can be interchangeable. However, EMA and FDA have different definitions about what is means for a new medicine to be interchangeable.[6]

In Europe, there is interchangeability if it is possible to exchange one medicine for another, with the same clinical effect. Besides interchangeability, there are two important concepts. When switching a drug, it is the prescriber that decides to exchange the medicine for other with the same therapeutic intent, while in case of substitution is the pharmacist that can exchange the medicine. In practical terms, only switching is performed in Europe. [2]

In the United States of America (USA), in order to be classified as interchangeable, a biosimilar needs to have clinical switching studies. After being classified as an interchangeable product, the switch from the originator to a biosimilar can be performed by the pharmacist, without the intervention of the prescriber. However, until the date of writing this article, FDA did not approve any medicine as interchangeable. The lack of these types of approvals are probably related to the fact that the development of switch clinical studies is very complex and expensive. Because of this, switch studies are usually not performed, in the standards required by the FDA, during the development period.[9]

The main concern associated with biosimilar switch is the development of immunogenicity, however, during the approval process of biosimilars physicochemical characteristics, incidence and neutralizing capacities of ADAs (anti-drug antibodies), the presence of aggregates and immunogenic impurities are evaluated. These parameters are the most relevant in the development of immunogenicity and should be similar in the reference product and the biosimilar. In addition, the post marketing switch studies already performed, have concluded that there is no differences in immunogenicity when a patient is switched from the reference product to a biosimilar.[2,5,8]

Even though the necessity of switch studies in the approval process may be discussed, the importance of them being performed post marketing authorization is clear. For some medicines these studies have been performed in the last years. However, for all biosimilars, the switch studies are only performed with the reference drug as an active comparator leading to a lack of knowledge when it comes to switching between two biosimilars of the same reference drug. [2]

2.4 Clinical Trials- Biosimilars in oncology

2.4.1 Switch Clinical Trials

During the approval process, it is essential to perform clinical trials to assure efficacy and safety of the new medicine being approved. The regulatory agencies such as EMA and FDA released some guidelines in how to perform and analyze these trials. Since biosimilars need to show they have similar efficacy and safety two types of designs can be used. Ideally, equivalence trials should be performed, since they have the ability to show that the differences between the two medicines are not large in either direction. On the other hand, non-inferiority clinical trials only assure that the new drug is not

substantially less efficacious, therefore when these trials are performed, extra scientific support is necessary in order to approve the new medicine as a biosimilar. [10,11]

Independently of the trial design, it is important to define a minimally clinically important difference (MCID). This margin is determined using previous trials performed with the reference drug or other biosimilars already approved. When a smaller MCID is used, generally, a bigger sample size is needed. [11]

The endpoint and population chosen in efficacy and safety trials should allow to identify possible differences while minimizing the influence of patient and disease factors. The population chosen needs to be homogeneous to the ones used in previous clinical trials with the reference drug, and before a subject enters the trial, previous treatments and diseases need to be accessed.[8]

2.4.2 Endpoints used in oncology

After defining the target population of a clinical trial, the following step is determining the endpoint of the study. The choice of an endpoint determines the conclusions that are able to be concluded from the study. Two different kinds of endpoints can be used in clinical trials. The primary ones usually need more time in order to have results. In response to this, surrogate or secondary endpoints have been studied. These are able to substitute primary endpoints. With the use of secondary endpoints, it is possible to have the study results faster and use a smaller population in the study. In addition to the classification as primary or secondary endpoints, in oncology there are patient centered endpoints and tumor centered endpoints. Recently, patient centered endpoints have been preferred since they are able to show evidence of clinical benefit. However, these kinds of endpoints are more subjective and cannot always be used.[12]

To determine the more useful endpoints for a study a few things must be taken into account cancer types, histological subgroups, type of study performed if evaluates curative treatment or adjuvant, treatment step and life expectancy of the patients after diagnosis. A good endpoint should be clinically relevant and beneficial and be able to be effectively measured- needs to have an appropriate scale, be sensitive and specific. Most of the times, in clinical trials, more than one endpoint is used- usually a primary and a secondary endpoint are included.[12]

In the last years, majority of the trials have used overall survival (OS), which is a patient centered endpoint. This endpoint is a time measure from the time of randomization

and the beginning of relevant treatment until the death of the patient. The major use of this endpoint comes from its' importance since the major goal of cancer treatment is to provide cure. Besides being a patient centered endpoint, it is also considered a gold standard for clinical benefit. In spite of the advantages, since it is a survival endpoint, the trials need to have a longer follow up time and need a bigger population, therefore higher costs associated. [13]

The other patient centered endpoint that is sometimes used is Quality of Life (QoL) but is not used in curative treatments but rather on palliative treatments. This endpoint can also be used in specific clinical trials that are performed with the intent of comparing toxicities between two different drugs. In clinical trials, in addition to the evaluation of patient centered endpoints, there is a need to evaluate some tumor centered endpoints. Usually, these endpoints are used as surrogate markers in clinical trials since they are faster and easier to obtain. [14]

Long term tumor response despite of the failure in progression-free survival (PFS) has become one of the most used endpoints in oncology trials. Its utilization comes from the fact that it is the endpoint that correlates more with the drug activity, however, a longer PFS does not equal a longer OS. With the use of this endpoint, clinical trials have shorter durations, and a smaller number of patients can be used. The other benefit is that is possible to have evidence about the clinical benefit of only one drug in these trials, with following survival medicines not interfering with the trial results. In spite of being used as a surrogate marker most of the times, it is used as a primary marker in hormonal cancers such as breast cancer. The benefit of using PFS as a primary marker, comes from the fact that these cancers are slowly progressive diseases and most of the drugs cause a small benefit in OS. Time to progression is an endpoint similar to PFS, however, in this endpoint, only disease progression is considered as an event, with death not being considered.[15]

Objective response rate (ORR) is defined by the number of patients with partial or complete response obtained by the treatment. Is used occasionally and it is able to reflect antitumor activity of the drug. The results are obtained in 2-3 months. This endpoint cannot be considered as a primary marker; however, it is a useful a surrogate marker in cases when OS or PFS are not possible to be evaluated, therefore, it is used is mainly on cancers with limited therapeutic options or bad treatment outcomes. This endpoint is also used in breast cancer therapy, in cases where a certain medicine is used

as a neoadjuvant therapy. Disease free survival (DFS) (or recurrence free survival) is the time to the develop a disease after complete resolution of tumor. It is more used in trials that evaluate drugs as adjuvant, therefore it can only be applied when a curative treatment is possible. Pathological complete response (pCR) evaluates tumor diameter and is used in neoadjuvant studies. In spite of the small use, it is a marker that has results in a short period of time, allowing for accelerated approvals. [12]

In the past, majority of trials have used OS, however this rate is decreasing. Response rate keeps on being the more used endpoint in oncology trials submitted for approval by FDA. The rise of non-survival endpoints has allowed for accelerated approvals by the regulatory identities. [12,13]

2.5 The example of TNF-α inhibitors

The development of biosimilar drugs is related to the end of the patents of the reference medicine. In oncology, most of the biosimilars approved are first generation biologics, which include smaller and simpler molecules. Therapeutic monoclonal antibodies are classified as second generations biosimilars. In the moment of writing, only six second generation reference medicines had biosimilars being approved by EMA: the 3 spoken above- bevacizumab, rituximab and trastuzumab- and 3 Tumor necrosis Factor alpha (TNF-α) inhibitors- adalimumab, etanercept and infliximab. [16]

Like discussed previously, in oncology, for the 12 biosimilar drugs approved, there are only 2 switch clinical trials. This discrepancy is even bigger when evaluating all switch clinical trials available. For all biosimilars, first and second generation, 178 switch studies were performed. However, 74% of those studies used as main molecules TNF-α inhibitors, with 100 of the 178 using infliximab as the reference drug. [16]

The most relevant switch clinical study was the NOR-SWITCH trial (main trial and its' extensions) which compared safety, efficacy and immunogenicity of infliximab originator and the biosimilar CT-P13. This randomized, non-inferiority and double-blind trial included patients with 6 different conditions in which infliximab has approval. It was also a phase 4 study, therefore, was performed after the marketing authorization for this biosimilar. The study population included patients with previous treatment with infliximab that were randomized to either continue the reference product or switch to CT-P13. All parameters were evaluated- safety, efficacy and immunogenicity- and were

similar in both groups. This was a trial supported by a direct grant from the Norwegian government. [17]

In a similar way, in 2000, Denmark elaborated a data base that included registries of all patients with rheumatologic diseases. With the possibility to analyze these data, it was possible to study the outcomes in patients that switched from the originator- Remicade- to the biosimilar- CT-P13. When evaluating 802 patients, the switch showed no negative impact on disease activity.[18]

The development of blinded and randomized trials are able to give us robust scientific evidence and are used as a foundation to clinical decisions. However, most of the times, the population of these trials, does not reflect the population in the real world. These data-bases, such as the DANBIO registry, are useful to provide real world data on switching and help understand the clinical responses to switching in a less controlled environment.

When comparing the use of TNF-α inhibitors to biologic drugs that are used in oncology, one major thing stands out. Most of auto-immune diseases are chronic, therefore, treatments with infliximab and adalimumab can last for multiple years. In oncology, therapeutic antibodies are until disease progression with additional recommendations that the therapies with monoclonal antibodies (mAbs) do not extend for more than 2 years since the beginning of the treatment. In the cases when there are multiple treatment phases- adjuvant or neoadjuvant- it is possible to define the time of switch. Determining the right moment to perform this switch, is more complicated in other therapy schemes.

3 Bevacizumab

ABP 215 (MVASI™), the biosimilar to Avastin ® (bevacizumab), was approved by EMA and the FDA in 2017. It is a is a recombinant Immunoglobulin G1 (IgG1) humanized monoclonal antibody produced by recombinant DNA technology using Chinese hamster ovary (CHO) cells.

The biosimilar was approved in the same indications as the reference product. This approval in all the indications as the reference medicine is based on the totality of evidence, since all the results have shown that there is similarity. This process of extrapolation can also be applied since the action mechanism is the same in all indications of this drug.

This medicine is not tested for application in pediatrics. In spite of the lack of data of the use in pregnancy, due to its action mechanism, bevacizumab alters the angiogenesis process and can lead to serious malformations and birth defects, therefore, this drug is contra-indicated in pregnancy and effective contraception during treatment is recommended. During treatment with bevacizumab fertility is affected, however ovary function is recovered. [19]

Table 1: Indications in which the reference medicine Avastin ® and the biosimilar ABP215 can be used. These are the indications approved in Europe. In the USA, bevacizumab cannot be used in ovarian cancer since there is an orphan drug exclusivity. This treatment is recommended until progression of the underlying disease or unacceptable toxicity. [19,20]

Metastatic carcinoma of the colon or rectum
Second line therapy in combination with fluoropyrimidine-based chemotherapy
Recommended dose:
5 mg/kg of body weight or 10 mg/kg of body weight once every two weeks
7.5 mg/kg of body weight or 15 mg/kg of body weight once every three weeks
Metastatic breast cancer
First line therapy in combination with paclitaxel
Recommended dose:
10 mg/kg of body weight once every two weeks
15 mg/kg of body weight once every three weeks
Unresectable advanced, metastatic or recurrent non-small cell lung cancer (NSCLC)
First line therapy in combination with platinum-based chemotherapy
Recommended dose:
7.5 mg/kg of body weight or 15 mg/kg of body weight once every three weeks
In combination with erlotinib it can be used in patients with Epidermal Growth Factor Receptor (EGFR) activating mutations
Recommended dose:
15 mg/kg of body weight once every three weeks
Metastatic renal cell carcinoma
In combination with IFN-α 2a
Recommended dose:
10 mg/kg of body weight once every two weeks
Advanced epithelial ovarian fallopian tube, or primary peritoneal cancer and also persistent, recurrent, or metastatic carcinoma of the cervix
In combination with chemotherapy
Recommended dose:
15 mg/kg of body weight once every three weeks

3.1 Mechanism of action

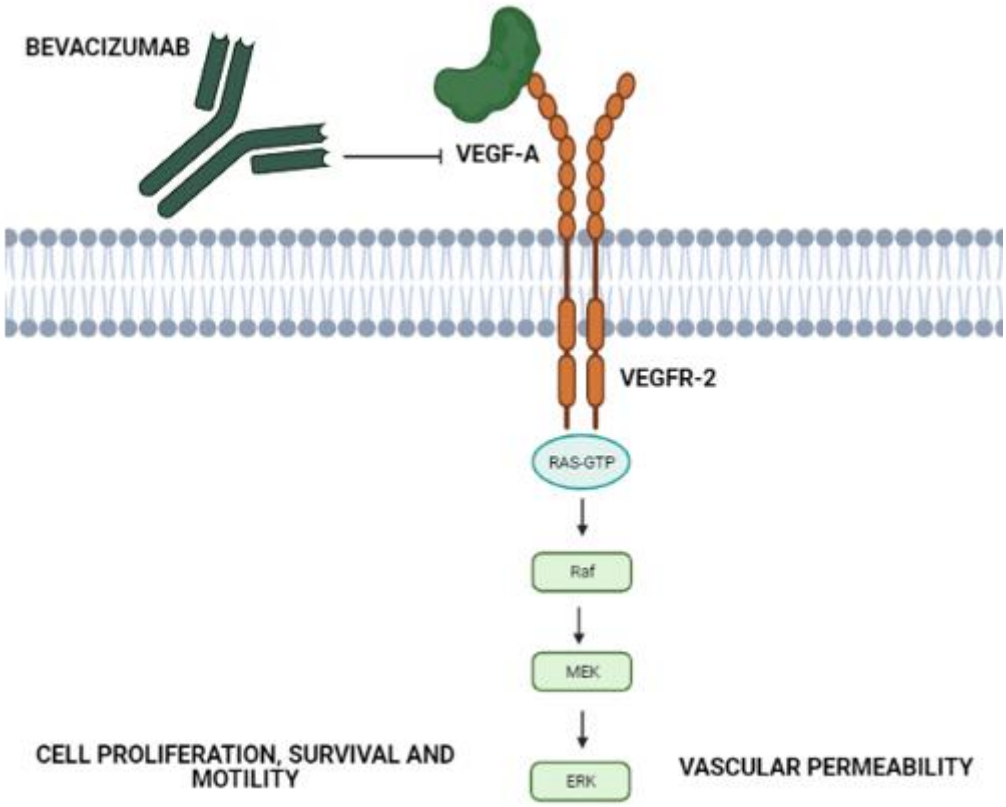

Fig.2. Schematic representation of the action mechanism of Bevacizumab

Adapted from Kanat O, Ertas H. Existing anti-angiogenic therapeutic strategies for patients with metastatic colorectal cancer progressing following first-line bevacizumab-based therapy. World J Clin Oncol.10, 52-31 2019

The tumorigenesis process is based on tumor growth. In majority of the cases this growth is possible due to the activation of hypoxia inducible factor 1-alpha (HIF-1α), since these cells have higher metabolic rates and are usually in a state of hypoxia, and consequently an increased expression of vascular endothelial growth factor A (VEGF-A). This factor, by binding to the VEGFR-2, the main receptor for signaling VEGF, will activate the Ras pathway that leads to an increase in cell division and migration, processes of angiogenesis and vascular permeability all biological processes that allow the process of tumor growth and metastasis. Both Bevacizumab and ABP 215 are monoclonal antibodies that bind to VEGF. With the administration of these mAbs, we are able to reduce the serum concentration of VEGF protein, resulting in a reduction of microvascular growth at the tumor level and also a higher vascular permeability that

increases the delivery of chemotherapeutic agents. This drug does not have any cytotoxicity functions. [21]

3.2 Drug Characterization

ABP 215 is commercialized in a sterile and preservative free liquid formulation in single use vials with the serum concentration of 25 mg/ml. The excipients used in formulation are the same used in the reference product and include trehalose dihydrate, sodium phosphate, polysorbate 20 and water for injections. It is available in 4 mL vials with 100 mg of bevacizumab and 16 mL vials with 400 mg of bevacizumab. The vials are type I glass. It is administered by intravenous infusion, in concentrations of 5, 7.5, 10, or 15 mg/kg. When stored in the vial at 2-8ºC, while kept in the outer carton, the shelf life is 24 months. In addition, this drug has shown stability for 35 days after dilution, stored at intravenous bag between 2 and 8 degrees, allowing advanced preparation of this medicine The route of administration, formulation dosage form and formulation are the same as the ones in the reference product..[21–23]

3.3 Pre-Clinical Trials

In order for ABP 215 to be approved as a biosimilar, functional and structural similarity were evaluated, particularity critical attributes such as structure- primary and high order- particles and aggregates, impurities, degradation and biologic activities. The results have shown that these two drugs are similar. When it comes to physicochemical properties, slight differences exist , however, the biological activity and functional testing were not affected, therefore proving that the differences are not clinically meaningful. [24] Fab mediated and Fc-mediated binding, were also evaluated, with consistent results to the reference drug. [25] Since there are slight differences between the European and the American version of ABP 215, analytical similarity was also evaluated with similar results between the two medicines.

In vivo assessments for these medicines were performed in A431 and Colo205 xenograft models. In both models, the results were similar when using the reference product or the biosimilar. In these tests the inhibition of tumor growth and the inhibition of tumor vascularization were evaluated since they are crucial parts of the action mechanism of this product. [26]

3.4 Pharmacokinetic evaluation

In order to assure similarity, pharmacokinetic comparations were performed in healthy individuals. This was a 3-arm trial that used Bevacizumab (EU), Bevacizumab (US) and ABP215. This trial was also randomized, single blind and parallel. Exclusion criteria included hypertension or previous treatments with antibodies or drugs that target VEGF. In the beginning of the trial, each arm included 66 subjects. Only one dose of 3 mg/kg was administered to each individual. This concentration was chosen since it allows a linear kinetics of this drug while minimizing drug exposure. However, the use of this concentration is not representative of therapeutic doses. [27]

Maximum concentration was similar in all three medicines and it was observed 1.5-3 hours after the start of the infusion. Half-life time had a value of approximately 18 days, with exposure also being evaluated using Area Under the Curve (AUC). For all the values a GLSMR with a 90% confidence interval was done, with all the comparative values being between 0.80 and 1.25 which leads to the conclusion that the three medicines have bioequivalence.[28]

Pharmacokinetic evaluation also allowed for conclusion that there is no relevant interaction between bevacizumab and most antineoplastic agents and other drugs that are used in combination therapy such as erlotinib and IFN-α 2a. [23]

3.5 Efficacy and Safety Evaluation

Efficacy and safety of ABP 215 compared with bevacizumab was evaluated in a phase III clinical trial, the MAPLE study. The study population included patients with stage IV or recurrent NSCLC, which was defined as a sensitive and homogeneous population. Even though the primary objective was efficacy evaluation, the incidence of ADAs and AE (adverse events) was also evaluated. [29]

The total study duration was of 18 weeks, divided in 6 cycles with a 3-week interval between them. One group received treatment with ABP 215 and the other with Bevacizumab. The dose was 15mg/kg for both. Both groups also received chemotherapy with carboplatin and paclitaxel (6 cycles every 3 weeks). [30]

In this clinical trial, response to treatment was evaluated with radiography analysis. Approximately 40% of patients had an objective response during the treatment with most of them having a partial response. Only 0.6% of patients in each group achieved complete

response. The conclusion of clinical equivalence was achieved comparing risk ratio of overall response, a value that was within the predefined equivalence margin. In addition, duration of response and progression free survival were also evaluated and have shown comparable values in both groups. [30]

Safety was evaluated as a secondary endpoint of this study. Most of the related to drug adverse events were grade 1 and grade 2. The grade 3 events were related with the action mechanism- anti VEGF- and were comparable between groups. These events included hypertension, gastrointestinal perforation, pulmonary hemorrhage, wound healing complications and proteinuria. The incidence of serious and fatal adverse events were also comparable between the two treatment groups and similar to the results obtained in other bevacizumab studies. There is an higher incidence of neutropenia and infection in cases when bevacizumab is administered with platinum or taxane based therapies in cases such as metastatic breast cancer and NSCLC.[30]

Immunogenicity was also evaluated, with ADA evaluation during the whole study. The incidence of these antibodies was low (1.4% in ABP 215 group and 2,5% in bevacizumab group). Most of these ADAs were transient and none of them had neutralizing capacity. [30]

4 Trastuzumab

Trastuzumab (Herceptin) is the biologic drug used in oncology that has the most biosimilars approved. At the moment of writing, there were 5 biosimilars approved by EMA. This drug is a humanized IgG1 monoclonal antibody produced by Chinese hamster ovary cells. It is indicated in combination therapies for the treatment of breast cancer: early and metastatic and also gastric cancer. There are 5 trastuzumab biosimilars approved in Europe:Ontruzant, Zercepac, Trazimera, Ogivri, Herzuma and Kanjinti. All biosimilars were approved for the same indications as the reference medicine. [31–34]

Trastuzumab should only be used in patients which are human epidermal growth (HER 2) factor positive. Therefore, before treatment initiation with any of these medicines, HER 2 testing must be performed in a specialized laboratory.[35,36]

The main concern in a therapy with trastuzumab is the possibility of cardiac dysfunction, with patients having an increased risk of cardiac complications. This risk is higher in patients which had previous treatments with anthracycline (doxorubicin or epirubicin) or the ones which already have risk factors for the development of cardiac disease- hypertension, documented coronary artery disease, congestive heart failure (CHF), left ventricular ejection fraction (LVEF) of 55% or lower and older age. In order to reduce these consequences initial evaluation and regular cardiac monitoring should be performed. In addition, if LVEF drops below 50% treatment should be suspended. [35,36]

Studies conducted in animals have not shown any alterations in fertility or harm to the fetus, however, therapy with trastuzumab should be avoided during pregnancy unless the potential benefit outweighs the risk for the fetus. [37]

Table 2: Indications in which the reference medicine Herceptin® and all the biosimilars can be used. These are the indications approved in Europe. Treatment with trastuzumab is recommended until progression of the disease, however, in early breast cancer patients, treatment should not extend beyond one year. [35,36]

Metastatic breast cancer (HER 2 positive)

Monotherapy in patients who received at least two chemotherapy regimens. Monotherapy with trastuzumab should only be considered after hormonal therapy.

Combination therapy with paclitaxel/ docetaxel when the patients have not received any chemotherapy treatment. The administration of chemotherapy drugs happens one day after the administration of trastuzumab.

Combination therapy with aromatase inhibitors- only applied in post-menopausal patients hormone receptor positive. There are no restrictions about the moment of administration of anastrozole.

Recommended dose:

8 mg/kg of body weight as a loading dose and 6 mg/kg of body weight once every three weeks or 4 mg/kg of body weight as a loading dose and 2 mg/kg of body weight once every week

Early Breast Cancer (HER 2 positive)

Following surgery, chemotherapy and if applicable radiotherapy

Following adjuvant chemotherapy (doxorubicin and cyclophosphamide or docetaxel and carboplatin) either as a monotherapy or in combination with paclitaxel or docetaxel.

Recommended dose:

8 mg/kg of body weight as a loading dose and 6 mg/kg of body weight once every three weeks or 4 mg/kg of body weight as a loading dose and 2 mg/kg of body weight once every week. The weekly regimen is administered concomitantly with paclitaxel.

Metastatic Gastric Cancer (HER2 positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction)

Combination therapy with capecitabine or 5-fluorouracil and cisplatin. Only used in patients who have not received any treatment for metastatic cancer.

Recommended dose:

8 mg/kg of body weight as a loading dose and 6 mg/kg of body weight once every three weeks or 4 mg/kg of body weight as a loading dose and 2 mg/kg of body weight once every week.

4.1 Mechanism of action

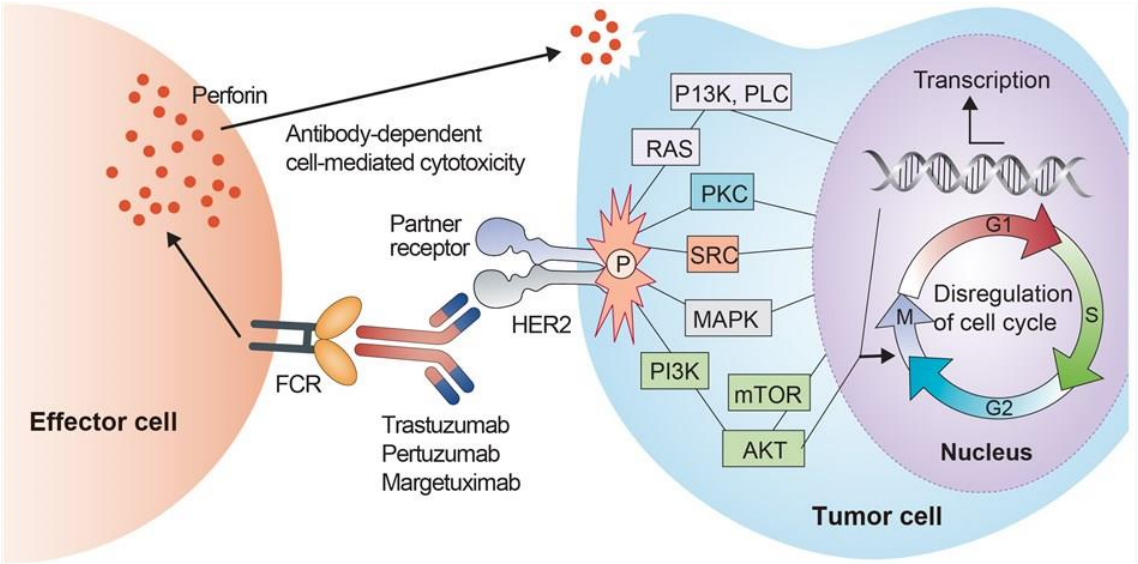

Fig.3. Schematic representation of the action mechanism of Trastuzumab. Adapted from https://www.creativebiolabs.net/rituximab-vcMMAE-21455.htm.

Trastuzumab is a humanized mAb that binds to HER2 (human epidermal growth factor 2), a transmembrane tyrosine kinase receptor. This molecule is an important marker in cancer, in particular in breast cancer. The overexpression of HER happens not only in the primary tumor site but also in the metastatic sites, resulting in an upregulation of signal transduction pathways involved in cell survival and migration. Because of its' biological action, overexpression of HER2 is associated with a worse prognosis. The administration of trastuzumab, has two main consequences. Since it binds to the extracellular domain of HER, inhibits phenomena like cell proliferation, invasion and migration. In addition, the Fc region of this antibody also has the capacity to bind to receptors in NK (natural killer) cells and macrophages, inducing cellular cytotoxicity, allowing the reduction of tumor size. [33,38,39]

4.2 Drug Characterization

Herceptin is sold as a lyophilized powder, which needs to be reconstituted in a solution for infusion, with a concentration of 21mg/mL. The dosage strength of the lyophilized power is 150 mg. The excipients are L-histidine, L-histidine hydrochloride monohydrate, polysorbate 20 and sucrose. In these cases, biosimilars and the reference medicine have slightly different formulations, with different products using different disaccharides.

The reference product has two different formulations, one for intravenous administration and other for subcutaneous administration, however, there are no biosimilars approved that are able to be administered subcutaneously Herceptin can be used in combination with other drugs such as paclitaxel, docetaxel and. aromatase inhibitors. [37]

Shelf life of these products is 48 months at temperatures between 2 and 8 degrees Celsius with a stability of 48 hours after reconstitution. [37]

4.3 Pre-Clinical Trials

The pre-clinical testing was performed using in vitro functional and binding assays. Both the Fab and Fc domain were evaluated since they are both relevant to the mechanism of the product. Antibody dependent cell cytotoxicity (ADCC) activity in NK cells and binding to FcγRI, FcγRIIb, FcγRIIIb, FcRn, and C1q protein were evaluated and shown similar results to the ones presented for the reference product. [37]

4.4 Pharmacokinetic evaluation

For the five biosimilars, pharmacokinetic evaluation was performed in phase I clinical trials. All of the trials were performed in healthy males and only a single dose was administered. The dose chosen was 6mg/kg, which is consistent with the highest doses administered during the treatment. The five clinical trials also had, as exclusion criteria, previous treatments with mAbs or fusion proteins. Trazimera, Ontruzant and Kanjinti were compared in a parallel 3 arm trial, using the US and EU Trastuzumab. For the other two drugs, a head-to-head trial was performed. The endpoints used were always the same: Cmax evaluation, half-life time and also AUC at last sample and also extrapolated for infinity. In order to assure bioequivalence adjusted least squares geometric means with 90% confidence interval was performed comparing each biosimilar to its' reference. The results were all near 1, being within the interval defined. Even though there are multiple trials between the reference and biosimilar, no trial was performed between the biosimilars available. The values were pretty similar for all of them, however bioequivalence conclusions can only be achieved with the appropriate trial design. [27,29,40–42]

4.5 Safety and Efficacy evaluation

Only 3 clinical trials have compared efficacy and safety of biosimilars and trastuzumab. The population of these trials included HER 2 positive patients with early breast cancer. All of them used two groups- biosimilar and reference- in adjuvant and neoadjuvant phases of treatment. However, in the adjuvant phase, the concomitant chemotherapy scheme was slightly different between the trials. Two of them used cycles of chemotherapy with docetaxel, 5-fluoruracil, epirubicin and cyclophosphamide, while the LILAC trial only used epirubicin and cyclophosphamide. In order to evaluate efficacy all trials used pathological complete response and the results were similar between both groups, reference and biosimilar. The trial which compared SB3 to trastuzumab also compared the breast pathologic complete response and overall response rate. All these variables had similar results in both groups. With these results it is visible that the efficacy is similar between the reference and biosimilars. However, due to the different clinical trial designs, it is not possible to conclude that the biosimilars are similar between them. [43–45]

In the 3 clinical trials referenced before, safety evaluation was also performed. The incidence of adverse events was similar between groups in all of them. However, between the 3 trials the most common adverse events were sightly difference, with neutropenia, infusion reactions, alopecia and asthenia appearing in all trials. Immunogenicity was also evaluated in both trials with an incidence of ADAs inferior to 1% in all trials. However, the cut-off points and methods were not explained. [43–45]

5 Rituximab

This drug is a human/murine, chimeric anti-CD20 monoclonal antibody that is used in multiple B-cell malignancies. Similarly to the previous mAbs, this drug is also a IgG1. Rituximab (MabThera) has 5 biosimilars approved by EMA: Truxima, Rixathon, Riximyo, Ruxience and Blitzima. All of the biosimilars can be used in the same indications of the reference medicine, which include non-Hodgkin's lymphoma and chronic lymphocytic leukemia (CLL). These medicines are also used in other non-oncologic diseases such as rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis and pemphigus vulgaris, however, the last ones will not be detailed in this work. [11,46]

The treatment with rituximab should be preceded by premedication as a prophylactic measure for reducing adverse reactions. This premedication consists of an anti-pyretic and antihistaminic. In hematology indications such as non-Hodgkins lymphoma and Chronic lymphocytic leukemia, the premedication can also include a glucocorticoid, in the cases when that drug is a part of the chemotherapy protocol. In patients with chronic lymphocytic leukemia who have a low lymphocyte count, the administration of prednisolone before infusion with rituximab is also recommended. [47,48]

Table 3: Indications in which the reference medicine Mabthera® and all the biosimilars can be used. These are the indications approved in Europe. This product can be use in pediatrics if previously untreated. In pediatrics the indications include advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukemia (mature B-cell acute leukemia) (BAL) and Burkitt-like lymphoma (BLL)[47,48]

Non-Hodgkins lymphoma

Combination therapy in previously untreated adult patients with stage III-IV follicular lymphoma with chemotherapy.

Recommended dose:

375 mg/m^2 body surface area per cycle, for up to 8 cycles. The administration of this product should happen in the first day of the cycle, after the administration of a glucocorticoid.

Maintenance therapy in patients responding to induction therapy for the treatment of adult follicular lymphoma.

Recommended dose:

375 mg/m^2 body surface area once every 2 months if the patient was not previously treated for follicular lymphoma. 375 mg/m^2 body surface area once every 3 months, in cases of relapsed or refractory follicular lymphoma

Monotherapy in adult patients who are chemoresistant or are in their second or subsequent relapse after chemotherapy for treatment stage III-IV follicular lymphoma.

Recommended dose:

375 mg/m^2 body surface area, administered as an intravenous infusion once weekly for four weeks

Combination therapy with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) in patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma.

Recommended dose:

375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP.

Chronic lymphocytic leukemia

Combination with chemotherapy is indicated in previously untreated patients with relapsed/refractory CLL.

Recommended dose:

375 mg/m^2 body surface area administered on day 0 of the first treatment cycle followed by 500 mg/m^2 body surface area administered on day 1 of each subsequent cycle for 6 cycles in total.

5.1 Mechanism of action

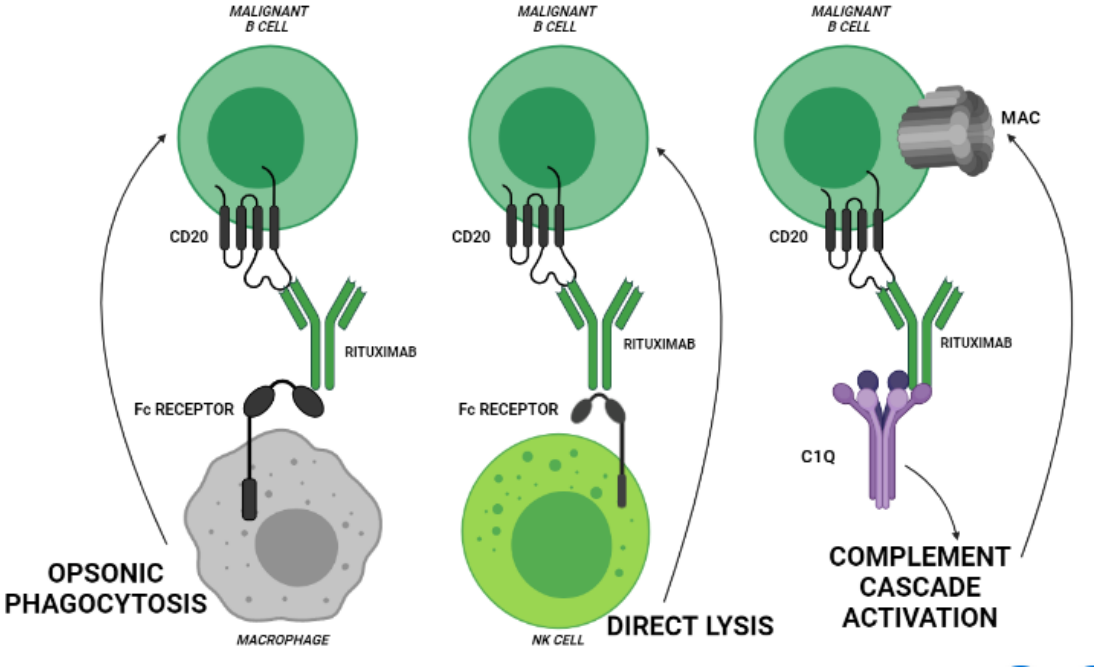

Fig.4. Schematic representation of the action mechanism of Rituximab. Adapted from Taylor, R., Lindorfer, M. Drug Insight: the mechanism of action of rituximab in autoimmune disease—the immune complex decoy hypothesis. Nat Rev Rheumatol ***3,*** *86–95 (2007).*

Rituximab is a mAb that binds with CD20, a transmembrane receptor. This receptor is present in some circulant B cells, and, in malignant cells, it is overexpressed. This drug has the ability to reduce malignant cells trough 4 different mechanisms. Fc mediated phagocytosis and ADCC rely on the capacity of the Fc portion of the immunoglobulin binding with receptors present in cells such as macrophages and NK cells, respectively. With the binding of the antibody with CD20 receptors, two different processes are initiated: reorganization of the CD20 receptors in lipid rafts inducing complement dependent cytotoxicity and also cross links in CD20 which leads to the activation of the non-classical pathway of apoptosis. [49]

5.2 Drug Characterization

Rituximab is sold in a liquid formulation, as a sterile solution for injection, in vials with a concentration of 10mg/ml. Each vial has 500mg of rituximab as an active substance. This pharmaceutical formulation is administered by infusion. The excipients include sodium chloride, tri-sodium citrate dihydrate, polysorbate 80 and water for injections.

When stored between 2-8º C the shelf life of this product is 3 years, however, in order to assure this stability, the glass vial should be kept inside the outer carton. The prepared infusion solution is stable for 24 hours at the same temperature. [50]

5.3 Non-Clinical Trials

In order to assure biosimilarity, some in vitro pharmacodynamic studies were performed. Using a cell line expressing CD20, the binding activity was evaluated and compared between the reference product and the biosimilar. In this same cell line, apoptosis induction was also evaluated. In addition other binding affinities were evaluated- binding affinity to FcRn, FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa, FcγRIIIb, C1q. Functional evaluation included ADCC activity and complement dependent cytotoxicity (CDC) activity analysis. [50]

Before the clinical trials, in vivo testing was also performed, using cynomolgus monkeys as a model. After infusion once a week of the reference product and the biosimilar, during 8 weeks, the depletion of B cells and alterations in the mesenteric lymph nodes were similar between the two groups. [50]

5.4 Pharmacokinetic evaluation

With the objective of evaluating CT-P10, a phase III, non-inferiority clinical trial was performed. It evaluated pharmacokinetics, safety and efficacy, and the study population included patients with stage II–IV, CD-20 positive, low-tumor-burden follicular lymphoma. Similarly to what happens in other clinical trials with biologics, patients needed to be naïve to therapy with rituximab or its biosimilars. In this study the treatment cycles only included this drug that was administered in a dose of 375 mg/m² during the induction period- one administration a week for 4 weeks. Only continued in the study patients with a response to the treatment, either complete, unconfirmed, or partial. During the maintenance period the dose administered was the same (375 mg/m²) and the administration was every 8 weeks during 6 cycles. [51]

In this study pharmacokinetics were evaluated as a secondary endpoint and included the evaluation of maximum [C_{max}] and trough [C_{trough}] serum concentrations. The mean serum concentration (µg/mL) profiles were similar between the two drugs.

5.5 Efficacy and safety evaluation

The primary endpoint for this trial was evaluation of overall response in the intention to treat population. The overall response was, at month 7, 83 % for CT-P10 and 81% for the reference product. With the statistical evaluation was possible to conclude that the two medicines were similar, and the two drugs had therapeutic equivalence. The same similarity was observed when evaluating bone marrow lesions. When it comes to safety evaluation, one important topic was the evaluation of B cell depletion, which was similar between the two treatment groups. The incidence of adverse events was also similar. The most common adverse events included infusion reactions, upper respiratory infections and fatigue. Immunogenicity was also evaluated in this group of patients with a very low incidence of ADAs and with similar values between the two groups. However, the presence of these antibodies was correlated with lower serum concentrations of the drug, B-cell reappearance and higher incidence of infusion reactions. [51]

6. Switch Clinical Trials in Oncology

Like discussed before, only the FDA has special regulations in order to classify a biosimilar as interchangeable. In order to obtain this classification, switch clinical trials need to be performed. The design of these trials must assure that the safety or loss of efficacy risk is the same when switching is performed when compared to the use of the reference without any alternation/switch. Despite the fact that EMA does not require switch clinical trials, the existence of appropriate studies to base the switch decision are needed, since biosimilarity studies usually are performed in treatment-naïve patients. [52]

Just like what happens in other clinical trials, an adequate design is important in order to assure the validity of the results. These studies need to include at least one switch, even tough FDA recommends the inclusion of at least 3 switches. Also in these recommendations, it is said that the primary endpoint should consist on the evaluation of clinical pharmacokinetics, because it has the capacity to show the impact in exposure and immunogenicity development. In addition, a safety evaluation should also be performed during these studies. [52]

In the oncology area only two switch trials were performed, one of them with the trastuzumab biosimilar Kanjinti- LILAC trial- and the other used Truxima, a Rituximab biosimilar- NCT02260804. These two trials had different experimental designs. Besides that, these two drugs are used in different areas, Kanjinti is used in oncology, in particular breast cancer, while Truxima is used in hematology, having an important impact in the treatment protocols and the use of biologics in these conditions.

The clinical trial that compared Kanjinti with Herceptin was performed in women with more than 18 years with early-stage breast cancer. The choice of this population was made accordingly to the guidelines that recommend the use of a homogenous population. The trial had 3 different phases, with the biologics being used in only 2 of them. The first phase consisted of an induction period with epirubicin 90 mg/m^2 and cyclophosphamide 600mg/m^2. This phase lasted for 12 weeks. Following these 12 weeks, the individuals that had response to chemotherapy were exposed to a second treatment period- the neoadjuvant phase, which consisted of 4 cycles administered with a 3-week interval between them. In this phase, one group was treated with paclitaxel 175 mg/m^2 plus Kanjinti while the other was treated with paclitaxel 175 mg/m^2 plus Herceptin. Following the neoadjuvant phase, subjects had removal surgery. After surgery, adjuvant phase started, a phase that lasted for one year. This phase was the only one where switch was performed, with three different treatment groups. One which kept Kanjinti, another which kept Herceptin while others switched from Herceptin to Kanjinti. In consequence of the trial design, data on switching are only available during the adjuvant phase. Besides that, in order to be consistent with previous trials using trastuzumab, efficacy evaluation was performed using pathological complete response, evaluated after the neoadjuvant phase and surgery. Therefore, in the switch portion of this trial only safety was evaluated. During the trial, the incidence of adverse events was similar in the adjuvant and the neoadjuvant phase, even in the switch group. However, the highest incidence of adverse events was during the adjuvant phase in the group treated with Kanjinti. These events have not shown a correlation with treatment with Kanjinti and are probably the result of complications due to surgery or chemotherapy. The most common adverse events included neutropenia, infection and infusion reactions. An important concern in therapy with trastuzumab is also the decline in LVEF, however, during this study, cardiac alterations did not have an influence in the treatment course. The adverse events that occurred during the study only implicated withdrawal from the study in 1% of patients,

the same percentage in both treatment groups. Immunogenicity and the development of anti-drug antibodies was also evaluated in this trial. Only 2% of all patients in the study tested positive for ADAs and none of these antibodies had neutralizing capacity. Moreover, the presence of this antibodies was transient and did not represent a safety concern.[43]

The NCT02260804 trial compared the biosimilar Truxima with its originator Rituxan. The switch portion only included the last 6 cycles of treatment; therefore, the safety and efficacy results were only possible to evaluate at 24 and 36 months. This trial included patients with low tumor burden follicular lymphoma who have not received previous treatment with Rituximab. In the beginning of the trial patients were randomized and allocated to the Truxima group or the Rituxan group. The treatment was kept the same during the induction period and the first year of maintenance. In the second year of the maintenance period, the patients in the Rituxan group were switched to treatment with the biosimilar. The doses used and the treatment scheme were already described in the Rituximab section of this article. A similar number of subjects enrolled in the second year of the maintenance period, assuring a similar population in both treatment groups. The withdrawal rate was similar between the two groups and had loss of efficacy as a major cause. 24 and 36 months after the beginning of the study efficacy was evaluated . Progression free survival, time to progression and overall survival was similar in both groups. These results support the conclusions that the switch from the reference medicine to a biosimilar do not result in a lower efficacy. However, with this trial design, in the switch portion only secondary efficacy points were evaluated, since the primary efficacy endpoint was evaluated at 7 months- overall response rate. During the study, the incidence of all-cause mortality and serious adverse events was similar in both treatment groups. The most common non serious adverse events were infusion reactions, infections, fatigue and neutropenia and had a similar incidence in both groups. These types of adverse events are common and expect in therapies with mAbs. In this study immunogenicity was not evaluated. [51,53]

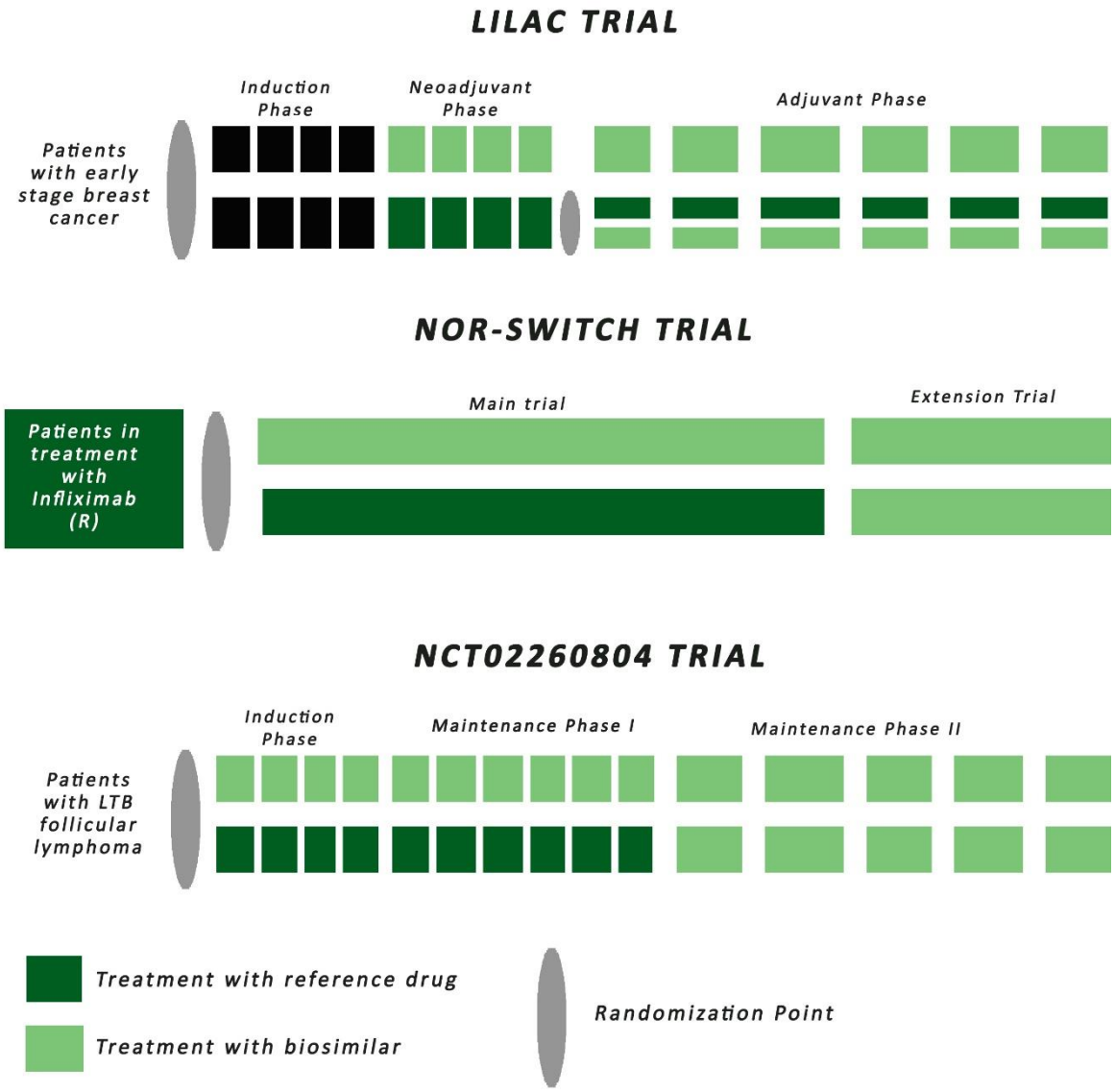

Fig. 5. A graphic representation of the switch clinical trials performed in oncology and the NORSWITCH trial, the most recognized switch trial for biosimilars overall. With the graphics is easy to understand the different trial designs used and the implications in the conclusions that can be obtained.

7 Factors that influence the use of biosimilars in oncology

7.1 Economy, Market Competition and sustainability

In Europe, biosimilars usually enter the market at a price 30% inferior to the reference medicine. However, with the entrance of a biosimilar in the market, a decrease in the price of the reference medicine is also observed. Besides the tabled prices for these medicines, usually companies have confidential reductions that, in some cases, decrease the drug price in 90%. This nontransparent differential pricing leads to a lack of fair competition in the biologics market. Studies also reveal that national negotiations allow substantial price decreases in reference products, with the biosimilars loosing their advantage due to a phenomena of market equilibration. Even though the problem of market harmonization exists, leading to difficulties to the biosimilar market penetration, with the approval of biosimilars and consequent reduction of costs, resources become available to either increase access to biologics to more patients and in the earlier stages of diseases or be used in new therapies, technologic advances or the healthcare services. [54]

With the rise of biosimilars, and in particularly in Europe, brands that produce the reference drug, in order to keep a market share, develop products that either have a new route of administration, dosing improvements or second-generation products. A good example of these happened with Roche® and the development of a antibody-drug conjugate of trastuzumab with the drug emtansine. [55]

When we talk about health policies that influence the penetration of biosimilars, multiple factors need to be analyzed: regulatory landscape, awareness- patient and health professionals- incentives, pricing rules and purchasing mechanisms. In order to evaluate the market for biosimilar uptake, volume development and price competition also need to be analyzed. However, when evaluating the market share of a biosimilar, other topics may need to be taken in consideration. Trastuzumab is a good example of discrepant market shares of biosimilars in Europe. The development of a subcutaneous formulation, that allows cost reduction and more comfort for the patient, was the medicine of choice for some countries, therefore, the use of IV trastuzumab was reduced, leading to a very reduced market share for the biosimilar. [56]

Policies applied in this area must assure that the market of biosimilars remains competitive and sustainable. In order to assure sustainability multiple factors ended to be taken in consideration. A sustainable market for biologics needs to assure patient access and prescription choice; the involvement of all stakeholders in the decisions; budget evaluation in the long term and the efforts for the market to remain competitive and assuring the adequate supply. With a sustainable market for biosimilars it is possible not only to reduce costs and increase the use of biological drugs but also to incentivize the production and the development of safe and high-quality biologics. In spite of already high levels of market share of biosimilars, in the next 5 years and with the loss of exclusivity of innumerous biological medicines an explosion of the number of biosimilars will occur. In the oncology area, the PD-1 inhibitors are the main candidates for the biosimilar development, with high market penetration. In Portugal, and for the mAbs used in the oncology area, biosimilars represented approximately 30% of the total market, with the market as a whole experiencing a price reduction of 14%. However, the price reduction did not result in lower costs, since the cost of treatment per day/per capita increased since the approval of the first biosimilar in oncology. These values allow the conclusion that more patients had access to biological treatments since biosimilar approval. The real advantage of biosimilars is related to health costs and treatment access. With this in mind, biosimilars should be presented as a solution to affordability issues, huge medical bills and consequently non-adherence to therapy. However, the economic impact of biosimilars is not the same in every region with 40% cost reductions in Europe and only 9% of estimate savings in the US. This slower uptake has multiples causes such the higher standards in order to consider a medicine interchangeable but also regulatory and patent litigation processes. [55]

7.2 Health workers' opinions on biosimilars

In order to assure that biosimilars have the right market uptake, these medicines need to be prescribed by physicians.

In 2019 a survey was performed that evaluated the knowledge and opinion of American rheumatologists. Most of the doctors that responded to the survey were familiar with the definition of a biosimilar and other concepts such as interchangeability. When asked to rank the criteria used on choosing a reference product or a biosimilar, 57% used effectiveness as the first criteria to their decision, with factors such as reduced cost or data on switching only appearing as the 4th and 6th criteria, respectively. In addition, physicians

also considered to switch a patient from the reference product to a biosimilar in cases of loss of efficacy. The foundation used to make these kinds of decisions shows a lack of knowledge about biosimilars, since they proven similar safety and efficacy, therefore are not a solution in cases of lack of therapeutic response. The same lack of knowledge was observed in similar studies with oncologists. [57]

In spite of this and in a different direction to previous studies, most of doctors (73%) will likely prescribe a biosimilar to a treatment naïve patient with the same disease which supported approbation. This percentage is much smaller when we talk about patients with conditions with approval by extrapolation or the ones in treatment with the reference medicine. In oncology, since therapies have such higher costs, physicians have also evolved in a direction in prescribing more biosimilars. [58]

In addition to doctors, pharmacists also have a role in biosimilar uptake. As members of the pharmacy and therapy commissions, these professionals are responsible to elaborate therapeutic formularies and have the decision to include them or not. These decisions are based on totally of evidence but also take in consideration economic and administrative factors. Pharmacists are also responsible for the development of educational materials to patients and doctors, a tool that is important in order to better uptake. When deciding on including a biosimilar in a therapeutic scheme, protocols need to be actualized and a robust infrastructure must be developed in order to track the biosimilars used and have a good pharmacovigilance system in place. [59]

7.3 Patients' opinions on biosimilars

Nowadays patients want to be involved in their treatment choices and decisions, even though usually clinicians make the main decision about the treatment. A negative opinion on biosimilars can impact the treatment adherence and the treatment outcome. Therefore, it is important to educate patients about biosimilars, with a positive message about these medicines.

When talking to patients about biosimilars, in particular, when presenting a biosimilar switch, there are a few points to consider. In first place, the message should be understandable, concise and using simple language. It is also relevant to make sure that the information is accordingly to the most recent knowledge. A positive and empathic communication is preferable, with emphasis on the equalities and positive points of biosimilars. Every patient is different and consequently the information must be tailored

to their needs and concerns regarding also their demographics and health literacy. Regardless of the patient, the use of supportive material is always a plus. These materials should also be updated and adapted to the literacy level of the patient. When it comes to health decisions, in particular when talking about biosimilar switch, the patients should not be exposed to mixed messages. Therefore, it is of highest importance that all healthcare providers and stake holders transmit the same message in order to assure correct decisions and treatment success. [60]

With the right communication and education strategy, a small percentage of patients will decline therapy with biosimilars. This study was performed with patients with rheumatoid arthritis and anti TNF-alpha therapy. The results shown that patients are more likely to refuse therapy with a biosimilar if they already have a negative attitude towards generic medicines. The non-acceptance of biosimilars is also more common in older patients. The concurrent use of a biosimilar does not have any influence on the choice of a reference medicine vs a biosimilar. [61]

7.3.1 Nocebo Effect

The definition of the placebo effect is widely known, and it is, in most clinical trials taken in consideration. In a complimentary way, there is also a phenomenon called "the nocebo effect". The first definition of nocebo effect was proposed by Kennedy in 1961 and it was the development of an adverse effect from an inert treatment. More recently, the term nocebo effect is used when an adverse effect occurs, and it can not be attributed to the pharmacological properties of the therapy. In a clinical point of view the main problem with the nocebo effect is the lack of adherence to therapy and higher costs. [62]

There are a few factors that can increase the rise of a nocebo effect: contextual factors, individual negative expectations, and symptom attribution. All of these factors have been studied in multiple trials, however, there is still few research studies in how to reduce this effect. Most of the strategies in order to reduce the nocebo effect are educational and involve a contextualized description of the adverse effects or an explanation about this effect and the possible outcomes in a study.[62]

The nocebo effect is of high relevance when we talk about biosimilar switches, since there are still some negative perceptions about these therapies. The nocebo effect translates it self in higher discontinuation rates when compared to the reference medicine.

Johlee et al. analyzed the impact of this nocebo effect by comparing discontinuation rates in double blinded trials versus open-label studies. Even though more research is needed, open-label studies with biosimilars of infliximab had higher discontinuation rates than the blinded ones. The main problem with the development of a nocebo effect in these cases is the social perception of less safety and efficacy of biosimilars. In the particular case of biosimilar switch, lower discontinuation rates were observed when the patients were involved in the switch decision when in contrast to cases when the switch was mandatory.[63,64]

In spite of the need for studies with an adequate design in order to evaluate the impact of the nocebo effect in biosimilar switches, the focus should be on clinician-patient communication in order to reduce concerns about the therapy and reduce the possible development of this effect. In addition, it is important to not forget that even though the clinical studies back up safety and efficacy of biosimilars, the manufacturing process and molecular structures of these medicines is slightly difference, with the possibility to increased adverse events in a real world population, different from the one tested in clinical trials. [64]

8 Multiple Switching

The development of new biosimilars has allowed for better therapeutic opportunities. However, with the current health policies scenario, multiple switches may occur. These switches may occur in cases when a new biosimilar is introduced with better conditions or when a patient has a worst therapeutic outcome with a new medicine. When talking about switching it is important to distinguish two types of switching. A medical switch occurs when the patient does not have good clinical results with a medicine. When we talk about biosimilar switch, most of the cases, are non-medical switches when the decision is based on politic or economic incentives. With the biosimilar market in a constant change, there is a risk of complications due to multiple switches.[65]

The studies performed in the area of biosimilar switches only include one switch, leading to a lack of robust evidence about multiple switches. In addition, the few studies that include multiple switches, have conflicting results. The main challenge with multiple switches is caused by the fact that these medicines have slightly different structural components, such as glycosylation patterns. Due to this, the immune system of the patient can recognize the drug as a foreign body, leading to immune reactions. These reactions can be translated into a loss of efficacy or the development of adverse events. Even though the loss of efficacy, development of adverse events and tolerability issues impose themselves as a concern, their impact is not well known. The discontinuation rates following a switch have highly variable values in multiple studies. In addition, these studies did not have the minimum requirements to be considered as robust evidence. The reactions described in the last paragraph- tolerability issues, adverse events and loss of efficacy- can be caused by the development of anti-drug antibodies. The development of immunogenicity is a amplified in the cases of multiple switches. However, most of the times ADAs are transient and their incidence in clinical trials and real-world evidence is low. [66]

Another challenge that arises with multiple switches of biosimilars is the difficulty to trace adverse reactions to the medicine that caused them, a problem that is increased since most of these reactions only appear months after the drug administration. With the biosimilars that can be used in a non-hospital setting such as subcutaneous formulas, the problem increases, since the ability to report and identify adverse reactions is much lower.

Multiple Switching of biosimilars includes 3 different scenarios which have different challenges. The switch can occur between an originator and a biosimilar, between two or more biosimilars of the same drug or between a biosimilar and the reference drug, which is also called a switchback.

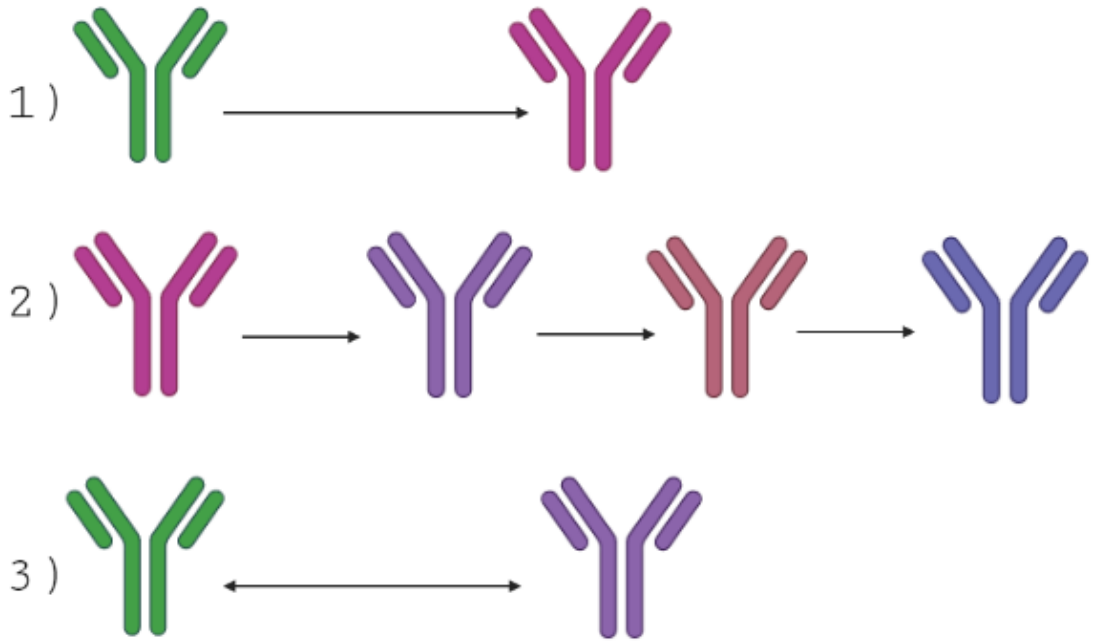

Fig. 6. Schematic representation of the 3 different scenarios of multiple switching.

The patient starts the treatment with the reference medicine and is then switched to a biosimilar. This switch can be motivated by political and economic factors.

The patient starts the treatment with a biosimilar and during the process is switched to multiple biosimilars of the same drug.

The patient that switched to a biosimilar is switched back to the reference drug due to a lack of response, tolerability issues or adverse events. The switchback process can also happen due to non-medical reasons- political and economical factors.

Majority of biosimilar switches fall in the first scenario, in cases when a reference drug loses the market exclusivity and, due to economic reasons, the patients are switched to the biosimilar drug, since it was proven to have the same efficacy, safety and quality with lower costs for the health system. However, due to health politics, the third scenario is getting more common, when a reference drug has its price lowered and becomes competitive with the biosimilar, resulting in a switchback. [65]

Scenario 2 is simultaneously the less common but also the one with more challenges due to a lack of evidence. During the approcal process of a new biosimilar, safety, efficacy and quality are compared to the reference medicine, and the evidence allows the conclusion that the biosimilar can be used in the place of the reference drug. Even though all biosimilars pass trough this process, there are few trials that compare similarity between to biosimilars of the same drug. Therefore, the switch from one biosimilar to another is not assured by scientific evidence and the structural changes present can lead to adverse events and tolerability issues.[65]

The challenges of multiple switches are greater in anti- TNF-α medicines since the treatment periods are longer. In most of cancers, the treatment cycles last for 2 years and, in that period, economic and politic changes in biosimilars are less relevant. However, with the rise of biosimilars the market will become more competitive in the following years, with these alterations becoming more significative. Another concern is the lack of supply of some of these medicines, leading to abrupt switches to other biosimilars in order to assure treatment continuity. On either case, more evidence is needed in order to make the choice of to switch or not to switch.

9 Conclusion

Biosimilars started being a topic of discussion 20 years ago, with the development of the first molecules. Since then, they have been implemented in multiple areas. In oncology, the development and use of biosimilars is more recent. In this area, biological products such as mAbs, allowed for better treatment outcomes in most cancers, transforming cancer in a chronic disease with high survival rates after diagnosis. With the development of biosimilars, is it possible to have the same clinical benefit, with similar efficacy, safety and quality, reducing the costs and increasing the market competitivity. The development of biosimilars is also a motor for innovation, with the development of new formulations and conjugated therapies.

The main discussion topic about biosimilars is the process of switching a patient from the reference product to a biosimilar. Since these two products have no meaningful differences in clinical aspects, most of these switches are based on non-medical criteria. In spite of this, it is important to have robust clinical evidence that can assure that the switch process does not come with disadvantages for the patient. In some areas such as inflammation and auto-immune diseases, this evidence already exists, however, in oncology the evidence available is scarce and the trials use different designs and endpoints. Therefore, the main challenge of biosimilar switch is the development of scientific evidence that can support the process of switching. This is a bigger difficulty in oncology when compared to other areas, since the treatment duration is smaller, and are less opportunities for switching a patient. These kinds of trials are also very expensive and could delay the authorization process of the biosimilar, one that must be faster and simpler than the one passed for the reference product. The other problem with these trials is that most of the time trial population does not have in account the target population of the drug. In a real-world context, multiple other factors such as patient and physicians' perceptions can affect the treatment adherence and benefit.

As a response to this challenge, and since switching is already happening in the oncology context in multiple hospitals, data on these patients should be collected and analyzed allowing for data on switching in the target population. In the following years, more biosimilars are going to be approved and started being used in oncology. With the possibility of multiple switching between biosimilars, it is even more important to have scientific evidence in this context.

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