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REVIEW
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Randomized clinical trials to register biosimilar trastuzumab drugs: a scoping review, Brazil, 2020

Estudos clínicos randomizados para registro de biossimilares trastuzumabe: uma revisão de escopo, Brasil, 2020

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ABSTRACT

Introduction: Breast cancer has high incidence rates in Brazil and worldwide and it is estimated that about 20% of them are classified as *Human Epidermal Growth Fator Receptor* – tipo 2-positive (HER2-positive). For the treatment of this type of cancer, the use of targeted therapies is indicated, using biological drugs, among them, trastuzumab. As it is considered a high-cost drug, the entry of biosimilars into the market can reduce costs to health care services. **Objective:** To analyze the phase III clinical studies of biosimilar trastuzumab approved in Brazil until 2020. **Methods:** A scoping review was conducted with clinical trials used to register biosimilar trastuzumab drugs at Anvisa. The data were analyzed regarding: i) treatment protocols involved in the studies; ii) endpoints and investigated population features; iii) biosimilar drugs safety profile. **Results:** Six randomized clinical trials were selected, analyzed, and compared. The studies were carried out with different treatment protocols, endpoints and drugs. The complete response rate was analyzed in most studies, followed by the complete pathological response. Regarding the investigated population, the studies involved the analysis of the intention-to-treat population and/or per-protocol. In all studies, the biosimilar safety profile was similar to that of the reference drug. **Conclusions:** The analyzed studies were able to demonstrate similarity between biosimilars and the reference drug regarding safety and efficacy; however, they showed differences in their methodology, population and outcomes analyzed.

KEYWORDS: Breast Cancer; Trastuzumab; Biosimilar

RESUMO

Introdução: O câncer de mama apresenta alta taxa de incidência no Brasil e no mundo e estima-se que cerca de 20% dos casos sejam classificados como *Human Epidermal Growth Fator Receptor* – tipo 2-positivo (HER2-positivo). Para tratamento desse tipo de câncer é indicado o uso de terapia-alvo, utilizando medicamentos biológicos, dentre eles, trastuzumabe. Por ser um medicamento considerado de alto custo, a entrada de seus biossimilares no mercado pode promover redução de custos aos serviços de saúde. **Objetivo:** Analisar os estudos clínicos de fase III de trastuzumabe biossimilares aprovados no Brasil até o ano de 2020. **Método:** Foi realizada uma revisão de escopo com estudos clínicos utilizados para o registro dos medicamentos biossimilares trastuzumabe no âmbito da Agência Nacional de Vigilância Sanitária (Anvisa). Os dados foram analisados quanto: i) aos protocolos de tratamento envolvidos nos estudos; ii) aos desfechos e características das populações investigadas; iii) ao perfil de segurança dos medicamentos biossimilares. **Resultados:** Foram selecionados, analisados e comparados seis estudos. Os estudos foram realizados com protocolos de tratamento, objetivos e medicamentos diferentes. A taxa de resposta completa foi o desfecho primário analisado na maioria dos estudos, seguido da resposta patológica completa. Em relação à população, os estudos envolveram a análise da população com intenção de tratar e/ou os pacientes que completaram o tratamento. Em todos os estudos, o perfil de segurança dos medicamentos biossimilares foi semelhante

ao do medicamento de referência. **Conclusões:** Os estudos analisados foram capazes de demonstrar similaridade entre biossimilares e o medicamento de referência em relação à eficácia e à segurança, porém apresentaram diferenças em relação à metodologia utilizada, população e desfechos analisados.

PALAVRAS-CHAVE: Neoplasia de Mama; Trastuzumabe; Biossimilar

INTRODUCTION

Breast cancer is one of the leading causes of mortality and morbidity in women, with a forecast of 66,280 new cases for each year of the triennium 2020-2022. Disregarding cases of non-melanoma skin cancer, female breast cancer stands out as the most frequent in all regions of Brazil[1].

It is estimated that around 20% of breast carcinomas are characterized by amplification and/or overexpression of Human Epidermal Growth Factor Receptor – type 2 (HER2), a transmembrane receptor with tyrosine kinase activity. This subtype of cancer has a worse prognosis if not treated correctly. However, the presence of HER2 increases the therapeutic possibilities, with the so-called target therapy, which uses drugs that act specifically on this receptor[2].

Trastuzumab is a monoclonal antibody, developed from the recombinant DNA technique. It acts selectively on the extracellular domain of the HER2 receptor protein. Its studies demonstrate that the drug inhibits the proliferation of human tumor cells overexpressing HER2. Its use in combination with chemotherapy has a direct impact on the overall survival of patients[3,4].

The reference drug, Herceptin®, was initially approved for the treatment of HER2-positive metastatic breast cancer in the United States by the Food and Drug Administration (FDA) in 1998, and in 2000 by the European Medicines Agency (EMA). Soon after, its use was authorized by the same regulatory agencies for adjuvant treatment of HER2-positive breast cancer with lymph node involvement and, in 2011, by the EMA, for neoadjuvant therapy for early HER2-positive breast cancer[5].

In Brazil, trastuzumab was incorporated into the Unified Health System (SUS) in 2012, through Ordinances of the Secretariat of Science, Technology, and Strategic Inputs of the Ministry of Health (SCTIE-MS) No. 18 and No. 19, of July 25, with indication for early and locally advanced HER2-positive breast cancer[6,7].

In 2017, after public consultation and evaluation by the National Commission for Technology Incorporation at SUS (Conitec), through Ordinance No. 29, of August 2, 2017, trastuzumab was incorporated into the SUS for the treatment of first-line metastatic breast cancer[8].

Since the early 2000s, biological medicines have become an essential part of the treatment of cancer and other diseases, however, due to their higher prices, they represent high costs for both patients and health systems in general. To guarantee reimbursement of research and development costs for the approval of these drugs, until May 2021, a patent protection period of around 20 years in Brazil was guaranteed, which could be extended. With the approval of the Direct Action of Unconstitutionality No. 5,529, this extension cannot be carried out and the term of validity of the invention patent was returned to 20 years and that of the utility model to seven years[9]. Once this period has expired, the registration, production, and marketing of biosimilars becomes legally permitted[10,11].

Biosimilars are biological products that are highly similar to those of reference, which present minimal differences in their clinically inactive components, without having significant differences in safety, purity, or potency, when compared to the reference product[12].

In Brazil, regulation regarding similar biological products is made by the Resolution of the Collegiate Board (RDC) No. 55, of December 16, 2010, which defines that, for registration, studies comparing the biosimilar and the reference biological product must be presented, containing sufficient information to predict that the differences detected in their quality attributes do not result in differences in their safety and efficacy[13].

As biosimilars are not considered identical molecules, but similar, pharmaceutical equivalence and bioequivalence studies used for the approval of generic drugs cannot be used to prove their therapeutic equivalence. Thus, comparative clinical studies between biosimilar and reference medicine are necessary. Furthermore, in order to be able to extrapolate the results to other approved indications for the biological product compared, it is necessary that the population studied be representative[14,15].

The studies carried out for the development of biosimilars are different from those used for the production of innovative medicines. While in the first case the randomized clinical trials are the most time-consuming and complex phases, in the second, the clinical phases can be carried out more quickly, provided that it is possible to prove, through extensive pre-clinical studies, that the molecule developed is in fact similar to the reference[16]. This process is interesting for the Brazilian scenario, since the country seems to be more prepared from the point of view of scientific and technological infrastructure to carry out phase II and III pre-clinical and clinical trials.

In this way, studies with biosimilar medicines begin through analyzes in relation to the reference medicine, in order to understand its characteristics so that it is possible to produce a similar product. This step is extensive and involves structural,

physical-chemical, and biological analyses, so that the new product can have similar qualities[16].

Then, for analysis of comparability in relation to pharmacokinetics, pharmacodynamics, and toxicity, *in vitro* and *in vivo* tests are performed in the pre-clinical phases. In order for the studies to proceed, it is important that the tested drug has similar profiles to the reference drug[17].

After proven similarity, clinical studies of comparability between the drugs must be performed. For this, it is necessary to select a homogeneous population, with sensitivity to detect any differences that may appear in relation to the analyzed drugs. The study design should be able to demonstrate similar efficacy and safety profiles and, therefore, equivalence studies are recommended[18,19].

The entry of biosimilar medicines on the market makes it possible to reduce costs by health systems, increasing access to health care in oncology, which is important, since the incidence of cancer has been increasing over the years[11].

For registration of biosimilar medicines in Brazil, there is a requirement that at least one phase III study comparing the reference medicine be carried out, but the Brazilian National Health Surveillance Agency (Anvisa) does not specify which methodologies should be used, causing the studies to present different designs[13].

Thus, the objective of the study was to analyze and compare the phase III randomized clinical trials of the biosimilar trastuzumab drugs used for registration approval with Anvisa until the year 2020 in relation to the methodologies used, types of population analyzed, outcomes, and safety results.

METHOD

A scope review was carried out with clinical studies used for the registration of biosimilar trastuzumab drugs within the scope of Anvisa.

First, the identification of biosimilar trastuzumab with active registration in Brazil was carried out using the query tool available on the Anvisa portal. The research was carried out using, in the search field, "*trastuzumabe*" (trastuzumab) as the active ingredient (https://consultas.anvisa.gov.br/#/medicamentos/q/?substancia=23119).

Drugs registered as biosimilars were selected and an analysis was made from the package inserts available to identify the name of the phase III clinical study carried out to compare biosimilar and reference drug.

Subsequently, a search was carried out in the MEDLINE and Web of Science databases, in June 2020, using the names of the collected studies, with the objective of selecting the articles and subsequent reading in full and analysis for comparison.

In the case of studies that presented more than one publication, the one considered the most recent was selected.

A form was created in Excel® to extract the main data collected and relevant information from each study: authors' name, year of publication, clinical trial identification number, study design, type of cancer treated, number of patients randomized (total and per treatment arm), treatment protocols, outcomes, and safety outcomes.

After reading the selected articles, the form was filled out and the collected data were compared. Data were analyzed in terms of: i) the treatment protocols involved in the studies; ii) the outcomes and characteristics of the investigated populations; iii) the safety profile of biosimilar medicines.

RESULTS

Six randomized clinical trials were selected, with five different biosimilars: MYL-1401O, PF-05280014, SB3, ABP 980, and CT-P6. In general, each biosimilar presented a study, in which the equivalence was analyzed. Only PF-05280014 presented two associated studies: one of equivalence analysis and one of non-inferiority[19,20,21,22,23,24].

Table 1 presents a summary of the main data collected from each of the studies.

Table 1. Summary of randomized controlled trials comparing biosimilar trastuzumab and the reference drug.

Biosimilar	Author (year)	Study	NCT	Sponsor	Design	N randomized (Biosimilar/comparator)	Type of cancer
MYL-1401O	Rugo et al. (2017)[20]	*Heritage*	NCT02472964	Mylan	Equivalence	500 (249/251)	Metastatic
PF-05280014	Pegram et al. (2019)[21]	*Reflections* B237-02	NCT01989676	Pfizer	Equivalence	707 (352/355)	Metastatic
	Lammers et al. (2018)[22]	*Reflections* B327-04	NCT02187744	Pfizer	Non-inferiority	226 (114/112)	Initial
SB3	Pivot et al. (2008)[23]	SB3-G31-BC	NCT02149524	Samsung	Equivalence	875 (437/438)	Initial
ABP 980	Von Minckwitz et al. (2018)[24]	Lilac	NCT01901146	Amgen	Equivalence	725 (364/361)	Initial
CT-P6	Esteva et al. (2019)[25]	CT-P6 3.2	NCT02162667	Celltrion	Equivalence	549 (271/278)	Initial

Source: Elaborated by the authors, 2021.
NCT: Clinical Trial Number.

The number of patients randomized ranged from 226 to 875, with a total of 3,582 patients. The Reflections B327-04 study had the fewest number of patients, 226. This was due to the different methodology applied to the study (non-inferiority study)[20,21,22,23,24,25].

Two studies were carried out with patients with metastatic breast cancer, in which the association of the biosimilar with chemotherapy for palliative use was analyzed[20,21,22,23,24,25]. Four studies were performed with patients with early breast cancer, analyzing neoadjuvant and adjuvant chemotherapy after tumor removal surgery[22,23,24,25].

The effects of a possible interchangeability with the reference drug were evaluated in only one study, Lilac, which presented, in its design, a switch, or exchange, in the adjuvant phase, where a part of the patients initially randomized to treatment with the reference drug switched their treatment to the biosimilar studied, randomly[24].

Protocols

The studies used different protocols (Table 2). The studies that performed palliative chemotherapy showed similar protocols, since the Reflections B237-02 study used a combination of biosimilar and paclitaxel and, in Heritage, the combination of biosimilar and taxane was also used, but the choice of taxane (paclitaxel or docetaxel) was at the discretion of the physician and the responsible institution[20,22,23,24,25].

Regarding the studies in which the treatment was performed in an adjuvant and neoadjuvant way, it is possible to observe similarities between the protocols used in the SB3-G31-BC and CT-P6 3.2 studies, in the neoadjuvant stage, in which the antineoplastic drugs used were docetaxel, epirubicin, 5-fluorouracil, and cyclophosphamide. In the Lilac study, the chemotherapy chosen was paclitaxel for adjuvant use, however, in the same study, an initial chemotherapy was performed, with four cycles of epirubicin and cyclophosphamide before starting treatment with the biosimilar. At this stage, there was no type of analysis regarding efficacy or safety[23,24,25]. In studies carried out with patients with early breast cancer, after surgery, only the biosimilar was used in the adjuvant.

Table 2. Protocols and medications used in each study.

Study	Protocol	Chemotherapy
Heritage	Palliative	Taxane
Reflections B237-02	Palliative	Paclitaxel
Reflections B327-04	Neoadjuvant	Docetaxel and carboplatina
SB3-G31-BC	Neoadjuvant	Docetaxel, epirubicin, 5-fluorouracil, and cyclophosphamide
Lilac	Neoadjuvant	Paclitaxel
CT-P6 3.2	Neoadjuvant	Docetaxel, epirubicin, 5-fluorouracil, and cyclophosphamide

Source: Elaborated by the authors, 2021.

The choice of treatment protocol was based on previous studies carried out with the reference drug, but it is possible to perceive the great variation between the protocols, where antineoplastics of different classes were used for the same purpose, making it difficult to compare them.

Outcomes and population analyzed

Table 3 describes the outcomes and the type of population analyzed in each study.

There are certain differences regarding the outcomes analyzed in each study. The most used, pathological complete response (pCR), refers to the complete response rate, that is, the percentage of patients who achieved a complete response after treatment.

Other similar outcomes were used in some studies, breast pathological complete response (bpCR), in two of them[23,25], and total pathologic complete response (tpCR), in only one[23]. The difference between them and the pCR is whether or not they consider the presence of axillary or *in situ*[25] tumors.

It is possible to highlight that this type of outcome was only possible in studies carried out with patients with early breast cancer, since they consider total remission of the disease, which would not be possible in patients with metastatic cancer.

For the two studies performed with patients with metastatic cancer, other outcomes were used. The main objective, objective response rate (ORR), used in both, refers to partial or complete response, with partial response defined by RECIST 1.1 as a reduction of at least 30% of lesions in relation to their diameter[20,21].

Other outcomes used for patients with metastatic breast cancer were duration of response (DOR, duration of response), progression-free survival (PFS), and overall survival (OS, overall survival), calculated in months.

Table 3. Outcomes and type of population analyzed per study.

Study	Primary outcome	Population analyzed
Heritage	ORR	ITT
Reflections B237-02	ORR, DOR, PFS, OS	ITT/PP
Reflections B327-04	pCR, ORR	PP
SB3-G31-BC	bpCR, tpCR, ORR, OS	ITT/PP
Lilac	pCR	PP
CT-P6 3.2	pCR, bpCR	ITT/PP

Source: Elaborated by the authors, 2021.
bpCR: *breast pathological complete response* (defined as the absence of invasive breast carcinoma, regardless of the presence of ductal carcinoma *in situ* or nodal involvement); DOR: *duration of response*; ITT: *intention-to-treat*; ORR: *objective response rate*; OS: *overall survival*; pCR: *pathologic complete response* (defined as the absence of invasive carcinoma in the breast and axillary lymph nodes, regardless of ductal carcinoma *in situ*); PFS: *progression-free survival*; PP: *per-protocol*; tpCR: *total pathologic complete response* (defined as the absence of invasive carcinoma and *in situ* carcinoma in the breast and axillary lymph nodes).

As for the analyzed population, it is possible to notice differences between the studies. The population called intention-to-treat (ITT) refers to the entire randomized population, regardless of dropouts or losses. The second type of population, per-protocol (PP), refers only to patients who completed treatment[20,22,23,24,25].

The analysis considering both types of population was performed in three studies, while three chose to analyze only one type, with ITT being chosen in one study, and PP in another two. Considering that protocol losses and deviations occur in a relevant part of the initially randomized population, such results may present significant divergences[20,21,22,23,24,25].

Safety

The analysis of the safety of biosimilar drugs, compared to the reference drug, was performed based on the occurrence of adverse events (AE), including those considered serious. Table 4 presents a summary of the data collected.

The occurrence of AE, in all studies, was high and affected most of the patients studied.

As for the occurrence of severe AEs, that is, those considered to be grade 3 or more, or requiring hospitalization, the numbers found for each study varied, but, in general, they affected a smaller number of patients.

In most studies, safety results were presented in general terms, in numbers that encompassed the occurrence of AE in both the neoadjuvant and adjuvant phases (except studies with a palliative protocol). However, the Lilac study presented such data considering the occurrence of each type of AE in each phase of the study.

The most common AEs were largely similar across studies, with emphasis on alopecia, neutropenia, and anemia. The Lilac and CT-P6 3.2 studies reported others, such as infections, infusion reaction, and rash, different from the others[20,21,22,23,24,25].

As trastuzumab is a drug capable of generating significant cardiotoxicity, the studies performed specific analyzes in relation to the drop in the left ventricular injection fraction (LVEF), an important factor for monitoring such adverse effects. All showed similar results between the group that used the biosimilar drug and the reference drug[20,21,22,23,24,25].

In all analyzed studies, it was concluded that there are no significant differences in relation to AE caused by the reference product and its biosimilars, demonstrating that all analyzed treatments are safe[20,21,22,23,24,25].

DISCUSSION

As with regulatory agencies around the world, such as the FDA and EMA, for approval of a similar biological drug, Anvisa, through RDC No. 55/2010, requires that at least one phase III study comparing the innovator drug be presented, not specifying which methodologies should be used and which outcomes should be analyzed[13].

This regulation opens the prerogative for each study to be carried out with a different methodology, which can generate certain difficulties in comparing biosimilar studies, which can interfere in the decision of interchangeability between them[13].

As exposed, it is possible to perceive that, firstly, the studies involve populations with different profiles. It is known from previous studies performed with the reference drug that trastuzumab is indicated for the treatment of both metastatic and early breast cancer. However, the studies presented were performed considering only one type of tumor and only one biosimilar was tested for both indications[20,21,22,23,24,25].

RDC No. 55/2010 allows for extrapolation of indication, that is, once the drug has been proven effective for one of the indications present in the package insert of the reference drug, it is possible to extrapolate the indication of the biosimilar to the other indications present[13].

Table 4. Occurrence of adverse events per study.

Study	Phase	Occurrence of AE			Severe AE			Main AEs
		Biosimilar	Reference	*Switch*	Biosimilar	Reference	*Switch*	
Heritage		96.8%	94.7%		38.1%	36.2%		Alopecia, neutropenia
Reflections B237-02		96.6%	96.0%		15.2%	15.9%		Alopecia, anemia, neutropenia
Reflections B327-04	All*	96.5%	94.6%		6.2%	5.4%		Alopecia, anemia, neutropenia
SB3-G31-BC	All*	97.5%	96.1%		12.8%	13.2%		Alopecia, neutropenia
Lilac	NA	80.2%	79.5%		4.9%	1.4%		Neutropenia, infections, infusion reaction
	A	57.6%	52.0%	57.3%	4.0%	2.3%	2.3%	
CT-P6 3.2	All	97.0%	95.3%		7.4%	11.9%		Neutropenia, anemia, rash

Source: Elaborated by the authors, 2021.
* All: adjuvant and neoadjuvant; NA: neoadjuvant; A: adjuvant; AE: adverse event.

Thus, analyzing the package insert of each of the biosimilars and comparing it with the package insert of the reference drug, it is possible to affirm that there was an extrapolation of indication for all biosimilars. Although the majority of studies have been carried out with only one type of breast cancer, they all have the same indications: metastatic breast cancer (in monotherapy or in combination with paclitaxel or docetaxel) and early breast cancer (after surgery, chemotherapy and radiotherapy, or in combination with chemotherapy). In addition, none of the studies performed analyzes with patients with advanced gastric cancer, but this indication is present in their package inserts, demonstrating that there was extrapolation for all indications of the reference drug[3,26,27,28,29,30].

Another important factor to highlight is that the choice of protocols also presented great variation. While the studies proposed for palliative treatment used a similar protocol, the studies carried out with a neoadjuvant purpose showed divergences regarding the choice of antineoplastic agents used, both in terms of quantity and classes.

Such choices were based on previous studies with the reference drug, showing that, in fact, for these protocols, biosimilars are effective, however, in practice, in each treatment center a type of protocol is used. If we take into account the context of public health, this choice can be quite limited, as the drugs available in each institution must be taken into account[31].

Only one study presented an analysis regarding the interchangeability between the biosimilar and the reference drug. This type of analysis is interesting, as it is able to demonstrate, in practice, the effects that a possible interchangeability can cause[24]. As this is a constant in clinical practice, it is important to be able to demonstrate, through detailed analysis, that it is not capable of generating losses for the patient regarding their treatment. Therefore, it would be interesting for future studies to be concerned with this fact.

In addition, the need for this type of study for interchangeability depends on the regulatory agency of each country. The FDA, for example, requires that switch studies be performed so that interchangeability is allowed[32].

Regarding the outcomes analyzed, the differences between the studies are justifiable due to the purpose of the proposed treatment.

The results presented by the selected studies were satisfactory, as they showed that, compared to the reference drug, there is similarity between them.

The safety analysis methodology used by the studies was similar and was able to demonstrate that, in general, many patients undergoing treatment with trastuzumab have AEs, including those considered severe. However, these effects, for the most part, are well tolerated and can be treated. The analyzes performed showed a similar safety profile between the study groups, confirming that treatment with biosimilars is as safe as treatment with the reference drug[20,21,22,23,24,25].

However, the present study has certain limitations, such as the use of data collected in studies used for registration, some of which are still in progress. In addition, each phase III study carried out may generate other publications, with interesting data, that were not analyzed. As future research, it is suggested to carry out studies that analyze the effect of the introduction of biosimilars in reducing prices and to carry out comparative clinical studies between biosimilars and reference drugs that can contribute to obtaining a greater set of data on effectiveness and security of these technologies.

CONCLUSIONS

Phase III randomized clinical trials performed with biosimilar trastuzumab were able to prove their equivalence to the reference drug, both in terms of efficacy and safety.

However, it is possible to highlight that there are great differences between the studies, both regarding the characteristics of the randomized population and in relation to the protocols and clinical outcomes analyzed. For this reason, there is some difficulty in comparing results.

To change this scenario, it is recommended that Anvisa propose a revision of the current regulations or issue technical notes that explain the methodologies that must be used, the size of the population to be included, and the outcomes that must be analyzed in clinical studies with biosimilar drugs.

Currently, there are no comparability studies between biosimilars, and it is not possible to prove that there is a possibility of interchangeability between them. Thus, it is important that these studies are carried out in the future so that the interchangeability can be carried out, without any damage to the treatment.

Finally, it is noteworthy that the introduction of biosimilars on the market made it possible to commercialize a fundamental drug in the treatment of breast cancer for the population, thus contributing to more patients having access to quality treatment.

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Author's Contributions

Kelmer TF - Conception, planning (study design), acquisition, analysis, data interpretation, and writing of the work. Silva MJS - Analysis, data interpretation, and writing of the work. Retto MPF - Conception, planning (study design), analysis, data interpretation, and writing of the work. All authors approved the final version of the work.

Conflict of Interests

The authors inform that there is no potential conflict of interest with peers and institutions, politicians, or financial in this study.