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Interchangeability and substitution of biosimilars: is health technology assessment (HTA) a tool for decision-making?

Intercambialidade e substituição de biossimilares: seria a avaliação de tecnologias em saúde (ATS) um instrumento para tomada de decisão?

Intercambiabilidad y sustitución de medicamentos biosimilares: ¿es la evaluación de tecnologías en salud (ETS) una herramienta para la toma de decisiones?

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Introduction

The discussion on interchangeability and automatic substitution of biological drugs with biosimilars has divided opinions among experts, patients, and health policymakers in Brazil and elsewhere in the world. Biosimilars are biological products that contain a similar bioactive component to that of an approved reference biological, for which biosimilarity can be proven through an exercise of complete comparability (quality, preclinical, and clinical) to guarantee similar safety and efficacy [1,2]. However, the confirmation of biosimilarity does not mean that the biosimilars are interchangeable. This requires clinical studies that analyze whether there is an additional safety risk or reduction in efficacy during the switch or treatment transition from a biological to a biosimilar or vice-versa [3,4]. Box 1 presents the main questions concerning the discussion on the substitution/interchangeability of biosimilars.

Three public hearings were held in Brazil in 2018 to discuss the process of procurement [5,6,7] and substitution and interchangeability [8] of reference biological drugs with their biosimilars in the Brazilian Unified National Health System (SUS) [5,6,7]. The Department of Health Logistics under the Brazilian Ministry of Health assessed the possibility of automatically substituting reference biological drugs with their biosimilar versions [5,6,7]. No health technology assessment (HTA) studies were presented, and what prevailed were discussions on economic issues. In the hearing on the regulation of substitution/interchangeability [8], even when the issue was raised on the need for medical consent at the moment of switch in dispensing the medication, no decision was made on regulation of the substitution/interchangeability in the SUS. Therefore, to date there is no regulatory policy in Brazil that ensures absence of loss of efficacy or safety in the treatment transition [5,6,7,8]. This situation notwithstanding, in two years there were 39 public purchases of approved biosimilars for infliximab, etanercept, and trastuzumab [9].

Various measures by Brazilian society and the Ministry of Health triggered a strong movement to draft a National Policy on Biological Drugs in the scope of the SUS. This policy aims to address issues in research and development, production, regulation, access, and monitoring in the use of biologicals supplied by the SUS [5,7,10,11]. The current context of design and implementation of national policies for the incorporation of these drugs is thus of the utmost importance for identifying which actors

Box 1

Principal issues in the discussion on interchangeability and substitution of biological and biosimilar drugs.

PRINCIPAL ISSUES
Complexity of the molecule and manufacturing process (live cells); possible immunogenic alterations [3,4,28,36]
Absence of standardization in the necessary evidence for assessment of biosimilarity and interchangeability by regulatory agencies [3,37,38]
Absence of national guidelines on substitution/interchangeability [4,5,7,10,11,26,39], standardization of nomenclature and pharmacovigilance systems [3,37,38]
Insufficient evidence from controlled clinical trials and real-world data that support substitution/interchangeability [3,4,24,38,40,41,42]
Absence of educational programs for physicians and patients on biosimilars and their reliability [3,4,39,41,43,44]

and institutions will participate in the decisions at the federal level concerning the HTA process for biosimilars.

This article aims to contextualize the Brazilian situation in the international debate on the incorporation of biosimilars by health systems, highlighting perspectives in the use of HTA studies, especially regarding challenges related to interchangeability and substitution of biosimilars.

Interchangeability and substitution of biologicals and biosimilars

Patients that use biologicals and biosimilars may experience various situations during treatment. Sometimes patients do not only replace the reference biological with a biosimilar, but also one biosimilar with another biosimilar, or a biosimilar with another biological from a different class [12]. This substitution can occur for medical reasons (for example, to minimize adverse reactions), or for nonmedical reasons (for example, cost reduction), also known as automatic substitution, in which there is no consent to the decision by either the prescribing physician or the patient [13]. There is also interchangeability, when the reference biological can be substituted with the biosimilar without consulting the prescriber, since there is proof that repeated switching between the drugs does not pose an additional safety risk or reduction in efficacy [14,15].

Demonstration of interchangeability is not a requirement for registering the drug, which is up to each regulatory agency. The definitions differ from one country to another [15,16]. In Brazil, the Brazilian Health Regulatory Agency (Anvisa) published a note of clarification on interchangeability and substitution of biosimilars and reference biologicals, emphasizing that interchangeability relates more directly to clinical practice than to regulatory status [17], thus involving broader aspects such as specific studies, data from the literature, case-by-case medical assessment, and issues of traceability and pharmacovigilance. Anvisa thus assumes its role as the regulatory body responsible for certifying the registration of new biosimilars in Brazil, but as for interchangeability, the agency reported that it is the responsibility of the Ministry of Health and the prescribing physician [17]. Nevertheless, we emphasize that numerous biosimilars have been registered with regulatory agencies for marketing purposes [18,19,20], no regulatory agency in the world has ever certified a biosimilar as interchangeable [14,15,21].

Although regulatory agencies have the role of authorizing the marketing of these drugs, registration does not guarantee their incorporation, coverage, and/or reimbursement by health plans. This mechanism is essential for guaranteeing access to effective and safe drugs for the population and that are cost-effective for health systems. There are HTA agencies or organizations responsible for conducting and assessing HTA studies, primarily to inform health decision-making [22].

HTA organizations like Brazil's National Commission for the Incorporation of Technologies in the SUS (CONITEC), the U.K. National Institute for Health and Care Excellence (NICE), and the Canadian Agency for Drugs and Technologies in Health (CADTH) use HTA studies (rapid reviews, mini-HTA, and full HTA [23]) in decision-making processes. HTA involves a systematic assessment of the properties and effects of a health technology, aimed at informing decision-making in order to rationalize the incorporation of technologies in health systems in a safe, efficacious, and cost-effective way, aimed mainly at the systems' sustainability [22]. Besides assessing equivalence or non-inferiority and safety/immunogenicity, HTA studies of biosimilars can also assess whether there is any risk in the treatment transition, by summarizing evidence from substitution/interchangeability studies and cost-effectiveness analyses of treatment transition between biologicals and biosimilars [13,24].

HTA agencies have adopted different strategies to develop HTA studies of biosimilars [16]. For example, agencies in New Zealand and France use the same process for assessing a new drug's clinical and economic benefit, while other agencies like the one in the United Kingdom adopt a customized assessment. Agencies in Canada and Australia use both approaches. Other agencies only conduct HTA studies if the reference biological has not been assessed or if it has been assessed but is not reimbursable. Agencies in Germany and the Netherlands do not conduct HTA studies of biosimilars [16].

The CADTH has a well-established policy with guidelines for the submission of assessment of biosimilars, in the form of a mini-HTA, including risk assessment of the treatment transition [25]. In the United Kingdom, representatives from the public regulatory and HTA agencies, the pharmaceutical industry association, and HTA experts met to discuss the role of HTA for biosimilars. The majority shared the view that the organizations should adopt greater flexibility in the choice of processes and methods to determine whether biosimilars should be assessed from the perspective of health economics [26]. Although HTA is consolidated as a scientific and technological practice and its influence is expanding among decisionmakers, there is still no hegemonic position on its role for biosimilars. In a survey of national associations of pharmaceutical companies from 32 European countries, 24 countries (75%) stated that the HTA process does not apply to biosimilars [27]. According to these associations, the evidence furnished for marketing registration and issues related to the drug's cost can be sufficient for the incorporation of biosimilars [16,26,28].

Application of HTA to biosimilars in the Brazilian context

Medical societies and patients' associations have positioned themselves in favor of introducing biosimilars in Brazil, as long as the scientific parameters are adequate [29,30]. They also emphasize the need for CONITEC to update the Clinical Protocols and Therapeutic Guidelines in relation to the biosimilars provided by the SUS and the supply of proof of biosimilars' efficacy and safety, especially in the case of monoclonal antibodies and fusion proteins, through studies with adequate equivalence margins capable of detecting significant clinical differences [31].

There is no regulation to date by Anvisa on substitution/interchangeability of any biological or biosimilar drugs, just as there are no HTA studies in Brazil to support interchangeability/substitution with any biosimilars approved in the country. *Law n. 12,401* of 2011 [32] provides that HTA of technologies submitted to CONITEC must consider the scientific evidence on the efficacy, accuracy, effectiveness, and safety as well as comparative economic analyses of the costs and benefits in relation to technologies already incorporated in the SUS [33].

A search in the Information System of the Brazilian Network of Health Technology Assessment (SISREBRATS) and reports with recommendations by CONITEC showed clearly that the topic of biosimilar products is recent in CONITEC, and that there is no standard understanding on definitions and decision-making processes involving biosimilars. CONITEC is represented in the Working Group that is participating in the National Policy on Biological Drugs in the context of the SUS, but it has still not reported officially whether it will apply the HTA process to assessments of biosimilars [34]. In 2018, the Department of Science and Technology of the Science, Technology, and Strategic Inputs Secretariat of the Ministry of Health participated in four meetings, including a deliberative dialogue. However, no product resulting from the discussions has been made available to the public so far [35].

The aspects discussed above call attention to the need for an official position by CONITEC concerning HTA for biosimilars. The commission should indicate the type of HTA study to be performed for biosimilars or whether their incorporation can be backed only by the evidence required at the time of registration of the biosimilar, which does not include risk assessment of substitution/interchangeability.

Conclusions

In the international scenario, HTA studies of biosimilars have still not been standardized, and policies for their regulation and incorporation are in the design and implementation phase to address issues of interchangeability and substitution of biosimilars [28]. The drafting is under way in Brazil on a National Policy on Biological Drugs in the context of the SUS, which can contribute to a transparent process of incorporation of biosimilars. However, with the growing supply of biosimilar drugs on markets, it is essential for HTA agencies to take a more consolidated position on the assessment of biosimilars. This theme relights the debate on evidence-based regulation of biological therapies and biosimilars in contemporary health systems, capable of preserving treatment efficacy and safety while promoting more efficient and sustainable health systems.

Contributors

B. O. Ascef contributed to the study's conception, design, and elaboration and data analysis and interpretation, agreeing to take responsibility for all aspects of the work, guaranteeing issues related to the precision and integrity of any and all parts of the study. R. G. L. Silva and H. A. Oliveira Júnior contributed to the analysis and critical revision of the intellectual content and approved the final version for publication. P. C. De Soárez oriented the study's conception and design, critically revised the intellectual content, and approved the final version for publication.

Additional informations

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