OPINION ARTICLE
ARTIGO DE OPINIÃO

Innovative mechanisms of pre-marketing authorization access for rare diseases in Brazil: a case study of pabinafusp-alfa for mucopolysaccharidosis type II

Mecanismos inovadores de acesso pré-comercialização a tecnologias para doenças raras no Brasil: um estudo de caso de alfapabinafuspe para mucopolissacaridose tipo II

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access to essential medicines and health technologies, clinical research, mucopolysaccharidosis II, rare diseases

ABSTRACT

Patients with rare diseases frequently face unmet medical needs due to the high costs, lengthy development times, and slow approval processes for new treatments. This case study discusses innovative access alternatives for rare diseases in Brazil, focusing on early access to pabinafusp-alfa for mucopolysaccharidosis type II (MPS-II), a rare genetic lysosomal storage disease characterized by a deficiency of the enzyme iduronate-2-sulfatase. From September 2018 to March 2023, 20 Brazilian MPS-II patients received pabinafusp-alfa through a clinical research protocol. This enzyme replacement therapy (ERT) crosses the blood-brain barrier to address central nervous system manifestations unmet by existing treatments. Patients' participation in the clinical study resulted in an estimated BRL 65 million in cost savings for the public healthcare system compared to conventional ERT with idursulfase-alfa and potentially better clinical outcomes. The case study underscores the importance of innovative mechanisms in addressing patients' medical needs. Early access alternatives include: a) clinical study access, with execution/development aligned with healthcare managers and linked to future access strategies; b) regulatory-level risk-sharing, considering effectiveness uncertainties and the possibility of market withdrawal and/or reimbursement in case of negative results; and c) drug pre-delivery, with payment contingent on positive phase III clinical study outcomes. Although public-private partnerships in clinical research are underused, they could benefit all stakeholders by accelerating drug development, facilitating early patient access to innovative medicines, and generating healthcare system savings, particularly for rare diseases.

Palavras-chave:
acesso a medicamentos essenciais e tecnologias em saúde, mucopolissacaridose II, pesquisa clínica, doenças raras

RESUMO

Pacientes com doenças raras frequentemente enfrentam necessidades médicas não atendidas devido aos altos custos, longos tempos de desenvolvimento e processos de aprovação lentos para novos tratamentos. Este estudo de caso discute alternativas inovadoras de acesso para doenças raras no Brasil, com foco no acesso precoce ao alfapabinafuspe para mucopolissacaridose tipo II (MPS-II), uma doença lisossômica de armazenamento genético rara, caracterizada por uma deficiência da enzima iduronato-2-sulfatase. De setembro de 2018 a março de 2023, 20 pacientes brasileiros com MPS-II receberam alfapabinafuspe por meio de pesquisa clínica. Essa terapia de reposição enzimática (TRE) atravessa a barreira hematoencefálica para tratar manifestações do sistema nervoso central não atendidas pelos tratamentos existentes. A participação dos pacientes no estudo clínico resultou em uma economia estimada de 65 milhões de reais para o sistema público de saúde, em comparação com a TRE convencional com idursulfase alfa, além

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de potencialmente melhores resultados clínicos. O estudo de caso destaca a importância de mecanismos inovadores no atendimento das necessidades médicas dos pacientes. As alternativas de acesso precoce incluem: a) acesso por meio de estudos clínicos, com execução/desenvolvimento alinhada aos gestores de saúde e vinculada a estratégias futuras de acesso; b) compartilhamento de risco em nível regulatório, considerando as incertezas de eficácia e a possibilidade de retirada do mercado e reembolso em caso de resultados negativos; e c) pré-entrega do medicamento, com pagamento condicionado aos resultados positivos do estudo clínico de fase III. Embora as parcerias público-privadas em pesquisa clínica sejam subutilizadas, elas poderiam beneficiar todas as partes interessadas ao acelerar o desenvolvimento de medicamentos, facilitar o acesso precoce dos pacientes a medicamentos inovadores e gerar economias para o sistema de saúde, especialmente para doenças raras.

Introduction

Over the last decade, the median time from clinical development to market approval by the Food and Drug Administration (FDA) for innovative drugs was approximately 8.3 years (Brown *et al.*, 2022). Approval in other countries, including Brazil, usually takes even longer. However, once a drug is approved, it is not automatically covered by insurance or reimbursed by the healthcare system. Additional steps are required to determine the drug's value, cost-effectiveness, and potential impact on the healthcare system and patient outcomes, which demands an extended timeframe.

Moreover, costs for bringing a new drug to the market are very high, with a median capitalized research and development cost per product estimated to be USD 1.1 billion; for antineoplastic and immunomodulating agents, median costs are around USD 2.8 billion (Wouters *et al.*, 2020). These investments are required to ensure that drugs are safe and effective for patient use.

However, the costs and time involved in bringing new drugs to market pose significant challenges for the pharmaceutical industry, particularly in rare diseases. These challenges can limit access to potentially life-saving therapies, which concerns patients and healthcare providers alike.

Through clinical research, this manuscript presents a case study of early access of pabinafusp-alfa for Mucopolysaccharidosis type II (MPS-II) in Brazil. We discuss alternatives for providing early access to innovative drugs for rare diseases.

Case study

Mucopolysaccharidosis type II (MPS-II), also called Hunter syndrome, is a rare genetic recessive X-linked disease. Approximately 229 individuals are affected in Brazil (Brazil. Ministério da Saúde, 2017). It is a lysosomal storage disease, characterized by a deficiency of the enzyme iduronate-2-sulfatase, which accumulates glycosaminoglycans (GAGs) in different organs (Martin *et al.*, 2008). The severity of disease progression and clinical manifestations vary widely between affected individuals. Approximately two-thirds of patients present central nervous system (CNS) manifestations, including developmental delay, neurological decline, abnormal behavior, and seizures. These symptoms are associated with poor prognosis and a high burden for the healthcare system, patients, and their caregivers (Wraith *et al.*, 2008).

In Brazil, enzyme replacement therapy (ERT) with idursulfase-alfa is available for patients with MPS-II. This treatment improves somatic manifestations such as functional capacity, liver and spleen volumes, and urinary GAG levels; however, it does not cross the blood-brain barrier and therefore does not affect CNS manifestations (da Silva *et al.*, 2016). It remains a significant unmet need for MPS-II patients.

Pabinafusp-alfa is an enzyme replacement therapy that crosses the blood-brain barrier, overcoming current challenges in treating MPS-II CNS manifestations. The clinical development of pabinafusp-alfa began in March 2017 with a phase I/II clinical trial in Japan (Okuyama *et al.*, 2019).

The Pharmaceuticals and Medical Devices Agency (PMDA) approved the technology in Japan in March 2021. In Brazil, pabinafusp-alfa has not been approved by Anvisa yet; nevertheless, due to direct and organized demands from rare disease patient associations to the drug manufacturer, the therapy is available for research protocols. In Brazil, studies with pabinafusp-alfa started in July 2018, and patients enrolled are currently in the extension phase (Giugliani *et al.*, 2021). In the absence of pabinafusp-alfa, due to the systemic manifestations of the disease, these patients would receive treatment with idursulfase-alfa, the only currently approved therapy for MPS-II in Brazil. In 2022, the Brazilian Ministry of Health purchased 27,693 vials of idursulfase-alfa 6mg for a total of 144,788,720 Brazilian reais (BRL), or BRL 5,228.53 per vial, equivalent to USD 1,021.70 (1 USD = 5,1173 BRL, contract date: August 25, 2022) (Brazil. Ministério da Saúde, 2022).

From September 2018 to March 2023, 20 patients with MPS-II in Brazil received pabinafusp-alfa as part of a clinical research protocol, with an average follow-up of 48 months. Assuming an average weekly dose of 3 vials of idursulfase-alfa per patient (recommended for a patient weighing 35 kg), we estimate that approximately 12,514 of idursulfase-alfa were

used during this period. So far, this has resulted in an estimated cost savings of approximately BRL 65,431,318 for the public healthcare system with ERT, in addition to the savings related to clinical care and potentially better patient health outcomes.

Discussion

Developing new drugs is time- and resource-consuming, making it difficult for smaller companies to bring new medicines to market and potentially limiting patient access to innovative treatments due to high costs and long timeframes for development and marketing authorization. From the patient's perspective, waiting for around a decade from clinical development to marketing approval, and potentially much longer for coverage/reimbursement by the healthcare system, does not meet current needs. These issues are particularly relevant for rare diseases, which are often targeted by smaller companies for drug development and for which several diseases do not have effective treatments.

One potential solution to these challenges is exploring new, more efficient, cost-effective drug development and approval approaches. For example, some researchers have suggested that artificial intelligence and machine learning could help streamline the drug development process by identifying promising drug candidates more quickly and accurately than traditional methods (Aliper *et al*., 2016; Stokes *et al*., 2020). Another approach is encouraging greater collaboration between industry, academia, and regulatory agencies, to share knowledge and resources and promote more efficient drug development. It could involve initiatives such as public-private partnerships and greater use of open-source drug development platforms (Robertson *et al*., 2014; Walwyn *et al*., 2018).

Flexibilization of drug approval processes for rare diseases is another potential solution to the challenges of bringing new therapies to needy patients. Because rare diseases often affect relatively few people, clinical trials for drugs targeting these diseases require smaller patient populations and can take longer to complete. Some regulatory agencies have implemented measures to address these challenges, such as expedited review processes and surrogate endpoints in clinical trials. One example of such flexibility is the FDA's Breakthrough Therapy Designation, which provides accelerated approval for drugs that show significant benefits in early-stage clinical trials. This designation has been used for several drugs targeting rare diseases, including spinal muscular atrophy and cystic fibrosis (FDA, 2016; FDA, 2019). In Brazil, since 2015, ANVISA has had a similar program called "Innovative Product Designation", showing significant benefits over existing treatments for severe or life-threatening conditions.

Some options are available for patients who cannot wait for a drug to be approved, although they can come with their challenges. One such option is to seek access to the drug through expanded access programs or compassionate use programs, which allow patients with severe or life-threatening conditions to access experimental medications before they are approved. These programs are typically reserved for patients who have exhausted all other treatment options and have no other viable options (Fountzilas *et al*., 2018). Another option is participating in clinical trials for the referred drug, though this may not be feasible for most patients.

The presented case study showcases how clinical research can provide innovative patient treatment options. Worldwide, 68 patients have participated in clinical studies of pabinafusp-alfa, with 29.4% from Brazil (Okuyama *et al*., 2019; Okuyama *et al*., 2021; Giugliani *et al*., 2021). These patients make up almost 10% of diagnosed MPS-II patients in Brazil, which has resulted in savings of approximately BRL 65 million for the public healthcare system, not including expenses for clinical care and treatment of disease complications.

A phase III randomized trial compares pabinafusp-alfa to idursulfase-alfa and recruits participants (NCT NCT04573023). The results of this trial are expected to be published in 2026, and regulatory approval is anticipated in several countries after that. However, the time from drug development to marketing authorization is expected to be at least nine years, a significant amount of time for patients with orphan diseases, who may progress to an irreversible state or death during this period. The experience of pabinafusp-alfa access in Brazil highlights the importance of innovative alternatives that can provide faster access to treatments for patients with unmet needs, particularly those with orphan diseases.

Public-private partnerships can provide additional options for early access to new drugs for rare diseases. Regulatory agencies must ensure that drugs are safe and effective for patient use, considering the clinical impact of delayed marketing approval and assessing its risk-benefit. Governments should support research and access to new technologies while ensuring the sustainability of the healthcare system and the efficient allocation of resources. New drugs, especially those without a phase III randomized trial, present more significant uncertainty regarding their benefits and harms. The pharmaceutical industries must bear part of the risk by reimbursing patients and/or healthcare systems in case of ineffectiveness.

Over the last decade, we have progressed in the regulatory process for orphan drugs, with initiatives such as FDA's Breakthrough Therapy Designation and Anvisa's DPI promoting faster and more flexible regulatory evaluation. However, critical unmet needs regarding access to orphan drugs still exist. In this context, some innovative alternatives for early access may include: a) access through clinical studies, with the execution/development aligned with healthcare managers and linked with potential future access strategies; b) risk

sharing at the regulatory level, considering the uncertainties in effectiveness and the possibility of market withdrawal and/or reimbursement to the system in case of negative results; c) pre-delivery of the drugs, with subsequent payment only if the results of phase III clinical study are positive.

Conclusions

This case study on pabinafusp-alfa highlights the significance of innovative mechanisms in meeting the medical needs of patients with rare diseases. By allowing patients with MPS-II to access the drug before it was fully approved, the drug provided a crucial lifeline to individuals who previously had limited treatment options. It was essential given the severity of MPS-II, a rare genetic disorder that can lead to developmental delays, intellectual disability, and other severe health complications. From an economic perspective, we estimate savings of approximately BRL 65 million for the Brazilian public healthcare system over the last five years. Since these patients are still receiving treatment through the research protocol, it will continue to result in savings for the public healthcare system of approximately BRL 16 million yearly. Although public-private partnerships in clinical research are underused, especially for rare diseases, they could result in win-win situations by promoting faster drug development, allowing patients to access innovative medicines early, and promoting savings for the system.

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