Access to advanced therapy medicinal products in low and middle-income countries : a systematic littérature review.

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OBJECTIVE

The emergence of advanced therapy medicinal products (ATMPs) promises to transform the medical landscape by addressing critical needs in global healthcare. By 2030, up to 60 new therapies could be introduced, potentially benefiting 350,000 patients and targeting a range of conditions from rare diseases to cancers. ATMPs, which include gene therapies, somatic cell therapies, tissue-engineered products, and combination therapies, offer innovative solutions but face significant challenges such as high costs, uncertainties regarding their effectiveness, and inadequate evaluation method (1)(2)(3).

While initiatives have been launched in developed countries to improve access, such as reimbursement policies and training programs, challenges remain. In low- and middle-income countries, access is nearly non-existent, raising concerns about equity and accessibility to these revolutionary treatments.

Our research aims to compare different strategies used in LMIC to improve access to these therapies.

METHODS

A systematic literature review (SLR) was conducted in the MEDLINE, SCIENCE DIRECT, and SPRINGER databases between November and December 2023.

Article screening was conducted using the Mendeley tool to eliminate duplicates and classify references during the selection process.

The selected articles, published between January 2009 and December 2023, had to address topics such as regulation, access and financing models, as well as the current situation of ATMPs, including at least one country classified as LMIC in the study.

Additionally, the websites of regulatory agencies in the countries included in the selected articles were consulted to obtain supplementary information or to update the data identified during the article analysis.

Five main parameters were identified to assess the situation regarding ATMPs in these countries these are detailed in the table TABLE 1.

Table 1 : Criteria and their Objectives.

Criteria :	Objectives:
ATMP regulation	Determine whether there is a legal classification of ATMPs and specific regulations and identify the agencies that govern them.
ATMP access models.	Determine the mechanisms by which patients can access therapies.
Financing models.	Specify the financing model for advanced therapies.
Investment and incentives.	Define resources and investments including allocated funds, established infrastructure, and research and development initiatives supporting ATMPs.
Current state of ATMP.	Evaluate the current status of therapies approved or in clinical development.

Table 2 : 2024 Ranking of Included Countries According to the World Bank.

Classification :	Country :
Upper middle income countries 4,516 $ < GNI per inhabitants < 14,005 $	Brazil, China, Thailand, South africa
Lower middle income countries 1,146 $ < GNI per inhabitants < 4,515 $	India, Pakistan, Tanzaniae
Low income countries GNI per inhabitants < 1,145 $	Uganda

RESULTS

1-Regulatory Entities Governing Advanced Therapies

Country :	2-Regulation of ATMP :
Brazil	Specific regulation since 2018, its guidelines comply with EMA and FDA standards.
China	Governed by the same regulations as other organic products.
South africa	Robust research regulatory framework. No law governs the production and marketing of ATMPs.
India	Governed by the same regulations as other organic products.
Tanzania	Still building and adapting their ATMP regulations.
Uganda	Still building and adapting their ATMP regulations.
Thailand	Governed by the medicines law, Thai FDA active in the development of specific regulations.

Country :	3-ATMP access models :
Brazil	Approval exemption : Expanded access for patients not eligible for clinical trials. Compassionate use. Supply of drugs post clinical trials. EA for advanced therapy products manufactured in an unconventional manner intended for a particular patient. Facilitated approval: Exceptional approval. Expedited approval: Priority approval.
China	Approval exemption : Expanded access for patients not eligible for clinical trials. Facilitated approval: Conditional approval. Expedited approval: Priority review.
India	Approval exemption : Exemption from marketing authorization for minimally modified ATMPs for homologous use. Facilitated approval: Conditional approval. Expedited approval: Accelerated procedure.
Pakistan	Participates in the Zolgensma® access management program.

4-Financing models :

Brazil : Established a risk-sharing model for the treatment of spinal muscular atrophy with the drug Nusinersen (Spinraza ®).

Country :	5-Investment and incentives :
Brazil	Investment in cell therapy centers.. Leveraging the development capabilities of reputable institutions.
China	In 2019, 102 hospitals were authorized to develop cell therapy products.
South africa	he hub-and-spoke model has been adopted and welcomes local and foreign patients.
India	Researchers at the Christian Medical College (CMC), Vellore, have demonstrated the possibility of creating CAR-T cells on site.
Uganda	The Gates Foundation helping create manufacturing systems in healthcare settings;
Thailand	Medical universities are working on gene therapy products, in collaboration with the United States, Europe, and Asia.

6-Current state of ATMP :

Brazil : 7 therapies have been approved (1 per exceptional recording).

China : 4 therapies have been approved (3 by priority approval).

India : 4 therapies have been approved (All under conditional approval).

DISCUSSION

Advanced therapies (ATMPs) represent the future of modern medicine, offering significant potential for treating difficult conditions. However, their acquisition faces numerous challenges, particularly in low- and middle-income countries (LMICs), including high costs, insufficient healthcare funding, complex regulatory processes, and a lack of infrastructure.

Despite these challenges, progress has been made in eight LMICs, such as India, China, and Brazil, which have already approved ATMPs. These countries have implemented innovative strategies tailored to their contexts, enhancing regulatory frameworks and improving access to these therapies.

The regulatory approaches vary widely among countries, influencing the development and commercialization of ATMPs. For instance, China allows the use of unregistered clinical trial data, expediting approvals, while Brazil has adopted legislation aligned with international standards to foster technological development (4).

Countries like South Africa face challenges due to the absence of specific guidelines for ATMPs, while others, like Thailand, are working toward models similar to Brazil's. Collaborative international efforts and investments in research institutions are key strategies for enhancing expertise and infrastructure.

Funding mechanisms are also crucial, with Brazil introducing a "risk-sharing" payment model to address high initial costs. Overall, the successful acquisition of ATMPs is closely linked to the strategies and investments made in these countries, highlighting the importance of tailored approaches to overcoming barriers and improving access to advanced therapies.

CONCLUSION

Advanced therapies represent the future of modern medicine and offer promising prospects for treating diseases that are currently difficult to manage. However, their revolutionary nature comes with significant challenges, including high costs, complex manufacturing processes, and strict regulatory requirements. Despite these obstacles, the successes seen in some low- and middle-income countries (LMICs) show that it is possible to overcome these challenges through innovative strategies to make these therapies accessible to patients. The lessons learned from these experiences can guide efforts in other countries with similar economic conditions, such as Algeria, although approaches to addressing these challenges may vary depending on the national context. Therefore, collaboration among pharmaceutical companies, payers, policymakers, and patient groups is crucial to develop tailored models (5). Optimizing access to advanced therapies in LMICs could not only transform the management of complex diseases but also reduce global inequalities in healthcare access by enabling more patients to benefit from these treatments.

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