The methodological challenge in the economic evaluations of advanced therapy medicinal products: a systematic review with recommendations

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Background & Aim

The number of available advanced therapy medicinal products (ATMPs) has grown considerably in recent years. These treatments are likely to present promising results for a wide range of diseases, but also high prices. Robust methodologies are needed to evaluate such therapies and ensure value for money for payers and health systems. The objective of this work is to compile the methodological aspects of conducting economic evaluations of ATMPs.

Methods

A systematic review was carried out and the following databases were consulted (11 September 2020): PubMed, Embase, Web of Science (WOS) and The Cochrane Library, complemented by exploratory search in Google Scholar. Two systematic reviews were located that served to identify further publications through the reference list. The search strategy was constructed with controlled and free terms, including the commercial names of ATMPs.

Inclusion and exclusion criteria: all articles that carried out a cost analysis or economic evaluation of ATMPs were included. Those articles that evaluated the production process were excluded; the search was limited to the previous 15 years. The results of the literature search were stored in a Rayyan QCR library and the screening process was performed in pairs.

Results

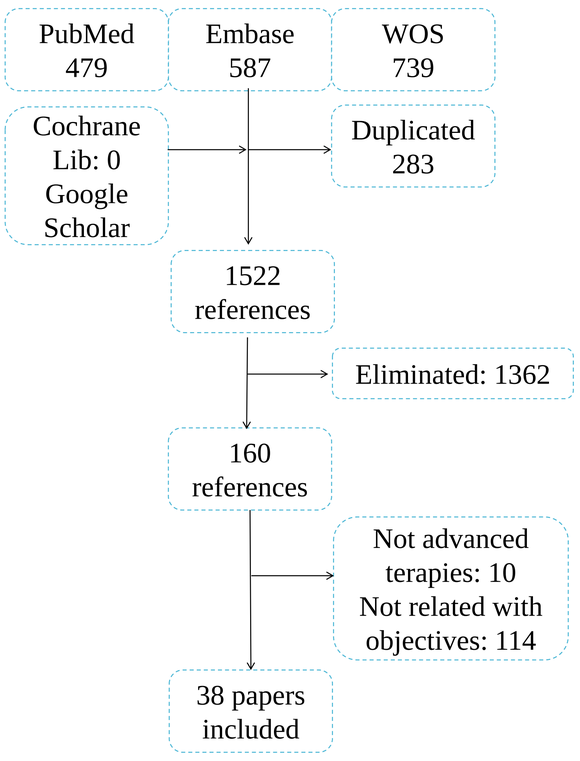

Fig 1. PRISMA flow diagram

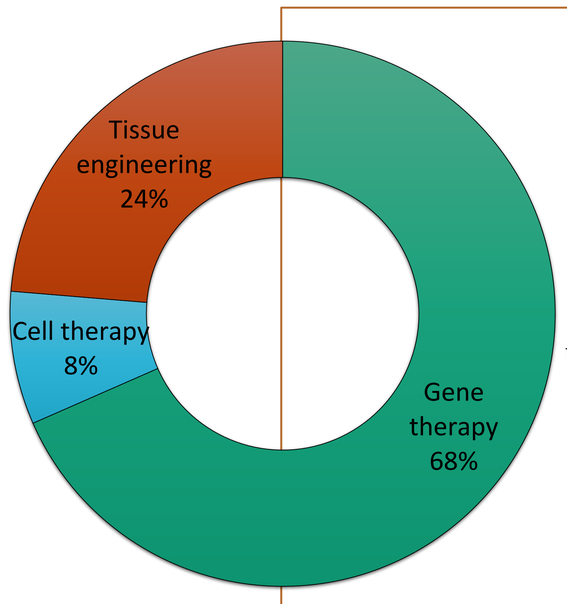

Fig 2. Percentages of the economic evaluations included according to the type of ATMPs

The economic evaluations included in the review are related to gene therapy medicinal products, indeed most of them resulted from the evaluation of the CART-cell therapies (Kymriah and Yescarta). Tissue-engineered products are the following category mainly due to their properties to regenerate cartilage defects in knee joints. Regarding cell therapy medicinal products, cost effectiveness analysis were performed for the treatment of ischemic stroke, Parkinson's and Chron's diseases.

	n = 3	n =26	n = 9	n = 38	100%
Pathology	CTMPs	GTMPs	TEPs	Total	Percent
R/R DLBCL	-	9	-	9	24%
R/R B-ALL	-	8	-	8	21%
Cartilage defects in knee joints	-	0	7	7	18%
Hemophilia A	-	2	-	2	5%
Spinal muscular atrophy	-	2	-	2	5%
Other	3	5	2	10	26%

Commercial ATMPs with EE	Percent
Alofisel	3%
Chondrocelect	5%
Kymriah	29%
Luxturna	3%
MACI	3%
Strimvelis	3%
Yescarta	11%
Yescarta & Kymriah	3%
Zolgensma	5%
Zynteglo	3%

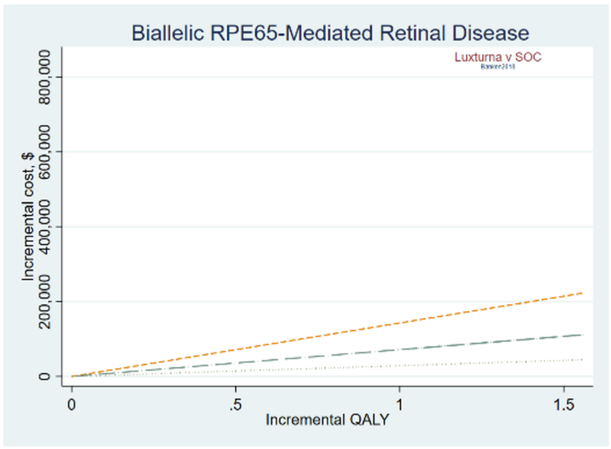

Fig 3. Example: Incremental costs and benefits of Luxturna® (orange) which suggest a modest incremental health benefit at greater cost

Cost-effectiveness is often one of the criteria that payers use for whether to adopt a therapy or the price at which it should be reimbursed.
*Cost-Effectiveness Analysis (CEA) includes cost and clinical outcomes for two or more treatment options.
*Cost-Utility Analysis (CUA) is a type of cost-effectiveness analysis in which the cost per quality-adjusted life year (QALY), or some other preference-based valuation of heath outcome, is estimated. The use of QALY as a measure of health outcome enables comparisons to be made across disease areas.

This review includes therapies which are represented in three of the four "quadrants" of the cost-effectiveness plane. Mostly ATMPs were associated with some positive QALY gained at greater cost than the current standard of care (fig.3). There are some cases in which the cost is lower (eg. Valoctocogene roxaparvovec for Haemophilia A)[1] and only one that the ATMP did not imply a positive QALY (cell therapy for stress urinary incontinence)[2].

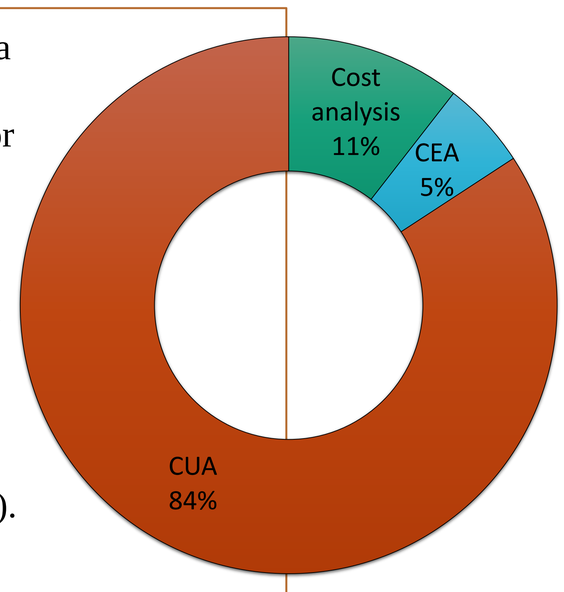

Fig 2. Percentages of the economic evaluations included according to the type of analysis

[1] Rind DM, Agboola F, Herron-Smith S, et al. Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A without Inhibitors: Effectiveness and Value Final Report Prepared For.; 2020. https://icer-review.org/programs/new-england-cepac/
[2] Vilsbøll AW, Mouritsen JM, Jensen LP, et al. Cell-based therapy for the treatment of female stress urinary incontinence: An early cost-effectiveness analysis. Regenerative Medicine. 2018;13(3):321-330. doi:10.2217/rme-2017-0124

Recommendations

This work makes it possible to identify the gaps in the existing literature, the common issues in the economic evaluations of ATMPs and reporting the main methodological approaches. We should remark difficulties derived from the small target population, the design of clinical trials, the available clinical evidence, the lack of long-term data and the important risk of bias. Here we offer some recommendations for researchers and policy-maker to overcome these challenges:

- More consistency and clarity about the criteria for P&R is required to help stakeholders target investment capital.
- Appropriate methods must be used when randomized clinical trials evidence is not available, specially ensuring that control and treatment groups are comparable.
- It is important that countries cooperate creating an international ATMP registry with data collection protocols, including QoL data.
- There is a high risk associated with conflict of interest, and HTA agencies should be cautious when accepting studies conducted by the industry.