CRITICAL REFLECTIONS ON REIMBURSEMENT AND ACCESS OF ADVANCED THERAPIES

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OBJECTIVES

The health economic literature has questioned the cost-effectiveness and affordability of advanced therapies, proposed adjustments to value assessment frameworks, and discussed the use of outcome-based managed entry agreements and staggered payments in the last few years. The aim of this study is to conduct a critical reflection on assessment criteria and access conditions for reimbursement of advanced therapies.

METHODS

A narrative review of the peer-reviewed literature and grey literature was conducted in April 2021 by searching PubMed; Google Scholar; policy and legislative documents; websites of health technology assessment agencies, advanced therapy organisations, governmental advanced therapy innovation programmes, consultancy agencies; ISPOR conference abstracts and presentations.

REFLECTION 1

Advanced therapies can be cost-effective at high prices set by manufacturers

Although their high prices inhibit the cost-effectiveness of advanced therapies, there are numerous examples across a variety of products and jurisdictions that advanced therapies are cost-effective (see Table 1).

REFLECTION 2

The narrow economic evaluation framework adopted by many payers does not capture all value elements of advanced therapies

Health economists have called for the methodology of economic evaluation to be adapted to fit advanced therapies and several health technology assessment agencies are adjusting their value assessment frameworks.

REFLECTION 3

Advanced therapies can be affordable and may not require spread payments

Their curative potential implies that high one-off costs of advanced therapies need to be compared with lifetime costs of current chronic treatments for these diseases.
Spreading payments over time may not be required for ultra-orphan advanced therapies or for advanced therapies at the lower price end. Decision makers need to identify criteria, such as disease prevalence, to inform the choice between single or spread payment(s) for a specific product.

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Table 1. Examples of cost-effective advanced therapies based on economic evaluation from payer perspective

Advanced therapy	Country	Indication	Specific design characteristics	ICER	Threshold value
Imlygic® (1)	England	Unresectable, metastatic melanoma for which systemic immunotherapy is not suitable	Lifetime horizon, 3.5% discount rate for costs and outcomes	£23,900/QALY vs dacarbazine, £24,100/QALY vs best supportive care	£20,000-£30,000/QALY
Kymriah® (2)	Japan	Children and young adults with r/r B-ALL	Based on 5-year kymriah® trial data, lifetime horizon, 2% discount rate for costs and outcomes	¥2,035,071/QALY vs blinatumomab, ¥2,644,702/QALY vs clofarabine + cyclophosphamide + etoposide	¥5 million/QALY
Kymriah® (3)	Spain	Children and young adults with r/r B-ALL	Lifetime horizon, 3% discount rate for costs and outcomes	€28,819/QALY vs salvage chemotherapy	€30,000/QALY
Kymriah® (4)	Netherlands	Children with r/r B-ALL	Lifetime horizon, 4% discount rate for costs, 1.5% discount rate for outcomes	€27,443/QALY vs clofarabine monotherapy; €28,611/QALY vs clofarabine combination therapy; €23,229/QALY vs blinatumomab	€20,000-€80,000/QALY
Luxturna® (5)	United States	RPE65-mediated inherited retinal disease	Lifetime horizon, 3% discount rate for costs and outcomes	$79,618/QALY vs standard care	$50,000-$100,000/QALY
Spherox® (6)	England	Knee articular cartilage defects	Lifetime horizon, 3.5% discount rate for costs and outcomes	£4,360/QALY vs microfracture, around £18,000/QALY vs MACI	£20,000-£30,000/QALY
Strimvelis® (7)	England	Adenosine deaminase deficiency–severe combined immunodeficiency	Lifetime horizon, 1.5% discount rate for costs and outcomes	£16,704/QALY vs haematopoietic stem cell transplant from haploidentical donor	£20,000-£30,000/QALY
Valoctocogene roxaparvovec (8)	United States	Severe haemophilia A	Assuming price similar to that of currently available gene therapies, lifetime horizon, 3% discount rate for costs and outcomes	Dominant vs prophylactic FVIII replacement therapy	$50,000-$100,000/QALY
Yescarta® (9)	Italy	Adults with r/r DLBCL	Lifetime horizon, 3% discount rate for costs and outcomes	€44,746/QALY vs salvage chemotherapy	€50,000/QALY
Yescarta® (10)	United States	Adults with r/r DLBCL	Lifetime horizon, 3% discount rate for costs and outcomes	$58,146/QALY vs salvage chemotherapy	$50,000-$100,000/QALY
Zolgensma® (11)	United States	Spinal muscular atrophy 1 patients with 2 copies of SMN2 gene	Lifetime horizon, 3% discount rate for costs and outcomes	Dominant (at drug price of $4 million) vs nusinersen	$50,000-$100,000/QALY
Zynteglo® (12)	Sweden	Transfusion-dependent β-tha-lassaemia	Lifetime horizon, 3% discount rate for costs, 0% for outcomes	583,767 SEK/QALY vs red blood cell transfusions and iron chelation	700,000- 1,220,000 SEK/QALY

Notes:
* Formal threshold value or threshold value commonly proposed in literature for a country.
ICER = incremental cost-effectiveness ratio; MACI = matrix-applied characterised autologous cultured chondrocyte implant; QALY = quality-adjusted life year; r/r B-ALL = relapsed/refractory B-cell acute lymphoblastic leukemia; r/r DLBCL = relapsed/refractory diffuse large B-cell lymphoma.

REFLECTION 5

The cost-effectiveness of advanced therapies depends on the outcome-based managed entry agreement and payment approach

The use of managed entry agreements that tie (staggered) payment(s) to actual outcomes influences whether, when and how much of the acquisition price is paid, thereby affecting the cost-effectiveness of advanced therapies.

REFLECTION 6

There is a role for pan-European collaborations to manage market access and reimbursement of advanced therapies

Pan-European collaborations such as BeNeLuxA offer flexible pathways to share information, determine cost-effectiveness, negotiate prices and procure advanced therapies.

RECOMMENDATIONS

- Stakeholders need to appreciate that high acquisition costs of advanced therapies can be offset by long-term health care savings and health gains.
- Payers need to adopt a broad economic evaluation framework which considers all value elements that are relevant to advanced therapies.
- Manufacturers and payers need to identify criteria to determine the suitability of a single payment or spread payments to fund acquisition costs of advanced therapies.
- Manufacturers and payers need to develop a decision tree to guide the choice for a specific type of financial-based or outcome-based managed entry agreement for different types of advanced therapies.
- Stakeholders need to set up a standardised framework supporting the practical design and roll-out of outcome-based managed entry agreements for advanced therapies in terms of data collection, outcome selection, payment correction, funding, IT infrastructure and data ownership.
- Policy makers need to strengthen pan-European collaborations on access to medicines and further invest in their activities related to horizon scanning, health technology assessment, price negotiation, procurement and information sharing.

REFLECTION 4

Outcome-based managed entry agreements for advanced therapies are theoretically attractive, but challenging in practice

Several jurisdictions are taking steps to develop a legislative framework, set up a data infrastructure and design a governance model to support the implementation of outcome-based managed entry agreements (for advanced therapies) (13,14).

Illustration: Spain's Valtermed

The Spanish National Service introduced Valtermed in 2019, a web-based information system which serves to elicit the therapeutic benefit in real-life clinical practice of medicines with a significant health and economic impact. Valtermed was piloted using the cases of Kymriah® and Yescarta®, and is proposed to be used for Luxturna®.

Illustration: AIFA's monitoring registries

The Italian Medicines Agency, AIFA, uses a web-based platform of monitoring registries which serve to follow up the use and therapeutic benefit of medicines in real-life clinical practice and the application of outcome-based (and financial-based) managed entry agreements. Such registries have been set up in the context of outcome-based agreements for Kymriah® and Yescarta® and to monitor appropriate prescribing of Onpattro®, Luxturna® and Zolgensma®.

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