POSTER
#PBI35

HEALTH TECHNOLOGY ASSESSMENT (HTA) REVIEW OF CELL & GENE THERAPIES: THE ROAD TO REIMBURSEMENT

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PURPLE SQUIRREL ECONOMICS

BACKGROUND

- Cell and gene therapies are generally produced with the objective of providing substantial clinical benefits in the management of diseases with few or no alternative treatments. (CADTH, 2018)
- The majority of cell and gene therapies are indicated for advanced-stage cancers or hematological conditions, and rare or inherited disorders.
- Recently approved cell and gene therapies are a one-time treatment for severe or terminal conditions that results in a life-term benefit.
- Due to the novelty for these medical advances in the market, positive reimbursement for cell and gene therapies could prove challenging for manufacturers due to the novel treatment pathways and price structures.
- As cell/gene therapies are novel and lauded as “cures”, current cost structures formed with other types of medical interventions in mind (small molecule drugs, biologics, diagnostic tests, medical devices, etc.) are not yet tailored for these novel therapies.
- Price tags frequently exceeding $100,000 are likely to impede access, especially for less affluent payers. Different HTA agencies each have unique sets of criteria regarding their HTA evaluations (Decision Resources Group, 2019).
- Due to the novelty of this treatment, different criteria across HTAs, the limited availability of data, and cell/gene-therapy-specific HTA guidelines, it is expected that recommendations and findings would differ between HTA agencies.

OBJECTIVE

To collect recommendations, justifications for positive or negative recommendations and assess submission within and across HTA agencies

METHODS

- From January 1, 2016 to November 15, 2019, reimbursement recommendations for cell/gene therapies were identified from four different HTA agencies databases, Canadian Agency For Drugs And Technologies In Health (CADTH), National Institute for Health and Care Excellence (NICE), Scottish Medicine Consortium (SMC), Australian Government Department of Health (AGDH) [Pharmaceutical Benefits Advisory Committee (PBAC) and Medical Services Advisory Committee (MSAC)], which published HTA reports
- From the list of reports that were accessible online, medical interventions were classified into general treatment categories, including small molecules, protein-based therapies, and cell & gene therapies.
- Categories were validated by a clinical expert to ensure that treatments were accurately paired to the correct class.
- All data was extracted into an Excel spreadsheet using a predefined template provided. Reimbursement recommendation reports, clinical and economic evidence reports for each treatment were extracted. Extraction variables included study designs, target populations, efficacy outcomes, drug costs, incremental costs, quality-adjusted life-years and cost-effectiveness ratios as well as findings from sensitivity analyses.
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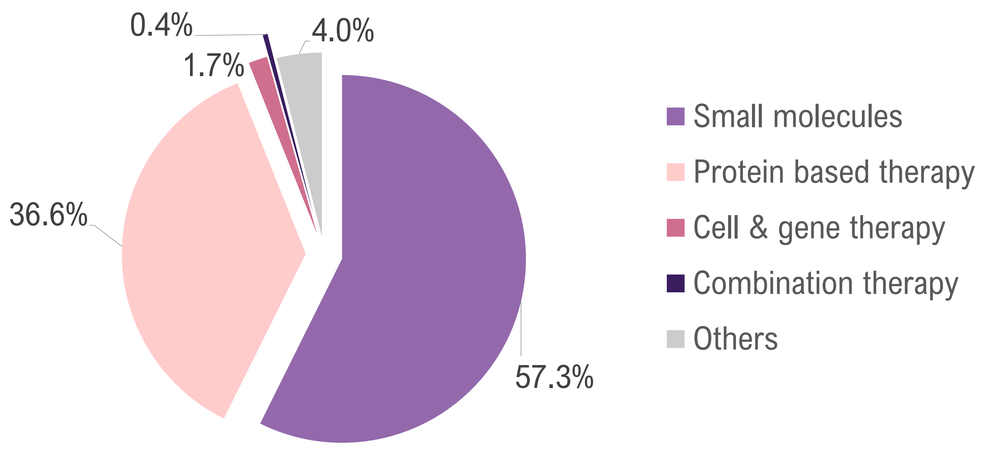
- Due to confidentiality, missing data were seen across all submissions. Only accessible data were reported in this study.
- Reasons for positive and/or negative recommendations were also collected. Two analysts extracted all data and compared their findings. Discrepancies between findings were resolved through roundtable discussion with a third analyst.
- Positive recommendations were submissions that received a recommendation from the agencies for a specific indications, whereas recommendations that are classified as negative were those that were rejected or did not received any recommendations from HTA bodies.
- Using collected data, descriptive comparisons within HTA agencies and across all HTA agencies were undertaken.

RESULTS

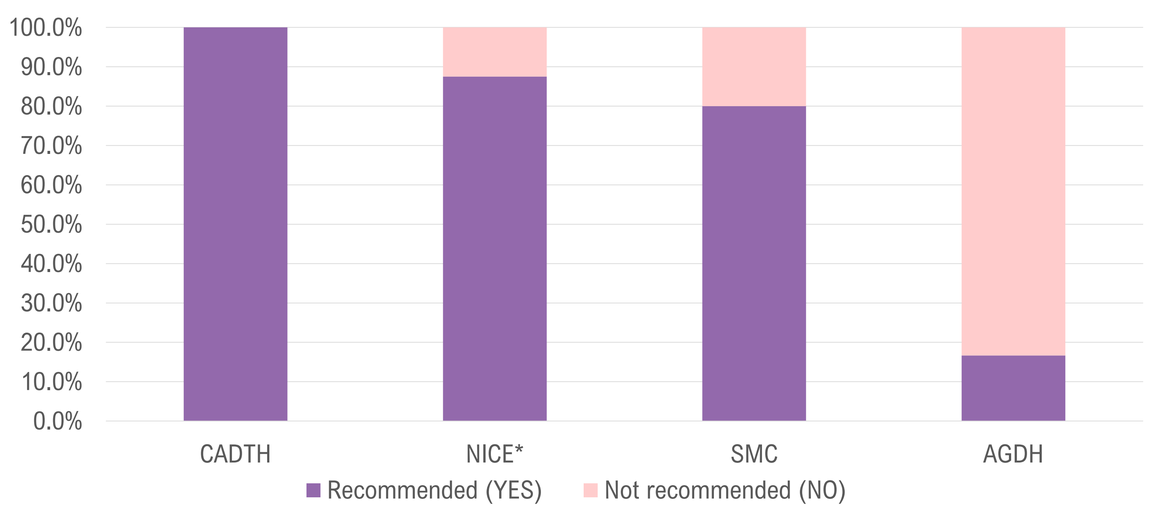
- 1.6% of all HTA submissions were for cell and gene therapies across all agencies, indicating that this treatment class is relatively small compared to others such as small molecules and biosimilars.
- Most submissions were for small molecules (57%) or protein-based therapy (37%) (see Figure 1).
- From the limited amount of cell and gene therapies observed across all four HTA agencies, a total of 25 recommendation reports were submitted to CADTH, NICE, SMC and AGDH (6, 8, 5 and 6, respectively)
- Among those, 17 (68%) had a positive recommendations, with seven of the HTA submissions being rejected, deferred or still pending for a decision (see Figure 2).
- Difference in the proportion of cell and gene therapies recommended/not recommended between CADTH and AGDH were most likely due to the number of submissions that were still under reviewed or deferred.
- Nusinersen was the only gene therapy that was recommended in Australia.

Figure 1: Total proportion of types of therapy across all HTA agencies



*Combination therapy defined by the combination of both small molecules and biologics

Figure 2: Proportion of cell/gene therapies recommended/not recommended



* Some HTA submission were recommended through the Cancer Drug Fund by NICE; CADTH, Canadian Agency for Drugs and Technologies in Health; NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicine Consortium; AGDH, Australian Government Department of Health.

Clinical

- Among all cell and gene therapies, twenty-one submissions provided clinical data. Nine (9/21) were supported by at least one phase 2 trial, eight (8/21) were supported by phase 3 trials, and three (3/21) had phase 1/2 trial in their clinical reports.
- Axicabtagene ciloleucel was supported by a phase 1/2 clinical trial which formed the basis of its clinical efficacy in CADTH, NICE, and SMC clinical reports.
- Sample size across trial population ranged from 12 to 497 patients.
- Tisagenlecleucel [relapsed/refractory acute lymphoblastic leukemia (ALL) and relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL)] and axicabtagene ciloleucel (r/r DLBCL) were the only therapies that were reviewed based on four distinct studies, all of which were phase 2, single-arm trials. They received positive recommendations in all HTAs except AGDH.
- Other cell and gene therapies included nusinersen, patisiran, voretigene neparvovec, darvadstrocel, and inotersen, all of which were supported by phase 3 randomized clinical trials (RCTs).

Economic

- In total, 21 of 25 submissions reported economic data. The other four submissions were still under review or they were deferred.
- With CADTH, manufacturer base-case ICERs ranged from $53,629–24,387,422/QALY, with NICE ranged from £16,704–421,303/QALY, with SMC ranged from £25,238–78,088/QALY, and with AGDH were either not reported or described as >$200,000/QALY.
- For CADTH, which reported the high ICERs, price reductions of up to 98% were found necessary for treatments to fall under the $50,000/QALY threshold.
- Among the eight cell and gene therapies in NICE, only three reported the costs of the treatments (£462,498–£3,203,766) and five reported incremental QALYs (4.42 QALYs–10.7 QALYs. In total, NICE rejected three cell therapy’s submissions, of which two were for tisagenlecleucel (r/r B-cell ALL and r/r DLBCL) and one for darvadstrocel (complex perianal fistulas in Crohn’s disease).
- NICE also reported the mean probabilistic ICERs, which ranged from £16,121 to £86,856/QALY. Additionally, reported willing-to-pay thresholds ranged from £20,000 to £500,000 with the probability of cost-effectiveness going from 0% to 90% across all NICE HTA reports.
- Among all submitted reports to SMC, only tisagenlecleucel was rejected for adult patients with and r/r DLBCL after two or more lines of systemic therapy. The justification was that it had a poor ICER as the treatment’s cost in relation to its health benefits was insufficient.
- In Australia, nusinersen provides a significant improvement in efficacy over standard of care for patients with spinal muscular atrophy, with the ICERs considerably uncertain. However, the committee decided to give a positive recommendation.

LIMITATIONS

- A limitation of our study relates to the number of HTA agencies included. The selection of HTAs was based on the accessibility of submission reports.
- Lack of several variables due to the data confidentiality in HTA reports did lead to incomplete data in some cases.

CONCLUSIONS

- **Generally, HTA agencies accepted earlier data with smaller sample sizes from phase 2 trials and high ICERs exceeding regular willingness-to-pay thresholds for cell and gene therapies offering potentially substantial long-term benefits in sick patients with limited options.**
- **One reason could be related to the logistical challenge of running phase III trials in ultra-orphan populations.**
- **Moreover, to address the uncertainty of long-term effectiveness in cell and gene therapies, HTA bodies relied on assumptions that effectiveness is durable. As observed with past failures, small numbers of potential patients and remarkably high cost are also concerns that could affect the commercial viability of cell and gene therapies.**
- **Hence, the use post-approval data collection and risk-sharing arrangements could aid in addressing limitations. Transparency regarding risk-sharing agreements and price reductions would help manufacturers assess economic viability and potentially spur greater investment in cell and gene therapies.**

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