Evidence Gaps in Evaluating Comparative Effectiveness, Safety, and Cost-effectiveness of Biologics in Health Technology Assessment (HTA) Submissions for the Treatment of Severe Asthma

Poster #HTA67

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Background

- Asthma is a heterogeneous, complex disease commonly characterized by recurring wheezing and airflow restriction.[1-4]
- Asthma represents the foremost prevalent chronic respiratory disease, affecting approximately 8.2% of the United States population and more than 300 million patients worldwide.[1]
- Severe asthma constitutes a significant proportion of the overall disease burden and contributes to approximately 50% of the direct costs attributed to asthma.[2]
- Biologic treatments have demonstrated improvement in outcomes and reduction of corticosteroid treatment burden.[1,2,4]

Objective

- This research aimed to evaluate submissions to health technology assessment (HTA) agencies for biologics to treat severe asthma and to identify gaps in the clinical and economic evidence.

Methods

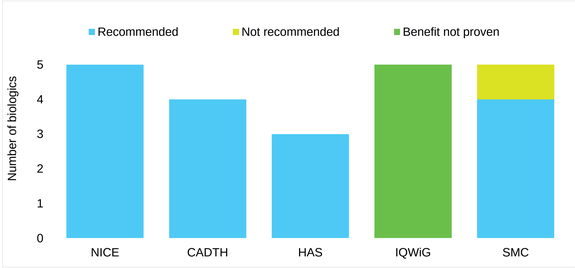
- The websites of the National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWiG), Canadian Agency for Drugs and Technologies in Health (CADTH), and the Institute for Clinical and Economic Review (ICER) were reviewed until December 2022 for HTA appraisals of biologics in severe asthma.
- Severe asthma was defined as asthma that requires treatment with high-dose inhaled corticosteroids with a second controller to prevent it from becoming uncontrolled, according to the first European Respiratory Society/American Thoracic Society guidelines.[3-4]
- Biologics of interests were:
  - Omalizumab
  - Benralizumab
  - Dupilumab
  - Reslizumab
  - Mepolizumab
  - Tezepelumab
- Critiques by the HTA agencies, as well as concerns addressed by the sponsors, were collected and grouped in the categories listed in Figure 1.

Figure 1. Areas of concerns regarding the HTA submissions

Results

- Twenty-four appraisals were identified for omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, and tezepelumab. Among the 22 appraisals providing reimbursement recommendations, 16 had a final positive outcome (Figure 2).
- All IQWiG appraisals concluded that added benefit was not proven due to insufficient data for comparator standard-of-care therapy or lack of generalizability of the trial population.
- CADTH and SMC recommended omalizumab with clinical criteria and/or conditions after initial negative recommendations followed by resubmissions.
- Reslizumab was not recommended by SMC due to the lack of robust economic analyses but was recommended by NICE and CADTH.

Figure 2. HTA recommendations

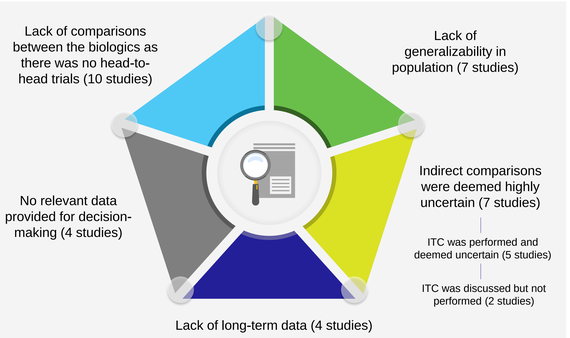


Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; HAS, Haute Autorité de Santé; IQWiG, Institute for Quality and Efficiency in Health Care; NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicines Consortium

Figure 3. Areas of uncertainty identified for economic analyses

- The cost-effectiveness estimate using an anticipated price was over the recommended threshold in three appraisals. On the other hand, four appraisals deemed that cost-effectiveness varied based on assumptions.
- Uncertainty in mortality rate and utility value estimates were mainly due to the lack of direct data on the survival benefit of the drugs and the lack of robust health-related quality of life (HRQoL) data from the clinical trials, respectively (Figure 3).
- The lack of generalizability in the population was mainly due to heterogeneity in asthma severity, in exposure to previous biologics and in unapproved drugs, as well as small sample size and excluding certain patients with comorbidities (Figure 4).

Figure 4. Criticism on clinical evidence



Abbreviation: ITC, indirect treatment comparison

- Given the lack of head-to-head trials due to the difference in the mechanisms of action of drugs, indirect treatment comparisons (ITC) between biologics were performed in six submissions (Table 1).
- However, five out of six ITCs were deemed highly uncertain and unsuitable for decision-making (Table 1). Instead, the comparison with the standard of care was deemed appropriate.

Table 1. Criticism on the performed ITCs between the biologics

Only the NMA submission to NICE for mepolizumab vs benralizumab and reslizumab was deemed suitable.		
Type of ITC	**Comparisons**	**Criticism/comments by HTA authorities**
NICE		
NMA	Mepolizumab vs benralizumab, reslizumab	• Potentially relevant studies were omitted. • There was variation between studies in the length of follow-up, dosing and administration, asthma severity, blood eosinophil counts and previous exacerbations.
PMA	Reslizumab vs omalizumab	• Adjusting for drug differences in the very small overlap population was unlikely to be robust.
CADTH		
Not available	Mepolizumab vs omalizumab	• Number of source trials was limited.
SMC		
NMA	Mepolizumab vs omalizumab	• Heterogeneity in the population • Not comparing within the population eligible for both medicines • No comparison of safety outcomes
MAIC	Benralizumab vs mepolizumab	• Heterogeneity in the population • Not comparing within the population eligible for both medicines • No comparison for PROs and safety outcomes
NMA	Reslizumab vs mepolizumab, omalizumab	• Heterogeneity across the studies in study design, disease severity, eosinophilic phenotype, blood eosinophil concentration, concomitant asthma medications, definitions of clinically significant asthma exacerbation and adverse events • Some comparisons for efficacy and safety outcomes were based on small number of studies.

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; HTA, health technology assessment; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; NICE, National Institute for Health and Care Excellence; PMA, pairwise meta-analysis; PRO, patient-reported outcome; SMC, Scottish Medicines Consortium

Discussion

- There was significant heterogeneity in the indications for the six biologics: allergic vs eosinophilic asthma and starting ages of 6, 12, or 18 years, reflecting the difference in the mechanisms of action between the biologics as well as patient heterogeneity in severe asthma.
- Both economic analyses and clinical evidence received criticism on population, with common reasons including using a highly heterogenous population and small sample size, underscoring the complexity of the disease and patient population.
- IQWiG considered that added benefit was not proven for any biologic in patients who were already on moderate-/high-dose inhaled corticosteroids, mainly due to the flaws in the trial designs not comparing the drugs with appropriate comparators, such as standard of care with appropriate dosing schedules or other biologics with the similar patient population.
- The majority of uncertainty on economic analyses arose from the lack of appropriate clinical data for model inputs such as robust HRQoL data and survival data, suggesting the impact of trial designs on the HTA appraisals.
- Heterogeneity in patient characteristics (e.g., disease severity, prior/concomitant therapy, eosinophil counts) and the resultant small overlap population, as well as a limited number of source trials, were the main reasons for HTA bodies to deem ITCs inappropriate, highlighting the need for a pragmatic trial designed to evaluate their comparative efficacy.

Conclusions

- The majority of HTA bodies had positive appraisals on the clinical benefit of biologics, acknowledging that standard of care is an appropriate comparator due to the lack of head-to-head trials.
- This study underscores the significant gap in clinical data for the evaluation of comparative effectiveness, safety, and cost-effectiveness of biologics in the management of severe asthma.
- As such, further research is warranted to design a large, pragmatic trial or observational study that compares all available biologics.
- Identifying clinically significant differences among biologics will help determine specific subpopulations of patients who may benefit from a particular therapy.

References

1. Schoettler N, Strek ME. Recent Advances in Severe Asthma: From Phenotypes to Personalized Medicine. *Chest*. Mar 2020;157(3):516-528. doi:10.1016/j.chest.2019.10.009.
2. Cote A, Godbout K, Boulet LP. The management of severe asthma in 2020. *Biochem Pharmacol*. Sep 2020;179:114112. doi:10.1016/j.bcp.2020.114112.
3. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. Feb 2014;43(2):343-73. doi:10.1183/09031936.00202013.
4. Holguin F, Cardet JC, Chung KF, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*. Jan 2020;55(1). doi:10.1183/13993003.00588-2019.

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