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BACKGROUND

Asthma affects more than 300 million people worldwide. In Malaysia, the asthma prevalence was estimated between 8.9% and 13.0% in children and 6.3% in adults (National Health Morbidity Survey 2011). According to Global Initiative for Asthma (GINA) 2024, global severe asthma prevalence was approximately 3% to 10% of people with asthma have severe asthma.

According to GINA 2024, severe asthma is asthma that is uncontrolled despite adherence with optimised high-dose ICS-LABA therapy and treatment of contributory factors or that worsens when high-dose treatment is decreased. Type 2-inflammation of asthma (T2-asthma)
is found in majority of patients with severe asthma and characterised by cytokines production such as interleukin-4 (IL-4), IL-5 and IL-13 as an adaptation process towards immune system on recognition of allergens. The immune system also triggered production of other cytokines including thymic stromal lymphopoeitin (TSLP).

Biologics therapies for severe asthma that are currently in the market target the key mediators of the T2-asthma to reduce the severity of the asthma. These biologics are anti-IL5 (mepolizumab), anti-IL5α (benralizumab), anti-IL4α (dupilumab) and anti-TSLP (tezepelumab).

POLICY QUESTIONS

- Should biologics be used to treat severe asthma?
- Which biologics should be used to treat different severe asthma phenotypes?

OBJECTIVE

- To assess the effectiveness and safety of biologics in treatment of severe asthma with regards to patient outcomes such as asthma control (exacerbation, spirometry, symptoms, quality of life [QoL], oral corticosteroid [OCS] sparing effects, hospital admission, Emergency Department ([ED] visit etc), mortality and adverse events or complications
- To assess the economic implication, social, ethical, and organisational aspects related to the biologics in treatment of severe asthma

METHODS

Literature search was developed by the main author and an Information Specialist who searched for published articles pertaining to biologics treatment in severe asthma. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to June 2023, EBM Reviews - Health Technology Assessment, EBM Reviews - Cochrane Database of Systematic Review, EBM Reviews - Cochrane Central Register of Controlled Trials, and EBM Reviews - NHS Economic Evaluation Database. Parallel searches were run in PubMed, US FDA and INAHTA database.
Search was limited to articles in English and in human.

RESULTS AND CONCLUSION:

Part A: Systematic Review

A total of 643 records were identified through the Ovid interface and PubMed while 5 were identified from other sources (references of retrieved articles). Following the removal of 594 duplicates and irrelevant titles, 53 titles were found to be potentially relevant, and abstracts were screened using the inclusion and exclusion criteria. Of these, 52 relevant abstracts were retrieved in full text. After reading, appraising, and applying the inclusion and exclusion criteria to the 52 full text articles, 30 full text articles were included in this report. Twenty-seven (27) articles were excluded as those primary studies were already included in systematic review and NMA / MA (n = 7) narrative reviews (n = 11) and overlapped with other included studies (n = 9).

The 30 full text articles which were finally selected in this review comprised of three systematic reviews with NMA, seven systematic reviews with MA, five systematic review, eleven RCTs, one observational study and three economic evaluation studies of individual biologics (dupilumab, mepolizumab and benralizumab). All studies included were published in English language between 2018 and 2024.

Effectiveness

Asthma exacerbations

All four biologics (mepolizumab, benralizumab, dupilumab and tezepelumab) showed consistent improvement in asthma exacerbation rate (AER) as well as in annual asthma exacerbation rate (AAER) compared to placebo. The pooled analysis study showed that the biologics significantly reduced the AAER by 44% (rate ratio [95% CI 0.52 to 0.62]; I^2 = 58.4%).

In term of subgroup analysis based on baseline blood eosinophils count (BEC), all four biologics showed consistent greater reductions in asthma exacerbation among patients with high BEC level (≥300 cells/uL) compared to low BEC count (<300 cells/uL). The pooled rate ratio was 0.38 (95% CI 0.29 to 0.49) versus 0.67 (95% CI 0.55 to 0.83); $P_{subgroup\_heterogeneity}$ = 0.001.

Asthma control

The most common tool reported involving all four biologics was Asthma Control Questionnaire (ACQ) score. All four biologics showed a positive effect in reducing the ACQ score when compared to placebo. Meta-analysis of mepolizumab, benralizumab, dupilumab and tezepelumab reported a reduction in the ACQ score by -0.34 points (95% CI -0.46 to -0.23, I^2 = 89.5%). However, the reduction did not reach the minimal clinically important difference (MCID) for the ACQ score (-0.50 points). The biologics were also found to improve the ACQ score in patients with high BEC level (≥300 cells/uL) compared to low BEC level (<300 cells/uL).

Lung function

Assessment of lung function in all four biologics was an improvement in forced expiratory volume in 1 second (FEV1). Studies retrieved showed that mepolizumab, benralizumab, tezepelumab and dupilumab significantly increased the FEV1 when compared to

placebo. The pooled analysis of all four biologics reported 0.11L (95% CI 0.09 to 0.14); I^2 = 50.1% improvement.

In subgroup analysis of high (≥300 cells/uL) and low (<300 cells/uL) BEC level, all four biologics showed greater and significant improvement in high BEC level compared to low BEC level. The recent pooled result was available for benralizumab, dupilumab and tezepelumab; 0.18L (95% CI 0.14 to 0.22) versus 0.07L (95% CI 0.04 to 0.10); $P_{subgroup\_heterogeneity}$ <0.001. Meanwhile, for mepolizumab when compared to placebo, the result was 0.1L (95% CI 0.04 to 0.15) among patients with high BEC level.

Hospital admission and Emergency Department (ED) visi
Reduction in hospital admission and ED visit due to exacerbation was observed in all biologics. The pooled result of mepolizumab, benralizumab and tezepelumab showed 60% reduction with rate ratio 0.40 [95% 0.27 to 0.60], I^2 = 32%). According to network meta-analysis, reduction in hospitalisation and ED visit due to exacerbation showed no significant difference between mepolizumab, benralizumab, dupilumab and tezepelumab as the tezepelumab leads other biologic in SUCRA ranked at 95%.

In subgroup analysis of BEC level, tezepelumab, dupilumab, benralizumab and mepolizumab reduced the hospitalisation and ED visit in patients with high BEC level (≥300 cells/uL) where greatest reduction was observed in tezepelumab (90% reduction).

Reduction in oral corticosteroid intake (OCS)
Based on the included studies, benralizumab, mepolizumab, dupilumab and tezepelumab increased the probability of OCS dose reduction to <5mg/day. In a meta-analysis of all four biologics, 74% reduction was reported with a risk ratio of 1.74 (95% CI 1.23 to 2.46); I^2 = 44.1%. The results also showed high probability of the biologics to reduce more than 50% of OCS which was 68% (95% CI 1.29 to 2.19; I^2 = 27.2%. The probability of OCS discontinuation also increased with biologics compared to placebo; the pooled rate ratio between benralizumab, dupilumab and tezepelumab was 1.63 (95% CI 1.29 to 2.19; I^2 = 27.2%) and for mepolizumab the rate ratio was 1.61 (95% CI 1.07 to 2.41). The reduction in OCS occurred as early as four weeks of biologics treatment.

One benralizumab extension study reported on sustained reduction of OCS used in high BEC level subgroup ranging from 17% to 29% with median dose reduction of 10mg – 15mg to 5mg – 10mg.

Other Outcomes
Reduction in blood eosinophils (bEos)
Many studies reported that mepolizumab, benralizumab, and tezepelumab reduced blood eosinophils in severe asthma. The pooled bEos reduction reported for mepolizumab, benralizumab, and tezepelumab were -609.19 cell/uL (95% CI -793.20 to -425.68), -518.68 cell/uL (95% CI -820.24 to -217.12), and (-151.05 cells/uL (95% CI -165.99 to -136.12), respectively.

Reduction in Fractional Exhale Nitric Oxide (FeNO) level
Significant reduction in FeNO level was reported in mepolizumab (-14.23 ppb [95% CI -19.71 to -8.75], tezepelumab (-12.41 ppb [95% CI -14.28 to -10.53]) and dupilumab compared to placebo. The FeNO

reduction concentration with tezepelumab was observed as early as week-2 and the reduction were sustained up to 52- to 104-weeks.

Reduction in Serum IgE

Reduction in serum IgE was reported in dupilumab and tezepelumab compared to placebo. The extension studies of both biologics reported a sustained reduction of serum IgE up to 104-weeks; -122.90 IU/mL (95% CI -167.80 to -78.01), p = 0.00, I^2 = 9.40% reduction in tezepelumab and 80% to 90% reduction with dupilumab.

SAFETY

According to the included studies, a few adverse events lead to the discontinuation of biologics treatment. Different biologics showed different risk of discontinuation such as RR 1.65 (95% CI 0.79 to 3.45) in benralizumab, RR 1.03 (95% CI 0.46 to 2.30) in dupilumab, RR 0.65 (95% CI 0.36 to 1.16) and RR 0.68 (95% CI 0.34 to 1.35) in tezepelumab. The reasons of the discontinuation were anaphylactic reaction, malignancy, live function abnormality, asthma-related event requiring intubation, pulmonary TB, non-asthma related events, no clinical improvement, severe headache, severe arthralgia, allergic rash, and conjunctivitis, persistent eczematous (on face, trunk and upper limb) and pruritis. Death during study period showed no difference between biologics and control groups (risk ratio 0.91 [95% CI 0.39 to 2.09], I^2 = 0%).

On the other hand, the most common adverse events reported in both biologics and placebo were nasopharyngitis, upper respiratory infection, headache, and injection-site reaction.

ORGANISATIONAL

One study assessed the effects of tezepelumab on healthcare utilisation (HCU) among patients with severe asthma. The study showed that, tezepelumab showed fewer asthma-related unscheduled specialist visits, fewer telephone calls with a healthcare provider, lesser ambulance transports due to asthma, and fewer home visits from a healthcare provider than placebo.

SOCIAL

The included studies reported that mepolizumab, benralizumab, dupilumab and tezepelumab improved quality of life (QoL) by improving the Asthma Quality of Life Questionnaire (AQLQ), and St George's Respiratory Questionnaire (SGRQ). One dupilumab extension study assessed the quality of life among paediatric patients as well as their caregivers. The LS mean difference (LSMD) in dupilumab versus placebo showed significant improvement since week-24 onwards and at week-52 the LSMD was 0.34 (95% CI 0.16 to 0.52); p = 0.0002 in Paediatric Asthma Quality of Life Questionnaire Interviewer-Administered (PAQLQ(S)-IA), and 0.25 (95% CI 0.00 to 0.50; p = 0.0531) at week-24 and 0.47 (95% CI 0.22 to 0.72; p = 0.0003) at week-52 in Paediatric Asthma Caregiver's Quality of Life Questionnaire (PACQLQ-IA) global score. According to the checklist, the improvements was observed in individual domain scores of emotional functions, activity limitation and symptoms.

ECONOMIC EVALUATIONS

Overall, most of the included studies reported an ICER/QALY gained was higher than Willingness-to-Pay (WTP) threshold. According to the studies, the potential saving was related to decrease rate of

hospitalisation, ED care, primary care visits and the management of clinically significant exacerbations. In economic evaluation study of mepolizumab in Singapore, the ICER/QALY was SGD335,486 (US$238,195) and the ICER/LY gained was SGD208,238 (US$147,846) with average of five exacerbations were avoided per patient over a lifetime. However, the ICER was above Singapore WTP threshold (SGD250,00). Meanwhile, an economic evaluation study of
benralizumab in Spain reported that benralizumab was within Spain WTP (€24,000) as the ICUR obtained was €18,177/QALY with Net Monetary Benefit obtained with benralizumab was €813. Another economic evaluation was on dupilumab in Japan. The study compared dupilumab with benralizumab, mepolizumab and omalizumab where the study reported that dupilumab was cost-effective compared to benralizumab and mepolizumab but not cost-effective compared to omalizumab. One of the key drivers for this analysis was price of each biologic per vial.

Part B: Economic Evaluation
A cost-effectiveness analysis (CEA) from the perspective of MOH was conducted.

Objectives
The objective of this CEA is to assess the incremental cost-effectiveness ratio (ICER) between asthma biologics (tezepelumab, benralizumab, mepolizumab and dupilumab) and Standard of Care (SoC) for the treatment of severe asthma.

Methods and Model Structure

Five-health states Markov model with a four-week cycle and a lifetime horizon was constructed and analysed using Microsoft Excel Workbook 2021.

The primary outcomes included total cost and quality-adjusted life years (QALYs) gained for each intervention in consideration. An annual discount rate of three per cent was applied to both costs and outcomes estimated.

The input on the treatment effects was drawn from the systematic review carried out in Section A of this report. Meanwhile, costs for drug acquisition and disease management were based on available local data. Health utility values for asthma health states and other key parameters applied to the model were sourced from previously published studies. This analysis also was based on one time of the Malaysian per capita gross domestic product (GDP) in 2022 (MYR 54,863 /QALY).

Results
The model indicated that adding biologics to the SoC improves QALYs but incurred higher costs. The ICERs for tezepelumab, benralizumab, mepolizumab, and dupilumab were RM 759,126, RM623,901.46, RM 1,543,407, and RM 883,807 per QALY gained, respectively. All ICERs
exceeded the Malaysian Willingness to Pay (WTP) or cost-effectiveness threshold of one GDP per capita per QALY gained.

In addition, three scenario analyses were performed in which the

provision of shorter treatment duration, the extension of dose treatment frequency and hypothetical percentage reduction of drug costs were explored. All the interventions showed reductions in the ICERs but were not cost-effective. Moreover, all drugs required more than 90% cost reduction, except for benralizumab which requires 81% cost reduction for the ICERs to be cost-effective.

One-way sensitivity analysis was performed to assess key drivers that impacted the estimated ICERs the most. Health utility value for long-term OCS use and drug cost were noted to show a remarkable impact on the ICERs. Meanwhile, a probabilistic sensitivity analysis was conducted to assess the robustness of model results. A Monte Carlo simulation of 1000 iterations was performed and the model results were shown to be consistent and robust.

CONCLUSION

Based on the above review, mepolizumab, benralizumab, dupilumab and tezepelumab significantly reduced exacerbations, ED visits and hospitalisation, improved lung function, asthma control, quality of life and reduced the use of oral corticosteroids especially among patients with high level of BEC (≥300 cells/uL).

In terms of economic implications, these biologics are effective but at a higher cost as the ICER / QALY are higher than the WTP threshold.

POLICY RECOMMENDATION

Biologics (mepolizumab, benralizumab, dupilumab or tezepelumab) may be used as an add-on therapy for severe asthma in patients with these criteria; high BEC level (≥300 cells/uL) and unresponsive to the optimal therapy. Taking into consideration the economic implications, effective price negotiations may improve the cost-effectiveness of this treatment.