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RESEARCH LETTER

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Biologics in severe asthma: Which one, When and Where?

To the Editor,

Biologics have transformed the treatment of patients with type 2 (T2) inflammation-driven severe asthma.[1] In appropriately selected patients, biologic use reduces asthma exacerbations and reliance on maintenance oral steroids (mOCS) and improves lung function and quality of life. The decision to initiate a biologic is usually led by specialist multi-disciplinary teams (MDTs). While The Global Initiative in Asthma (GINA) has published recommendations on the management of people with severe asthma,[2] in the UK access criteria for biologics are determined by the National Institute for Health and Care Excellence (NICE). A number of biologics are currently approved for the treatment of severe asthma (SA) but direct head-to-head comparison trials of these biologics are unavailable and indirect meta-analyses infer discordant results.[3] Therefore, there is no evidence-based guidance on biologic choice in co-eligible patients and variable recommendation on when and how clinical response should be assessed, leading to variations in practice by SA MDTs.

In light of the lack of consensus guidance, the NHS Improving Value Severe Asthma Collaborative, set up in 2018, propose a biologic prescribing algorithm that has been optimized following input from the UK Severe Asthma Network and British Thoracic Society Asthma Specialist Advisory Group (Figure 1). The algorithm addresses 2 key questions. Firstly, what are the clinical features that help stratify patients and guide initial choice of a biologic? Secondly, how early should biologic response be assessed?

When faced with a patient who is eligible for more than one biologic treatment, we propose early consideration of shared decision-making that brings together patient preference with the SA MDT. In addition to discussing the expected benefits and establishing common treatment goals, route and frequency of administration of the considered biologic and availability of self-administered treatment at home should be discussed as more or less frequent dosing may be desirable for an individual patient. Following this, clinical features that can guide initial choice of a biologic for a patient include the use of mOCS, clear allergen-driven symptoms, presence of food allergies, chronic spontaneous urticaria (CSU), level of eosinophilia, age of onset of asthma, presence of chronic rhinosinusitis with nasal polyps and co-morbid atopic dermatitis.

Anti-IgE treatment should be considered in patients who have clear allergen-driven symptoms and a history of food allergies or CSU, with the latter being approved by NICE as being suitable for treatment with omalizumab. The presence of elevated T2-specific biomarkers, FeNO and peripheral blood eosinophils (PBEs), predicted response to omalizumab in post hoc analyses,[3] but this has not been replicated in real-world data studies and may not be useful in prioritizing anti-IgE treatment.[4] Despite mOCS dependence being a NICE eligibility criteria for omalizumab, in co-eligible patients, omalizumab should not be prioritized as the data on its ability to facilitate OCS discontinuation is equivocal.[1,5] While randomized controlled trials evaluating the OCS sparing effects of omalizumab have not been performed, a recent meta-analysis of real-world studies suggests its use is associated with a reduction in OCS dependence and a modest decrease in the mean daily steroid dose.[6] In women who may be planning a pregnancy, and are co-eligible for more than one biologic, omalizumab should be prioritized as international registry-based safety data are currently available[7] (registries for mepolizumab, benralizumab and dupilumab are ongoing). However, we recommend that continuing biologics during pregnancy should only occur after a careful transparent discussion of risks and benefits with the patient.

Clinical characteristics associated with a positive response to anti-interleukin5/anti-interleukin5 receptor (anti-IL5/5R) pathway treatments include higher PBEs, frequent exacerbations, presence of nasal polyps and adult-onset asthma. For patients on mOCS, mepolizumab or benralizumab should be used in preference, as they have been specifically studied in this group of patients and shown to consistently and substantially decrease OCS usage alongside reducing exacerbation frequency.[1,3] Reslizumab remains a treatment option in this group, allowing weight-adjusted dosing which may provide added benefits in some patients.[8] However, the feasibility of providing intravenous dosing is an important consideration for clinical services.

Finally, in the presence of chronic rhinosinusitis with nasal polyps or severe atopic dermatitis, dupilumab should be prioritized, with the latter being approved by NICE as being suitable for treatment with dupilumab. While omalizumab, mepolizumab and benralizumab all have evidence of efficacy for nasal polyposis, the magnitude of this response appears greatest for dupilumab.[9] The beneficial effect of dupilumab has been found to be greater in patients with raised PBEs and FeNO, and it has also been shown to facilitate a decrease in total OCS dose.[1,4] At the time of writing this, dupilumab is still undergoing NICE review.

Once a biologic has been initiated, governing bodies and guidelines vary in their recommendations on when and how clinical response should be assessed. GINA recommends assessing response as early as 4 months and taking into consideration exacerbations, symptom control, lung function, side effects, OCS dose and patient

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satisfaction. The Australian Centre of Excellence in Severe Asthma advises reviewing patients at 22–26 weeks of treatment for a reduction in the Asthma Control Questionnaire (ACQ)-5 score by 0.5 units compared to baseline and mOCS dose by at least 25% from baseline.[10] In the UK, NICE recommends reviewing response to omalizumab at 16 weeks and defines clinical response to anti-IL5/5R biologics as a clinically meaningful reduction in exacerbations and oral corticosteroid (OCS) dependence after 12 months of treatment. While it is broadly accepted that a clinically meaningful reduction denotes a reduction by 50% in exacerbation frequency and mOCS dependence, ultimately it is the decision of the SA MDT. While biologics are associated with significant positive outcomes, up to 30% of patients in real-world clinical practice do not demonstrate a clinical response and timely identification of non-responders is crucial to enable biologic switching.[11]

We propose that response to all biologics should be evaluated between 4 and 6 months in order to identify patients who are failing treatment. The biologic should be stopped if the patient experiences worsening of their asthma or side effects from the biologic. They should be reassessed by the SA MDT to consider stopping/

Key Messages

- Biologic choice in co-eligible patients should be guided by shared decision-making, patient-related factors and co-morbidities.
- Response to biologics should be evaluated 4 to 6 months after initiation by reviewing asthma control, steroid dependence, exacerbation frequency and patient expectations.
- Home administration of biologics can be considered in suitable patients and should be reviewed regularly.

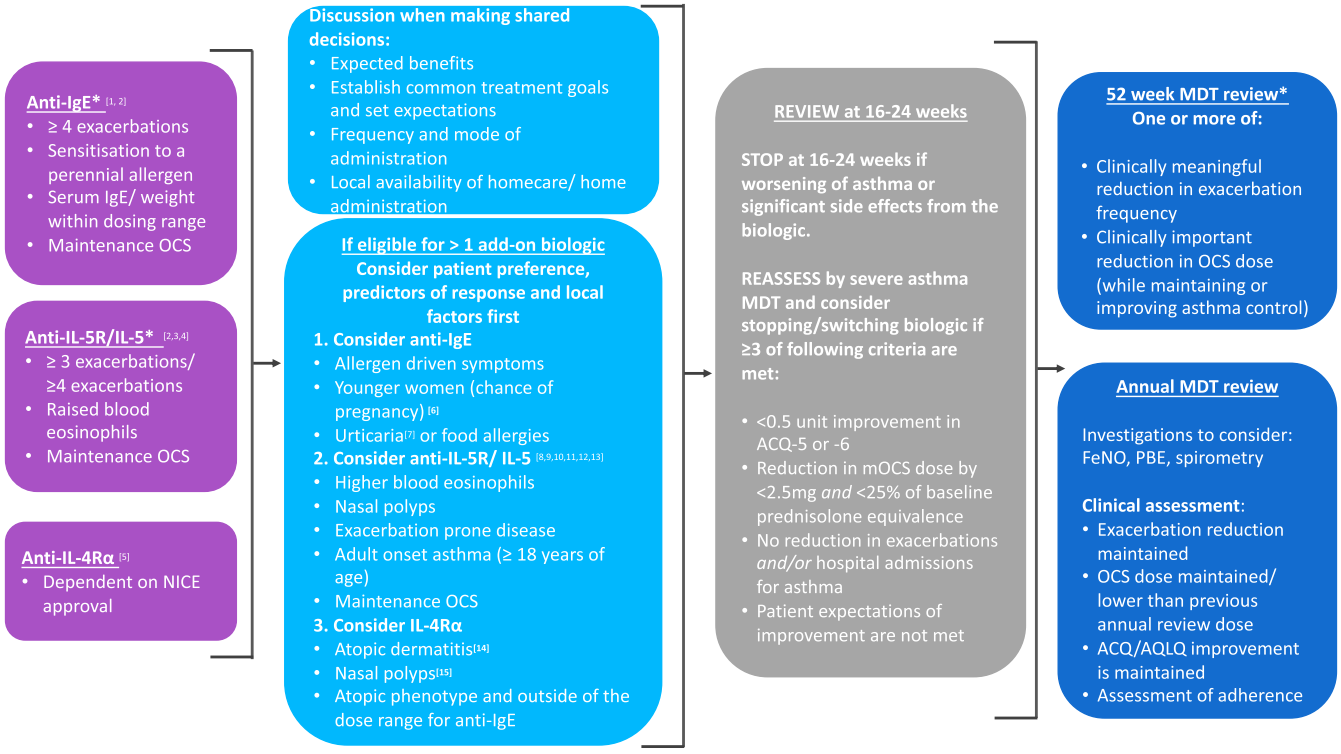

FIGURE 1 Algorithm for biologics choice, assessment of response and continuation. OCS, oral corticosteroid; MDT, multi-disciplinary team; FeNO, fraction of exhaled nitric oxide; PBE, peripheral blood eosinophil; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire, *denotes recommendations by National Institute for Health and Care Excellence. [1] NICE TA278 Omalizumab for treating severe persistent allergic asthma. Published 24 April 2013 https://www.nice.org.uk/guidance/ta278. [2] NICE TA671 Mepolizumab for treating severe eosinophilic asthma.03 February 2021 https://www.nice.org.uk/guidance/ta671. [3] NICE TA479 Reslizumab for treating severe eosinophilic asthma.04 October 2017 https://www.nice.org.uk/guidance/ta479. [4] NICE TA565 Benralizumab for treating severe eosinophilic asthma.06 March 2019 https://www.nice.org.uk/guidance/ta565. [5] NICE GID-TA10276 Dupilumab for treating severe asthma [ID1213] https://www.nice.org.uk/guidance/indevelopment/gid-ta10276. [6] Namazy JA et al. J Allergy Clin Immunol 2020;145(2):528–536. [7] NICE TA339 Omalizumab for previously treated chronic spontaneous urticaria. 8 June 2015 https://www.nice.org.uk/guidance/ta339. [8] Bleeker ER et al. Eur Respir J. 2018;52(4)1800936. [9] FitzGerald JM et al. Lancet Respir Med. 2018.6(1):51–64. [10] Kavanagh J et al. Chest 2020;158(2):491–500. [11] Brusselle G et al. Pulm Pharmacol Ther. 2017.43:39–45. [12] Harvey ES et al. Eur Respir J 2020 55(5):1902420. [13] Howarth P et al. J Allergy Clin Immunol 2020, 145 (6):173–175. [14] NICE TA534 Dupilumab for treating moderate to severe atopic dermatitis. 01 August 2018 https://www.nice.org.uk/guidance/TA534. [15] Bachert C et al. Lancet 2019;394(10209)11638–1650

switching biologic if ≥3 of the following criteria are met: (i) <0.5 unit improvement in ACQ-5 or ACQ-6 (ii) reduction in mOCS dose by <2.5 mg and <25% of baseline prednisolone equivalence, (iii) no change in exacerbations and/or hospital admissions for asthma and (iv) patient expectations of improvement are not met. The criteria are intentionally broad, and the 4–6 month time period was chosen to enable sufficient time for meaningful OCS stepdown in patients on mOCS (recognizing many maybe apprehensive to wean if mOCS use has been longstanding) and to minimize seasonal influences on exacerbations. Although 1-year responder status can be identified at 16 weeks, the positive and negative predictive values are considerably higher at 24 weeks.[11]

It is important not to wait longer than 6 months before identifying a non-responder to avoid ongoing uncontrolled disease (and associated burdens on the patient and healthcare systems), avoid unnecessary use of high-cost drugs and enable patients to switch to treatment that may provide greater benefit. The presence of airway infection, non-adherence to prescribed asthma treatments, significant other comorbidity, for example tracheobronchomalacia and the rare development of anti-drug antibodies, should be considered and addressed in biologics non-responders. Once established on a biologic, our algorithm emphasizes that continued use should be reviewed annually to review ongoing benefit from the biologic and adherence to prescribed medication.

Finally, patients who respond to biologics are likely to continue them for the long term unless they stop responding, develop side effects or contra-indications to asthma biologics. Shifting administration of the biologic into the patient's home/workplace facilitates reablement and return to a routine, reduces absence from work while also reducing the pressure on hospital clinics. The COVID-19 pandemic has prompted SA centres to move many patients to home self-administration. Again, there is no consensus on which patients and at what treatment time point clinicians transfer patients to biologic self-administration at home. We propose a pragmatic way for SA MDTs to transition patients to self-administration (Figure 2). Lower risk patients can be transferred to self-administration at home sooner while higher-risk patients should continue to attend healthcare facilities for dosing. Patients should be assessed regularly for ongoing suitability, including inhaler technique optimization and medication reviews, with the clinician having the ability to withdraw the service and revert back to biologic administration in the hospital clinic if the patient is non-adherent to their prescribed asthma treatment (including the biologic) or there are concerns that the patient is not safely administering the biologic. There is a need for the development of digital technology that includes notifications, reminders and patient-reported outcomes to support patients who are self-administering their biologic and enable clinicians to robustly monitor clinical outcomes.

In summary, we have provided a simple, pragmatic algorithm for biologic prescribing and delivery for clinical practice. We anticipate regular updates to the algorithm as novel biologics are approved for use. Our approach offers the potential to reduce variation in care across SA centres and will support meaningful future analysis of

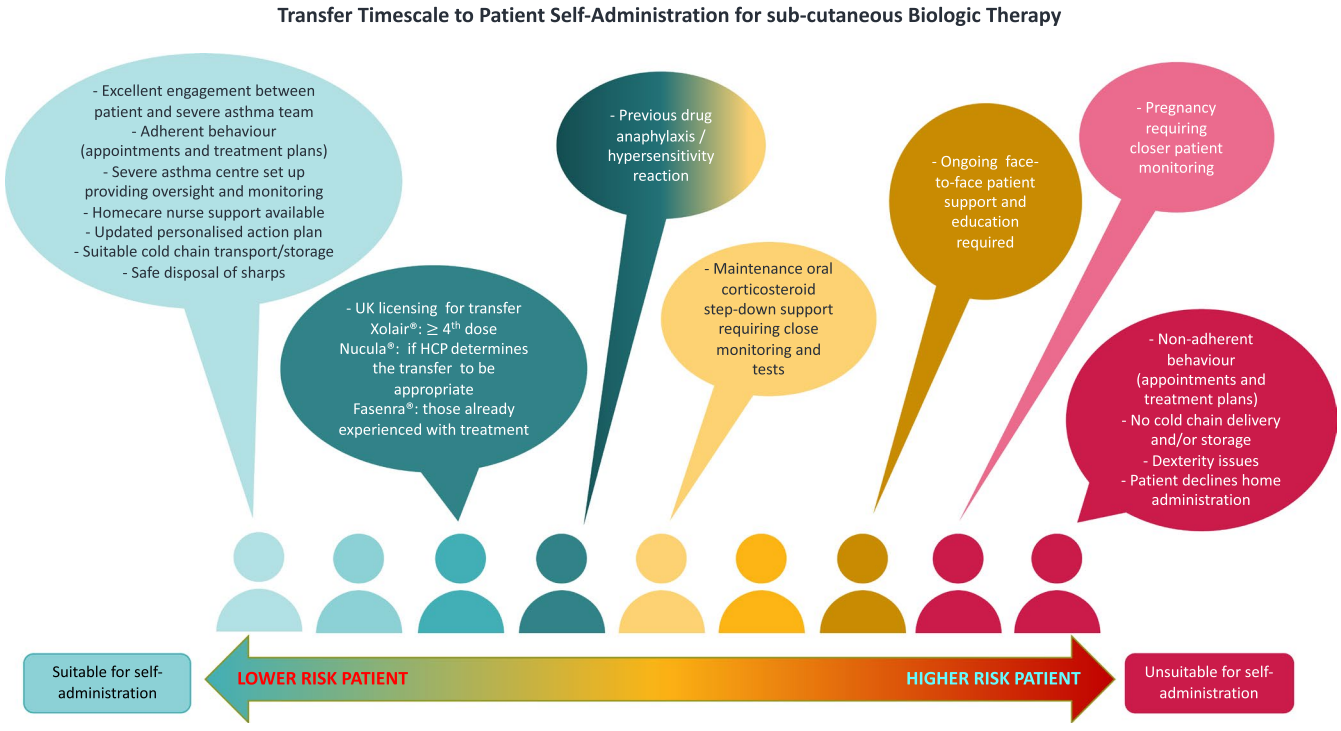

FIGURE 2 Sliding scale assessment to guide home care provision of current T2 biologics. Fasenra (benralizumab), Nucula (mepolizumab), Xolair (omalizumab). Cinqaero (reslizumab) currently not suitable for patient self-administration; HCP, healthcare professional

comparative effectiveness of biologics in national and international SA registries.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

HR, AM and SS conceived and drafted the manuscript and figures. All authors critically reviewed and revised the manuscript and figures and approved the final version of the manuscript submitted.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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