BRS Consensus Guidance on the use of biological therapies for Chronic Rhinosinusitis with Nasal Polyps

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Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a prevalent condition characterised by a significant impact on quality of life and productivity, with frequent recurrence after both medical and surgical treatment(1). Oral corticosteroids are effective at achieving short term symptom improvement(2, 3), but benefit is limited due to the risk of side effects which accrue with repeated use (4). Surgery has been shown to achieve more durable symptomatic benefits (5), but is associated with pain and discomfort, time for recovery, a small but definite risk of serious complications (6), and based on previous data, more than one in 5 patients will require another surgery within 5 years of follow-up(5). Poor disease control is commonplace, driving the search for alternative treatment strategies.

Monoclonal antibodies (Mabs) are biological treatments that target specific inflammatory mediators or immune cells. Growing understanding of the pathophysiological pathways found in CRSwNP and evidence of efficacy in similar patterns of Type 2 inflammation found in asthma and atopic dermatitis have led to trials evaluating use in CRSwNP. As such therapies have been evaluated and are shown to be effective, it will be essential to consider where they should be placed in current treatment pathways for CRSwNP, particularly with respect to the use of corticosteroids and surgeries.

We set out to create Consensus Guidelines, based on current evidence and relative risks of adverse effects and the costs of different treatments, that reflect the views of the BRS Council on where the use of biologics should be positioned within treatment pathways for CRSwNP, specifically in the setting of the National Health Service (NHS). These guidelines were created in early 2021 and it is anticipated that they will evolve as further evidence accrues and the relative costs and availability of treatments change.

Methods

Expert panel

An expert panel of 16 members was assembled. All BRS Council members were invited to participate, but could decline based on lack of availability, limited knowledge or experience within the area of specialist interest, or if working outside the NHS setting. Additional panellists were invited who had expertise in this area.

Literature review and evidence summary

A background literature review and synthesis of the evidence was undertaken by a core group of the panel, and key evidence summarised (see Appendix 1). A recently updated version of the Cochrane review, 'Biologics for chronic rhinosinusitis' was circulated in full, along with another recent systematic review of use in CRSwNP(7) and two previously published guidelines on indications for use of biologics, from EPOS(8) and EUFOREA(9). Key outcomes from relevant trials were summarised and circulated in data tables (Appendix 2).

Indications for consideration

The core group defined what symptoms, past medical history and relevant diagnostic tests might influence the decision regarding whether a biologic prescription might be appropriate. Their responses were used to form a series of matrixes that categorise patients according to these key indications. Specific combinations of associated comorbidities and previous treatment were considered, alongside wider statements concerning the delivery of biologics. One hundred clinical scenarios were considered, stratified by the presence of co-morbid asthma, N-ERD or AFRS, the number of previous surgeries (or if a patient was unfit surgery), and the use of INCS or OCS (or if a patient was unable to use them). Other characteristics such as baseline symptom scores, the importance of radiological imaging and the extent of disease on radiological imaging were also considered.

Consensus process

We used the RAND/UCLA methodology with a multi-step process (www.rand.org)(10). Our expert panel undertook a 2 round modified Delphi process of ranking and classifying

appropriateness of different investigations and treatment options. Using a 9-point Linkert scale, for each indication the panellists scored whether a treatment was either:

- Not recommended/ Inappropriate; should not be prescribed for the indication described within the NHS, based on current evidence base and costs (scored 1 to 3),
- Uncertain; (scored 4 to 6),
- Recommended / Appropriate; should be prescribed for the indication described within the NHS, based on current evidence base and costs (scored 7 to 9)

Free text comments were encouraged if greater context was required, if the question was ambiguous or if anything had been overlooked.

The final recommendation was based on the median ranking scores collated from each clinical scenario provided that there was consensus. Consensus was defined as the requirement for more than 70% of responses to fall into the category defined by the median, and when this score fell in either recommended or not recommended, less than 15% of responses were scored as the opposite.

The scores at the end of round 1 were analysed and presented back to the group, with the distribution of scores summarised for each question. The panel was then asked to repeat the scoring for any items where consensus has not been reached having considered if they wished to revise their previous score.

Round 2 scores were evaluated in the same way. When the median fell between 4-6, or if the median fell in either 1-3 or 6-9 and the definition of consensus was not met, no recommendation was made, and the use of biologics for the given indication was considered uncertain.

Results

Sixteen panellists completed the first round, and 15 completed the second round. Of the 100 clinical scenarios, consensus was reached on 77 (36 at round 1, increasing to 77 after round 2). Of the remaining 23 scenarios, the median fell between 4-6, or if the median fell in either 1-3 or 6-9 and the definition of consensus was not met, no recommendation was made.

Recommendations

The recommendations are summarised in figure 1 and 2

Figure 1 summarised all situations where agreement was reached that biologics should be considered in the treatment of CRSwNP within the NHS at the current time.

Figure 2 summarised all situations where agreement was reached that biologics should NOT be considered in the treatment of CRSwNP within the NHS at the current time.

For all other combinations of OCS, surgery and comorbidity, agreement was not reached. In almost all remaining scenarios, the median answer of the was 'uncertain' and there was no move towards consensus between rounds.

More specifically;

In all patients, regardless of severity or comorbidity,

Biologics should NOT be considered if the patient has not used corticosteroids in any form in the preceding 12 months.

Biologics should be considered if patients have received 2 or more courses of OCS, or are unable to take OCS AND have had 3 or more surgeries, or are considered unfit for surgery (under local or general anaesthetic)

Patients should have at least moderate symptoms measured on the SNOT-22 (20) or VAS scale (>4) on current treatment, and a Lund-Mackay score of 8 or more to be considered for a biologic

In patients without asthma or N-ERD; in addition to the criteria above for all patients

Biologics should NOT be considered if the patient has not used oral corticosteroids in the preceding 12 months.

Biologics should NOT be considered if the patient has not had previous surgery

Biologics should NOT be considered if the patient has required 1 - 2 courses of oral corticosteroids in the preceding 12 months AND has not undergone previous surgery or has undergone one previous surgery.

In patients with asthma but no N-ERD, in addition to the criteria for all patients

Biologics should NOT be considered if the patient has not had previous surgery

Biologics should NOT be considered if the patient has not used oral corticosteroids in the preceding 12 months AND has undergone 2 or fewer previous surgeries

Biologics should be considered if patients have required at least 1 course of steroids in the last year or are unable to take OCS AND have had 3 or more previous surgeries or are unfit for surgery

Biologics should be considered if patients have received 2 or more courses of OCS, or are unable to take OCS AND have had 2 or more surgeries, or are considered unfit for surgery (under local or general anaesthetic)

In patients with asthma and N-ERD, in addition to the criteria above for all patients

Biologics should NOT be considered if the patient has not had previous surgery AND have not received more than 2 courses of OCS

Biologics should NOT be considered if the patient has not used oral corticosteroids in the preceding 12 months AND has undergone 1 or fewer previous surgeries

Biologics should be considered if patients have required at least 1 course of steroids in the last year or are unable to take OCS AND have had 2 or more previous surgeries or are unfit for surgery

Biologics should be considered if patients have received 2 or more courses of OCS, or are unable to take OCS AND have had 1 or more surgeries, or are considered unfit for surgery (under local or general anaesthetic)

In patients with AFRS

It was noted that at the current time there is insufficient evidence to support effectiveness, and therefore trials must demonstrate that biologics are effective in this cohort and to determine whether this requires surgery to be performed in parallel. However, providing these criteria are met by future research, the following conditional recommendations could be made;

Biologics should NOT be considered if the patient not had previous surgery

Biologics should NOT be considered if the patient has not used oral corticosteroids in the preceding 12 months

Biologics should NOT be considered if the patient has required 1 - 2 courses of oral corticosteroids in the preceding 12 months AND has not undergone previous surgery or has undergone one previous surgery.

Biologics should be considered if patients have required at least 1 course of steroids in the last year or are unable to take OCS AND have had 3 or more previous surgeries or are unfit for surgery

Biologics should be considered if patients have received 2 or more courses of OCS, or are unable to take OCS AND have had 2 or more surgeries, or are considered unfit for surgery (under local or general anaesthetic)

General recommendations on the provision of biologics in secondary and tertiary ENT care settings

Biologics should be available only in a designated specialist centres that can offer all alternative interventions

Specialist centres should be co-located with Severe Asthma clinics that are already providing biologic therapies.

A CT scan is required to establish extent of disease and that of previous surgery; a minimum score of 8/24 (Lund-Mackay) must be present.

Endoscopic confirmation is essential in the assessment of eligibility and response

Revision surgery should be considered prior to a biologic if the previous surgery was a polypectomy without opening the sinuses

Until there is evidence to support the safety and efficacy of biologics in CRS without nasal polyps, biologics should NOT be prescribed

Outside of the NHS, self-paying patients with CRSwNP may select biologic therapies as an alternative to surgery or OCS provided that they have been given information regarding the risks and benefits of each option

Discussion

The panel have made a series of recommendations which define a group of patients in whom the use of biologics is considered appropriate in the treatment of CRSwNP, and a group where use would be considered inappropriate, considering the current evidence base, costs and capacity in the setting of the NHS.

The RAND/UCLA appropriateness methodology is well described and has previously been utilised defining appropriateness criteria for ESS during management of uncomplicated adult CRS and adult recurrent acute rhinosinusitis (1, 11, 12). We have used a similar process to develop BRS guidance on the management of incidental findings in the maxillary sinuses with regard to dental implantation(13), and to develop guidance on the treatment of COVID-19 related loss of smell(14). It aims to detect and achieve consensus amongst a group of experts and is ideally suited to evaluating the appropriateness of use of medical interventions where the evidence base is limited, which consume significant resources or where use remains controversial. Defining appropriate use of biologics in CRSwNP would therefore seem to be well suited to the methodology.

Biologic therapy using Mabs that block the action of interleukins or other targets central to type 2 inflammation now play an important role in the management of difficult-to-treat asthma and many of these treatments have also been shown to be effective in the management of severe CRSwNP. Dupilumab, an anti IL4/13 receptor mab and omalizumab, an anti-IgE mab have been shown to achieve significant reductions in polyp size and nasal congestion in large phase 3 studies(15, 16). Both have now been granted FDA and EMA approval for use in patients with CRSwNP and are currently available for use in the US and selected European countries. Other drugs will likely soon follow, specifically with phase 3 trials completed for mepolizumab(17) and benralizumab, which target IL5.

Although biologicals have been shown to reduce the need for surgical intervention for CRSwNP(17), their high costs and the need for long term treatment mean that this is unlikely to be the most cost-effective treatment across the whole population with CRSwNP, even if superior in terms of long-term symptom control in the difficult-to-treat group. Scangas et al

undertook a Markov decision tree cost-effectiveness model over 20 years(18), and found, based on US costs (which may not be applicable in all healthcare setting), that a strategy of sinus surgery cost circa $50,000 producing 9.80 QALYs while dupilumab treatment costs $535,000 but produced 8.95 QALYS. Surgery was more cost-effective regardless of the frequency of revision surgery. Similarly, in asthma, although the efficacy of biologic therapy is well established, none of the currently available drugs have been found to be cost-effective(19).

Currently, no biologic treatments have been approved by NICE for the treatment of patients with CRSwNP. NICE considers evidence of effectiveness of new interventions, but applies a standard threshold range with an upper limit of £20-30,000 per QALY and a budget impact test, where drugs that cost more than £20 million in any one of their first three years of use trigger commercial discussions to mitigate the impact on the wider NHS, or further restrictions on usage (www.nice.org.uk). Using the data from Scangas et al, with a £43,500 cost per QALY at current currency conversion rates, it is unlikely that the NICE threshold could be met if biologics were prescribed to all patients with CRSwNP.

However, the panel's recommendations identify a group who are more likely to fail to achieve long term benefit from conventional treatment pathways and to undergo repeated interventions with higher associated healthcare resource utilisation. A recent study has shown that patients with a history of previous surgery are twice as likely to need further revision surgery, or those with a history of N-ERD five times more likely to require further revision when undergoing endoscopic sinus surgery (Hopkins, Lund). Therefore, as the patients identified by the panel have higher direct costs over their lifetime that other patients with CRSwNP, use of biologics in this subgroup are more likely to be cost-effective. Patients with higher rates of revision surgery also likely derive less symptomatic benefit from conventional treatment pathways; indeed a recent study found that 43% of patients' symptoms were uncontrolled after sinus surgery and this again was more common after revision surgery and in the setting of N-ERD(20). Our criteria will also therefore help to identify patients for who current treatments are likely unsuccessful in achieving adequate disease control, and where biologics may offer the only option that may achieve long term disease control. We therefore hope that NICE and other organisations will consider our

criteria to define a group for whom biologics should be approved even if the usual threshold limit per QALY cannot be met, and not seek to impose further restrictions on usage over and above those defined by the panel (Fig 1).

The criteria used by the panel in reaching consensus where biologics are considered appropriate define a smaller group of eligible patients than either the EPOS(8) or EUFOREA(9) criteria for patient selection for biologic therapy. The scenarios where the panel felt that use of a biologic was uncertain included patients with at least one previous surgery, many of whom would meet the EPOS criteria for biologics, although it should be noted that the BRS set a lower threshold of symptom severity at baseline, measured using the SNOT-22 or VAS. Many of the patients recruited to published trials demonstrating the effectiveness of biologics would be included in the group where use would be considered uncertain, however these patients still achieved significant improvements in nasal polyp score and quality of life on biologics. Therefore, it is important to state that the BRS recommendations are not intended to predict response to treatment to biologics, but only to define a group where the panel felt use was appropriate given the financial restrictions with the NHS at the current time. It is very likely that recommendations for the scenarios rated 'uncertain' would change if the relative cost of treatment were reduced.

The panellists recommended that biologic treatments for CRSwNP, if approved for use within the NHS, should be delivered within centres of excellence co-located with difficult to treat asthma, where there is pre-existing experience of treatment with biologics. Centres should also be able to offer a range of other treatments. This will also have the likely impact that patients with difficult to treat CRSwNP, for example those with N-ERD, are directed to specialist centres that can ensure that surgery is performed optimally and that patients are considered for adjunctive treatments such as post-operative desensitisation, thus reducing the need for biologics. Indeed, a recent paper has shown that more extensive surgery was associated with lower rates of revision surgery (Hopkins, Lund); creation of specialist centres will therefore likely improve outcomes from other interventions such is sinus surgery. Panellists commented that in future, the extent of previous surgery and the interval between previous surgery may also be considered in the decision-making process, and perhaps

patients who have only had more limited surgery be considered for revision surgery before biological therapies.

While the panel made recommendations for use in AFRS, it was noted that clear evidence of efficacy on trials was needed before these should be implemented. The panel also agreed that there was no indication for use in patients with CRS without nasal polyps in the absence of evidence in this group

Once biologic therapies are initiated, the response to treatment must be assessed to determine if a patient should continue treatment; how this should be determined is beyond the remit of the current study. Further limitations of these current recommendations are that biomarkers, such as eosinophil levels in blood or tissue, were not considered in the clinical scenarios, as the panel felt that there is insufficient evidence to determine how these aid selection or predict response to treatment. Biologics were considered as a collective intervention but in reality, different biologics, defined by their inflammatory target, differ in terms of costs and effectiveness. The impact of COVID-19 on healthcare delivery in the NHS at the current time was not considered – this may favour biologics over surgery, for example, if demand for surgery greatly exceeds capacity. Finally, we have not included patient preferences for different treatments into our recommendation, but these of course play an important role in the final decision making with regards to use if biologics become available within the UK.

Conclusions

Using a modified Delphi technique, we have defined a patient cohort with CRSwNP where the BRS Council believe use of biologics are appropriate. This group have higher rates of 'failure' with current treatment pathways, higher resource use and are more likely to suffer with uncontrolled symptoms. We would urge NICE to consider approval of biologics for such indications without applying further restrictions on use.

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