Cochrane Corner: Are Biologics for Chronic Rhinosinusitis effective and safe?

- A Cochrane Review summary with Commentary

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Conflicts of Interest:

Dr Hinks' research group has received funding from Kymab which has been acquired by Sanofi who produce Dupixent (Dupilumab).

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Key Messages:

- Dupilumab shows improvement in validated disease specific quality of life scores compared with placebo
- Larger studies are needed to improve the certainty of evidence for Omalizumab and Mepolizumab
- Further data on longer term outcomes, cost effectiveness and those with less severe disease are needed

Chronic rhinosinusitis (CRS) refers to inflammation of the nasal sinuses and mucosa, with persistence of sinus inflammation and clinical manifestations beyond 12 weeks[1]. CRS affects between 6 and 12% of adults, and is a cause of reduced quality of life (QoL), and high healthcare costs[2]. Management has consisted of topical and systemic glucocorticoids, antibiotics and often repeated sinus surgery. Over the past 20 years biologic therapies under investigation for asthma, with overlapping nasal polyposis have showed significant improvement in sinonasal CRS symptoms and reduced nasal polyp swelling[3.] This Cochrane Corner aims to summarise the effectiveness, safety and role of biological therapy in CRS to aid clinicians in the decision-making process.

Cochrane Abstract: Biologics for Chronic Rhinosinusitis by Chong LY, Piromchai P, Sharp S, Snidvongs K, Webster K, Philpott C, Hopkins C and Burton M.

Disclaimer

This is an abstract of a Cochrane review published in the Cochrane Database of Systematic Reviews 2021, Issue 3. (see www.cochranelibrary.com for information). Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Library should be consulted for the most recent version of the review.

Background

This living systematic review is one of several Cochrane Reviews evaluating the medical management of patients with chronic rhinosinusitis.

Chronic rhinosinusitis is common. It is characterised by inflammation of the nasal and sinus linings, nasal blockage, rhinorrhoea, facial pressure/pain and loss of sense of smell. It occurs with or without nasal polyps.

'Biologics' are medicinal products produced by a biological process. Monoclonal antibodies are one type, already evaluated in other inflammatory conditions (e.g. asthma and atopic dermatitis).

Objectives

To assess the effects of biologics for the treatment of chronic rhinosinusitis.

Search methods

The Cochrane ENT Information Specialist searched the Cochrane ENT Register; CENTRAL (2020, Issue 9); Ovid MEDLINE; Ovid Embase; Web of Science; ClinicalTrials.gov; ICTRP and additional sources for published and unpublished studies. The date of the search was 28 September 2020.

Selection criteria

Randomised controlled trials (RCTs) with at least three months follow‐up comparing biologics (monoclonal antibodies) against placebo/no treatment in patients with chronic rhinosinusitis.

Data collection and analysis

We used standard Cochrane methodological procedures. Our primary outcomes were disease‐specific health‐related quality of life (HRQL), disease severity and serious adverse events (SAEs). The secondary outcomes were avoidance of surgery, extent of disease (measured by endoscopic or computerised tomography (CT) score), generic HRQL and adverse effects (nasopharyngitis, including sore throat). We used GRADE to assess the certainty of the evidence for each outcome.

Main results

We included 10 studies. Of 1262 adult participants, 1260 had severe chronic rhinosinusitis with nasal polyps; 43% to 100% of participants also had asthma. Three biologics, with different targets, were evaluated: dupilumab, mepolizumab and omalizumab. All of the studies were sponsored or supported by industry. For this update (2021) we have included two new studies, including 265 participants, which reported data relating to omalizumab.

Anti‐IL‐4Rα mAb (dupilumab) versus placebo/no treatment (all receiving intranasal steroids)

Three studies (784 participants) evaluated dupilumab.

Disease‐specific HRQL was measured with the SNOT‐22 (a 22‐item questionnaire, with a score range of 0 to 110; minimal clinically important difference (MCID) 8.9 points). At 24 weeks, dupilumab results in a large reduction (improvement) in the SNOT‐22 score (mean difference (MD) ‐19.61, 95% confidence interval (CI) ‐22.54 to ‐16.69; 3 studies; 784 participants; high certainty).

At between 16 and 52 weeks of follow‐up, dupilumab probably results in a large reduction in disease severity, as measured by a 0‐ to 10‐point visual analogue scale (VAS) (MD ‐3.00, 95% CI ‐3.47 to ‐2.53; 3 studies; 784 participants; moderate certainty). This is a global symptom score, including all aspects of chronic rhinosinusitis symptoms.

At between 16 and 52 weeks of follow‐up, dupilumab may result in a reduction in serious adverse events compared to placebo (5.9% versus 12.5%, risk ratio (RR) 0.47, 95% CI 0.29 to 0.76; 3 studies, 782 participants; low certainty).

Anti‐IL‐5 mAb (mepolizumab) versus placebo/no treatment (all receiving intranasal steroids)

Two studies (137 participants) evaluated mepolizumab.

Disease‐specific HRQL was measured with the SNOT‐22. At 25 weeks, the SNOT‐22 score may be reduced (improved) in participants receiving mepolizumab (MD ‐13.26 points, 95% CI ‐22.08 to ‐4.44; 1 study; 105 participants; low certainty; MCID 8.9).

It is very uncertain whether there is a difference in disease severity at 25 weeks: on a 0‐ to 10‐point VAS, disease severity was ‐2.03 lower in those receiving mepolizumab (95% CI ‐3.65 to ‐0.41; 1 study; 72 participants; very low certainty).

It is very uncertain if there is a difference in the number of serious adverse events at between 25 and 40 weeks (1.4% versus 0%; RR 1.57, 95% CI 0.07 to 35.46; 2 studies; 135 participants, very low certainty).

Anti‐IgE mAb (omalizumab) versus placebo/no treatment (all receiving intranasal steroids)

Five studies (329 participants) evaluated omalizumab.

Disease‐specific HRQL was measured with the SNOT‐22. At 24 weeks omalizumab probably results in a large reduction in SNOT‐22 score (MD ‐15.62, 95% CI ‐19.79 to ‐11.45; 2 studies; 265 participants; moderate certainty; MCID 8.9).

We did not identify any evidence for overall disease severity.

It is very uncertain whether omalizumab affects the number of serious adverse events, with follow‐up between 20 and 26 weeks (0.8% versus 2.5%, RR 0.32, 95% CI 0.05 to 2.00; 5 studies; 329 participants; very low certainty).

Authors' conclusions

Almost all of the participants in the included studies had nasal polyps (99.8%) and all were using topical nasal steroids for their chronic rhinosinusitis symptoms. In these patients, dupilumab improves disease‐specific HRQL compared to placebo. It probably also results in a reduction in disease severity, and may result in a reduction in the number of serious adverse events.

Mepolizumab may improve disease‐specific HRQL. It is very uncertain if there is a difference in disease severity or the number of serious adverse events.

Omalizumab probably improves disease‐specific HRQL compared to placebo. It is very uncertain if there is a difference in the number of serious adverse events. There was no evidence regarding the effect of omalizumab on disease severity (using global scores that address all symptoms of chronic rhinosinusitis).

Commentary:

This Cochrane review evaluated the role of biologics in treating adult patients with severe chronic rhinosinusitis with nasal polyposis (CRSwNP) compared with placebo. Evaluation of the efficacy and safety profile of biologics in CRSwNP is clinically important and relevant, given the high rate of surgical treatment, with more than half of patients reporting to have required surgery and 46% of patients reporting to have required more than one operation with a mean of 3.3 surgeries [4].

The review included 1262 participants of whom 99.8% having nasal polyps, although the small sample sizes of some individual studies was the main reason for downgrading evidence, due to imprecision. All patients used intranasal corticosteroids concomitantly. The minimum study duration including follow-up period was 16 weeks. Although the risk of selection and performance bias was deemed low for the majority of the studies, the risk of attrition bias was high for 4 smaller studies, related to participant discontinuation.

The review found evidence of improvement in disease-specific health-related quality of life and disease severity for patients with severe CRSwNP treated with all three classes of biologics compared with placebo. There was no definite increase in short term serious adverse reactions, consistent with good safety data from more extensive experience of their use in asthma. Dupilumab had the highest certainty of evidence of the 3 biological agents evaluated. This was related to the higher number of participants (784) and use of validated scoring systems in the 3 RCTs.

The impact of biologics in those with less severe disease, and those earlier in their illness, and in children is yet to be determined. Further studies with larger population sizes, longer-term follow up, utilising validated disease specific tools and defined surgical criteria are needed to improve the certainty of evidence and evaluate the outcomes, especially for omalizumab and mepolizumab. As a ‘living systematic review’, it will be continuously updated when new important evidence is published, improving certainty of evidence over time.

The National Institute for Health and Care Excellence (NICE) has not approved these treatments for patients with CRS at this current time. These drugs work, but costs of biologics are high with UK list prices of £1264.89 per vial for dupilumab 300mg/2ml solution (*Dupixent,* Sanofi), £256.15 per vial for Omalizumab 150mg/1ml solution (*Xolair,* Novartis Pharmaceuticals) and £840.00 per vial for Mepolizumab 100mg/1ml (*Nucala,* GlaxoSmithKline UK Ltd) [5], although actual costs to providers are often reduced through discount schemes. Comparably, Functional Endoscopic Sinus Surgery is estimated to cost between £1,936 and £2,894 [6]. It should be noted however, that given the risk of disease recurrence following either form of treatment, with repeated biologic or surgical treatment in CRSwNP patients, the risks associated with surgery and the costs associated with hospital admissions, decisions regarding superiority of treatment are complex, requiring health economic analysis which has not been evaluated within this Cochrane review. Further analysis, including a network meta-analysis or head-to-head trials using consistent, validated outcomes are needed to help guide usage and the role of biologics in CRS treatment.

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