**Advances in the Use of Biologics in ENT: Where are we heading?**

Introduction

Biologics are gradually becoming introduced into the management of several conditions commonly seen in ear, nose and throat (ENT). Despite the National Institute for Health and Care Excellence (NICE) not yet approving the use of biologics for many ENT pathologies, biologics have been used off license in the management of sensorineural hearing loss, and, namely, chronic rhinosinusitis with nasal polyps (CRSwNP).1, 2 The use of biologics in the management of squamous cell carcinoma of the head and neck (SCCHN) is one of the few pathologies in which biologic drug treatment is approved by NICE.3 The evidence collected with regards to the use of biologics for these conditions has proven to be largely positive in relation to traditional treatment pathways. However, side effects produced as a result of biologic treatment may not be tolerable and there is concern on whether these new drugs are cost effective. Therefore, this essay aims to collate the evidence to determine whether the risk of side effects and large drug costs, outweighs the benefits of supporting patients in managing their ENT pathology with biologic drugs.

Biologics: the good, the bad and the future

As our knowledge of the human genome expands, so does our knowledge surrounding proteins related to human diseases.4 Biologics mainly work by interrupting signals within the immune system to alleviate patient symptoms and help prevent further damage as a result of autoimmune attack.5 The most common biologics used off licence in ENT include; interleukin-4 (IL4) inhibitors, immunoglobulin E (IgE) inhibitors and interleukin-5 (IL5) inhibitors for CRSwNP; epidermal growth factor receptor (EGFR) inhibitors for SCCHN; tumour necrosis factor alpha (TNF-alpha) inhibitors, anti-CD20 and interleukin-1 (IL1) inhibitors for sensorineural hearing loss.6-9

As with any immune modulating drug, patients will be immunocompromised so will be more susceptible to infections. This is of particular worry if the patient is also prescribed other drugs, such as steroids, which further contribute towards immunodeficiency. Other side effects can be encountered such as; eosinophilic granulomatosis with polyangiitis with the use of dupilumab (IL4 inhibitor) and omalizumab (IgE inhibitor); reactivation of tuberculosis with the use of etanercept (TNF-alpha inhibitor); angioedema and reactivation of hepatitis B, as well as multifocal encephalopathy with the use of rituximab (anti-CD20).10-13 In addition, there are several cautions to be aware of when using biologics. Furthermore, if a patients’ ENT pathology is well managed with biologics but then becomes pregnant, one must consider whether the benefits outweigh the risks of treatment or, indeed, instruct the patient to stop treatment in line with the BNF. The same also needs to be considered if the parent decides to breastfeed their baby. This then poses the question of how these patients would manage their symptoms without biologic drugs if they fall pregnant and/or breastfeed. Of course, these risks and adverse effects will need to be discussed with the patient before commencing biologic drug treatment to ensure that the patient is making an informed choice with regards to their care. This does, of course, incur costs in terms of the time required to adequately counsel patients, which may not be possible in an overrunning clinic, in a stressed and struggling healthcare system. However, if the patient is comfortable with the idea that adverse side effects may occur as a result of commencing biologic management, clinicians should abide by the patients’ choice to commence treatment. Investigations, both prior and during treatment, is essential in order to identify abnormalities once biologic drug treatment is commenced. This may consist of a chest radiograph in the context of reactivated tuberculosis, as well as basic bloods (such as a full blood count and inflammatory markers) to monitor immunodeficiency and/or new infection.

In addition, the technological complexity in the production of biologics contributes to their large costs. 150mg/1ml of injectable omalizumab costs £256.15, which may seem acceptable until one realises that 28 1mg tablets of prednisolone costs £0.68.14,15 300mg/2ml of injectable dupilumab costs an extortionate £1264.89.16 In fact, dupilumab was considered for the management of atopic dermatitis in 2018, but was denied approval from the NICE draft guidance as a result of the drugs extortionate price tag being deemed as an ineffective use of precious National Health Service (NHS) funding.17 However, dupilumab has since been approved in the management of atopic dermatitis due to the strong evidence base which suggests that dupilumab is an effective treatment option for this skin condition.18 Of course, the cost of using biologics is only made larger as a result of the use of investigations to monitor the potential adverse effects mentioned earlier. So, the real question is, why is dupilumab so much more expensive than other biologics? This is because there is yet to be a biosimilar drug produced for dupilumab.19 Biosimilars are drugs that are chemically similar to that of a biologic.4 As biosimilars are generally structurally similar, they are often used to manage the same conditions as the original parent biologic and, often, produce the same side effects.4 However, biosimilars can only be produced and sold once the patent on the parent biologic has expired.4 As more biosimilars are produced after the expiry of the patent, the market is, in turn, made more competitive. This drives prices down for a biologic drug, incurring less of a financial burden on budgets. Therefore, one can only assume that although the cost of biologic drugs may appear large, one can always hope that prices reduce in the future as a result of the development of several biosimilars. In addition, as our biotechnology improves, patients can be matched to an appropriate biologic once biomarker-based endotyping eventually becomes standard practise.20 This will help to protect NHS funding as patient treatment will be optimised as a result of making treatment specific to the patient.20

Chronic rhinosinusitis with nasal polyps

Chronic rhinosinusitis is a condition which causes inflammation of the sinus epithelium, leading to nasal congestion, discharge, hyposmia and/or anosmia, facial pain and headache which persist for more than 12 weeks.21 This chronic inflammation can lead to the development of nasal polyps, which are growths within the sinuses and/or the nasal passages.21 These polyps can cause obstruction, further exacerbating the symptoms of chronic rhinosinusitis, contributing towards symptoms of snoring, obstructive sleep apnoea as well as nasal congestion.21 10% of the UK population is affected by chronic rhinosinusitis, with around 25-30% of these people having CRSwNP.21,22 This demonstrates the shear impact that CRSwNP has on the general population, therefore, finding an effective treatment for this condition is paramount. CRSwNP is typically managed in a stepwise fashion, starting with intranasal corticosteroids, followed by oral corticosteroids with or without a nasal spray and, finally, injectable corticosteroids.21 In some cases, surgery may be required to remove the nasal polyps if medical treatments are unsuccessful in reducing the size of nasal polyps or managing the patients inflammation.21 Unfortunately, a systematic review of the existing literature by Chen et al.23 has found that these treatments are largely unsuccessful, finding that recurrence of nasal polyps is common after surgical intervention. The lack of an effective treatment for CRSwNP is mainly due to the fact that the pathophysiological process behind the development of this disease is largely unknown. This makes it difficult to identify the best way to manage CRSwNP. An allergic response to fungal microbes and aspirin sensitivity are proposed factors contributing to CRSwNP.21 Didehdar et al.24 identified that *Alternaria alternata* is an airborne fungus which is often present within the nasal discharge of patients with chronic rhinosinusitis. Therefore, this study suggested that *Alternaria alternata* is involved in the pathogenesis of chronic rhinosinusitis and, therefore, CRSwNP. Didehdar et al.24 investigated how this fungus interacted with the human innate and adaptive immune system, discovering that participants infected with *Alternaria alternata* had a greater expression of “cathelicidin, thymic stromal lymphopoietin, toll like receptors and T-helper 2 dominant immune responses”. This, in turn, resulted in “IgE mediated pathway activation and eosinophil degranulation”.24 These findings were also supported by the work of Schleimer25 who also found that CRSwNP was driven by IL-5, IL-13, type 2 innate lymphoid cells as well as mast cells. IL-5, IL-13 and mast cells are all involved in the allergic response, which makes it no surprise that common co-morbidities associated with CRSwNP include asthma and allergic rhinitis.23, 25, 26 Therefore, with an allergic picture in mind, it makes sense to block all complexes which are involved in the allergic response. Therefore, drugs that inhibit IL-4 and IL-13 (dupilumab), IL-5 (mepolizumab) and IgE (omalizumab) could prove beneficial. This is because IL-4 is responsible for B cell class switching to IgE, IL-13 leads to mucus production and airway remodelling causing asthmatic symptoms and IgE allows for crosslinking of mast cells for mast cell degranulation to cause allergic symptoms.25 In addition, IL5 works to promote histamine release from mast cells.26 A recent paper by Geng et al.27 evaluated the efficacy of biologic drug treatment for CRSwNP. The paper investigated the use of dupilumab, omalizumab and mepolizumab, which were all found to produce positive results at phase 3 clinical trials. With the study being performed in 2021, the results support the use of biologics in CRSwNP in this present era. However, it is not clear over what period of time the participants were followed up post-biologic treatment in this study, which means that recurrence of polyps could still be possible. In addition, when attempting to prove the efficacy of a new intervention, randomised control trials (RCT) tend to be the gold standard. Of course, there are several ethical issues with RCT’s, but future studies should aim to compare conventional treatments to biologic drugs in the management of CRSwNP to determine the efficacy of biologic treatment. Follow up should be made over the course of 3 years to determine a mean time frame for if nasal polyps return post-intervention. With the continual development of biotechnology, it may be possible for scientists to find more complexes which are involved in the allergic pathway to form new biologics to potentially improve patients’ signs and symptoms.

Sensorineural hearing loss

Sensorineural hearing loss affects the inner ear and the neural pathways to the auditory cortex.28 Sensorineural hearing loss can be differentiated from conductive hearing loss with the use of a tuning fork, performing Rinne’s and Weber’s tests.28

1 in 6 people are affected by hearing loss in the UK, with around 90% being sensorineural.29, 30 This demonstrates the impact that sensorineural hearing loss has on the UK population, thus investing funds to discover an effective treatment for this condition would be in the public interest, as hearing loss can have a huge effect on an individual’s quality of life. A paper by Vambutas and Davia27 found that although 60-70% of patients are initially responsive to the standard therapy of timely corticosteroids, this responsiveness unfortunately declines over time. This study also found that, in steroid resistance, IL1 expression increases, therefore, patients with sudden sensorineural hearing loss may benefit from an IL-1 inhibitor. Similar findings were determined by Gorthey et al.31 who studied the efficacy of corticosteroid treatment for sudden sensorineural hearing loss in the paediatric population. Gorthey et al.31 found that initial responsiveness was 61%, with sustained responses falling with multiple treatments, suggesting tolerance. Managing hearing loss during the developmental stages of a child’s life is paramount to allow these patients to achieve their developmental milestones, thus, finding an effective management for the paediatric population is of great importance.

A systematic review by Plontke et al.32 explored the efficacy of intratympanic corticosteroid treatment for sudden sensorineural hearing loss. The review found that although the evidence was limited, patients often didn’t experience a meaningful improvement in their hearing loss, but there was marginal improvement when using both intratympanic corticosteroids with systemic treatment. This suggests that further RCT’s need to be performed to determine the efficacy of combined corticosteroid treatment, as well as to determine the efficacy of exclusive intratympanic corticosteroid use. However, patients should be counselled on the risk of intratympanic corticosteroids, such as the risk of tympanic perforation as well as vertigo.32

These studies27, 31, 32 all demonstrate that an effective treatment for this condition is yet to be sought. A recent review of the literature, performed by Balouch et al.9, investigated the efficacy of anti-TNF alpha, anti-CD20 and IL1 inhibitors in the management of sudden sensorineural hearing loss. However, the review concluded that there were varying degrees of efficacy with no correlations made between outcomes and biologic drug category. This may be because the review included studies which used patients who had different aetiologies for their sudden sensorineural hearing loss. Again, performing large scale RCT’s may help to determine the efficacy of biologic drugs in the management of sudden sensorineural hearing loss. It would be of particular interest to see an RCT on the efficacy of IL-1 inhibitors given the findings from Gorthey et al.31, suggesting that IL-1 inhibitors could be an avenue worth exploring in finding an effective treatment.

Squamous cell carcinoma of the head and neck

SCCHN is the sixth most common cancer worldwide, so management, whether this is curative or palliative, should be effective given the number of people that this condition effects worldwide.8 The most common SCCHN sites include the larynx, oral cavity and the pharynx.8 Tobacco use and alcohol consumption continue to be significant risk factors to consider when presented with a patient who exhibits signs and symptoms of SCCHN.33 Surgical excision of the cancer normally provides the greatest chance of curative treatment, however, there may be circumstances in which the cancer will be rendered inoperable. This may be because of tumour invasion into the common carotid artery, base of the skull and/or invasion into the prevertebral muscles.8 In addition, patient factors, such as age and co-morbidities, also need to be considered when assessing whether a person is fit enough to survive the surgery and its potential complications. It should also be noted that even if multimodal treatment is adopted, 40-60% of patients relapse.8 If the patient’s cancer is not adequately resected after relapse post-multimodal treatment, the cancer is generally considered incurable.8

A study performed by Machiels et al.8 reviewed the use of EGFR inhibitors in the management of SCCHN. SCCHN usually cause an increased expression of EGFR, thus inhibiting this receptor would likely cause great benefit in terms of reducing the progression of the cancer.8 The review determined that cetuximab (EGFR inhibitor) combined with radiotherapy “improves locoregional control and overall survival rate compared with radiotherapy alone…”.8 Although radiotherapy can result in scarring and/or post-treatment pain in the treated area, using radiotherapy in combination with cetuximab surprisingly doesn’t contribute to any increase in radiation-induced side effects.8 However, there is yet to be a study which directly compares the efficacy of cetuximab with radiotherapy to radiotherapy alone. One may even suggest performing an RCT to determine whether cetuximab is effective enough on its own as a treatment to avoid the painful side effects that are often associated with radiotherapy. This may also be of benefit to frail and elderly patients who may not be candidates for surgical resection but may also be deemed too frail to withstand the side-effects of radiotherapy. However, one can appreciate the ethical implications of such RCT. As previously mentioned, cetuximab is recognised as a management option for SCCHN by NICE, but there does seem to be scope to further investigate the efficacy of cetuximab. However, like with most cancers, personalised medicine remains to be the hope of cancer treatment by identifying biomarkers to tailor treatments to a specific patient.8

Early detection often improves outcomes for all cancers. Regular skin checks on one’s self may help to identify SCCHN earlier. In addition, regular dental check-ups may help to identify potential oral cancers, but one must realise the financial burden that is now associated with routine dental appointments, which may not be feasible for some patients. Prevention is also important in reducing the chance of developing cancers. With smoking being one of the biggest modifiable risk factors for SCCHN, it would be interesting to see if the public health “stop smoking campaign” has been effective in reducing the frequency of these cancers.

Conclusion

From the research undertaken, it is clear that CRSwNP, sensorineural hearing loss and SCHNN all effect large numbers of the general population, so finding an adequate management for these conditions is paramount to optimise patient quality of life. Initial conventional treatments appear to have low efficacy for these ENT diseases. Proposed pathophysiological processes of the pathologies discussed suggest that biologic drug treatment may be effective in managing these diseases if unresponsive to first line conventional therapeutics. Although existing studies also suggest that biologics are effective in managing these ENT pathologies, carrying out further RCT’s to further determine the efficacy of these drugs will be required before approval by NICE is made. Due to the costs of biologics, a cost-benefit analysis of using biologics for these pathologies may prove helpful for NICE to approve these drugs in the management of CRSwNP and sensorineural hearing loss. Of course, some individuals may be reluctant to spend so much of the NHS budget on biologics for symptoms which may seem have a low impact on a patients’ quality of life (such as nasal congestion in CRSwNP), however, one must always realise that these symptoms can be debilitating, particularly if they are present throughout someone’s whole life.

I guess the future seems bright for the use of biologics in ENT to improve patients’ quality of life. With the development of biomarker identifying technology, it seems that future biologic drug targets can be identified to personalise treatment to a certain patients’ pathology. Cost may be a limiting factor to the licencing of these drugs, however, biosimilars can be produced in the future once biologic drug patents expire. Follow up investigations and safety netting is important when commencing biologic drug treatment to ensure that side effects are caught early and that discontinuation or dose modification is done to reduce these adverse effects if necessary.

**Words: 2987**

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