Asthma Update – What's in Store for 2021?

Written by Dr Lucy Power and Dr Breda Cushen, Department of Respiratory Medicine, Beaumont Hospital, Dublin, Ireland

Dr. Lucy Power, MB BCH BAO, is a registrar in Respiratory Medicine at Beaumont Hospital. She is a graduate from the Royal College of Surgeons in Ireland and completed Basic Specialist Training at Beaumont Hospital.

Dr. Breda Cushen, MB BCh BAO, MRCPI, PhD, is a consultant respiratory physician at Beaumont Hospital. She completed respiratory specialist training in Ireland, following which she worked as a consultant physician with expertise in severe asthma at the Royal Brompton Hospital in London, UK. Her specialist interests include the management of chronic airway diseases.

Asthma is a heterogeneous, chronic lung disease that effects an estimated 300 million people worldwide. Asthma is characterised by the development of airway inflammation and bronchial hyper responsiveness in response to airway irritants. This manifests as variable airflow obstruction and symptoms of wheeze, shortness of breath, chest tightness and/or cough. Ireland has the 4th highest prevalence of asthma worldwide, with 470,000 people reporting a diagnosis of asthma. Over the last decade the number of asthma-related hospital admissions in Ireland has increased from 1336 in 2009 to 2889 in 2016. An increase in asthma deaths has also been observed; In 2016, there were 1.52 asthma-related deaths per 100,000 of the Irish population.

However, there is reason to be optimistic that this trajectory will improve. In recent years, there have been substantial breakthroughs in the understanding of asthma and its immunopathogenesis. This had led to changes in the overall approach to asthma management and the development of new targeted therapies which for some patients have been transformative. Herein we provide an update of recent changes to the management of both mild and severe asthma. We provide an overview of treatments currently available and highlight important ongoing studies, the results of which are expected in 2021.

Mild Asthma

Mild asthma is that which causes infrequent symptoms. In 2019, the Global Initiative of Asthma (GINA) introduced a landmark change to the recommended treatment of mild Asthma. Up to 2019, the standard treatment approach was to prescribe short-acting beta 2 agonist (SABA) therapy on an as-needed only basis. However, GINA now advises against the use of SABA monotherapy in these patients in favour of as-needed Inhaled Corticosteroid (ICS) formoterol. This change was prompted predominantly by safety concerns. In the 2014 UK National Review of Asthma Deaths, 9% of deaths were in patients with mild asthma prescribed SABA monotherapy, while in 39% of deaths excess prescription and overuse of SABA monotherapy was evident.

GINA also recommend as needed ICS-formoterol as a suitable alternative to regular low-dose ICS in patients who experience more frequent symptoms (less than daily basis). This may be a preferred option for patients in whom adherence to inhaled therapy is a concern.

These shifts in mild asthma management are supported by data from the SYGMA 1 and 2 studies which demonstrated superior asthma symptom control and a 64% reduction in asthma exacerbations in patients prescribed as-needed ICS-formoterol compared to as-needed SABA. Additionally, as-needed ICS-formoterol was non-inferior to twice daily budesonide in preventing severe asthma exacerbations. Importantly, patients using as needed ICS-formoterol were exposed to less than one-fifth of the ICS dose of patients prescribed regular twice daily budesonide.

Severe Asthma

An estimated 5-10% of patients with asthma have severe refractory disease defined as that which "requires treatment with high-dose inhaled corticosteroids plus a second controller (and/or systemic corticosteroids) to prevent it becoming "uncontrolled" or which remains "uncontrolled" despite this therapy". Severe asthma is responsible for the majority of asthma-related healthcare use. An understanding of the primary inflammatory process underlying asthma is important when managing severe asthma patients. Two predominant types of inflammation, T2-high and T2-low, have been described and are illustrated in Figure 1. These are associated with distinct clinical phenotypes and identifiable biomarker profiles.

T2-high asthma is characterised by the presence of an elevated peripheral eosinophil count, elevated Fractional exhaled nitric oxide (FeNO) and/or elevated Immunoglobulin E (IgE). T2-high inflammation is responsible for both non-allergic and allergic eosinophilic asthma phenotypes and represents 50 60% of severe asthma cases.

The T2-low immune pathway is less understood. In T2-low asthma there is predominant neutrophilic or pauci-granulocytic airway inflammation. It typically accompanies obesity-associated and smoking-associated asthma. There are no biomarkers measurable in clinical practice which are indicative of T2-low asthma and therefore its diagnosis is based on the absence of T2-high biomarkers.

Early characterisation of asthma into T2-high or T2-low disease is recommended as it has important treatment implications. Treatment of T2-low asthma poses a particular challenge. Unlike T2-high asthma, patients with T2-low disease often demonstrate a poor response to corticosteroid therapy and to date, studies of targeted therapies for refractory T2-low asthma have been unsuccessful. Conversely, there are now several effective biologic treatments available which target T2-high inflammatory pathways.

Asthma Biologic Therapy

There are four biologic therapies currently in use as add-on treatment to maximal inhaled therapy for severe refractory asthma in Ireland. These therapies are indicated for patients who exhibit T2-high asthma phenotypes only.

Anti-IgE agents

Omalizumab (Xolair®) was the first biologic therapy approved for severe asthma. It is a humanised anti-IgE antibody, which binds to circulating IgE neutralising its effect. Omalizumab is indicated in patients with severe allergic asthma who demonstrate elevated total serum IgE levels and sensitisation to one or more perennial aeroallergens on skin prick or serum RAST testing. Omalizumab is administered as a subcutaneous injection either 2-weekly or 4-weekly, depending on patient's weight and total IgE level. In open-label studies, omalizumab reduced exacerbation rates by over 50% and significantly improved quality of life. Omalizumab has a favourable safety profile and is the only asthma biologic treatment with real-world safety data for use in pregnancy. In Ireland, omalizumab is not re imbursed by the HSE but paid for directly out of hospital budgets which may limit its availability.

Anti-eosinophilic agents

Mepolizumab (Nucala®), Reslizumab (Cinqaero®) and Benralizumab (Fasenra®) are monoclonal antibody therapies licenced for use in both allergic and non-allergic eosinophilic asthma. Mepolizumab and reslizumab bind to circulating IL-5 neutralising its effect on promotion of eosinophil production, migration, and accumulation in the airway wall. Benralizumab binds to the alpha-subunit of the IL-5 receptor on the surface of the eosinophil and to natural killer cell receptors inducing eosinophil apoptosis. This dual mechanism of action of benralizumab causes complete eosinophil depletion. Anti-eosinophilic therapies are

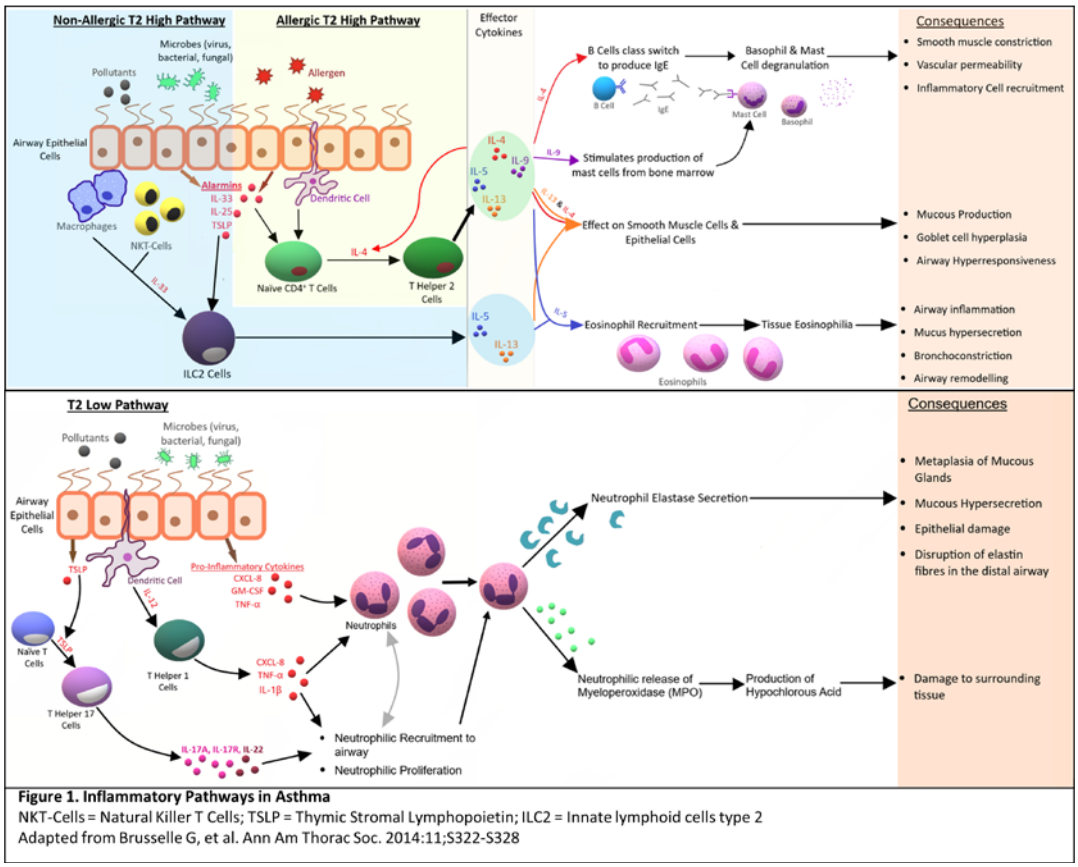

Figure 1. Inflammatory Pathways in Asthma
NKT-Cells = Natural Killer T Cells; TSLP = Thymic Stromal Lymphopoietin; ILC2 = Innate lymphoid cells type 2
Adapted from Brusselle G, et al. Ann Am Thorac Soc. 2014:11;S322-S328

indicated in patients with severe refractory asthma who have elevated peripheral eosinophil counts of ≥300 cells/μL plus frequent exacerbations and/or require maintenance systemic corticosteroids. A greater treatment response is observed in those with higher eosinophil counts and more frequent exacerbations.

In randomised controlled trials, these therapies were effective in reducing annualised exacerbation rates by at least 50%, improving asthma symptom scores, lung function and quality of life, and facilitating reductions in maintenance oral corticosteroids while maintaining a favourable safety profile. There is no data regarding use in pregnancy and they are not recommended in those who are pregnant or planning to conceive. No head-to-head comparison studies of these treatments have been performed but several meta-analyses have failed to show superiority of one therapy over another. The choice of therapy therefore should be a shared decision between physician and patient taking into consideration patient preference, cost, and access to therapy which in Ireland is limited and strictly regulated by the HSE.

Mepolizumab and benralizumab are administered as a subcutaneous injection. Mepolizumab is administered at 100mg once monthly whilst benralizumab is administered at 30mg monthly for three months and 30mg two-monthly thereafter. Reslizumab is a monthly intravenous infusion at a dose of 3mg/kg. Whilst mepolizumab and benralizumab are now also available in auto-injector pens to facilitate patient self-administration, these devices have not been approved for use in Ireland, and therefore all biologic therapies must be administered by a specialist nurse in a supervised setting.

LIMITATIONS OF BIOLOGICS

Adherence

Whilst asthma biologic therapies can be highly effective, they do not replace maintenance inhaled therapy. Data from the RCSI-based INCA group has demonstrated that in a cohort of patients deemed eligible for asthma biologic therapy, adequate asthma control was achieved in 45% following a 3 month personalised inhaler adherence education programme. By the study end, only 27% had truly refractory disease necessitating step-up to biologic treatment. This work emphasises the importance of thorough assessment of adherence to inhaled therapy prior to initiation of biologic therapy. The results of the follow-on INCA-SUN study which has examined whether these benefits are sustained over a prolonged period are expected in 2021.

Adherence to inhaled therapy may also be predictive of response to biologic therapy and should be assessed regularly. In a recent real-world study of 91 patients receiving mepolizumab therapy in the UK, investigators found that more than one-third of patients with poor adherence to ICS failed to respond to biologic therapy compared to only 10% of those who maintained good ICS adherence.

OTHER THERAPIES

Azithromycin

Azithromycin is a macrolide antibiotic with immunomodulatory effects which has a proven benefit in several chronic lung diseases including COPD and bronchiolitis obliterans. In the 2019 AMAZES study, thrice weekly azithromycin at a dose of 500mg was found to reduce annual exacerbation rates and improve quality of life in patients with severe asthma compared to placebo. Interestingly the beneficial outcomes were independent of the presence of T2 inflammatory biomarkers and as such, azithromycin may be a treatment option in patients with T2-low disease. Azithromycin may cause QTc prolongation, liver function derangement and hearing loss and patients should be closely monitored for these side-effects whilst on treatment.

The New Kids on the Block – What's coming in 2021?

Dupilumab is a subcutaneous monoclonal antibody against IL-4 receptor alpha which inhibits IL 4/IL 13 signalling pathways. Dupilumab is highly effective in severe T2-high asthma patients, reducing annual severe exacerbation rates, and improving pre-bronchodilator FEV1 and overall asthma control. Dupilumab has been approved by the European Medicines Agency (EMA) as an add-on therapy for patients with severe eosinophilic asthma but has not yet been approved for re imbursement in Ireland for this indication. Dupilumab is approved for use in patients with severe atopic dermatitis, making it an interesting treatment option for patients with both conditions.

The results of two Phase 3 randomised controlled trials of novel therapies for severe asthma are expected in 2021. These novel therapies have the potential to significantly alter the severe asthma landscape and may represent a much-needed treatment option for patients with T2-low disease.

Masatinib is an oral therapy which acts to reduce airway remodelling via its inhibitory effects on mast cells and Platelet-derived Growth Factor Receptor (PDGFR) signalling. Preliminary Phase 3 data indicates a 35% reduction in annual asthma exacerbation rate over placebo in patients with severe refractory asthma and eosinophil counts of ≥150 cells/μL.

Tezepelumab is a subcutaneous monoclonal antibody which blocks Thymic Stromal Lymphopoietin (TSLP), a key cytokine in the activation of both T2-high and T2-low inflammatory pathways in asthma. The Phase 3 NAVIGATOR study examined the effectiveness of Tezepelumab in reducing annual exacerbation rates in patients with severe refractory asthma. In November 2020, it was announced that NAVIGATOR has met this primary endpoint. Importantly the benefits of Tezepelumab were reported to be independent of eosinophil count. The full study results are due to be published soon.

Conclusion

Asthma encompasses a spectrum of clinical phenotypes and severity. Physicians should ensure adherence to inhaled therapy prior to escalating treatment. The development of biologic therapies for severe asthma has resulted in significant advances in the management of severe T2-high asthma. T2-low asthma remains an unmet clinical need, however the future is bright with several promising therapies with the potential to transform care for all asthma patients on the horizon.

References on Request