THERE'S MORE TO IgE – LET'S TALK SEVERE ASTHMA

Summary of Presentations from a Novartis-Supported Satellite Symposium, held at the 24th ERS Congress, Munich, Germany, on 7th September 2014

Chairperson

Roland Buhl[1]

Speakers

Gary Anderson,[2] William Busse,[3] Jan Lötvall,[4] David Price[5]

1. Mainz University Hospital, Mainz, Germany
2. University of Melbourne, Melbourne, Australia
3. University of Wisconsin, Madison, Wisconsin, USA
4. University of Gothenburg, Gothenburg, Sweden
5. Research in Real Life, Singapore

Disclosure: Prof Buhl has provided lecturing and consulting activities for Aerocrine, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Grifols, Novartis, Roche, Takeda, and Teva. He receives research support (Mainz University) from Boehringer Ingelheim, GSK, Novartis, and Roche. Prof Anderson has received compensation from Boehringer Ingelheim, AstraZeneca, MundiPharma, Novartis, Menarini, Takeda, and GSK for participating in meetings and advisory boards. Prof Busse is a consultant for Novartis, GSK, Genentech, and Roche. He serves on data monitoring boards and study oversight committees for Boston Scientific, Genentech, and ICON, and has research/organisational interests in AAAAI, ATS, AAP, ACAAI, AAI, ACP, CIM, NHLBI, and NIAID. Prof Lötvall has relationships with Abdilbrahim, Aerovant, AstraZeneca, GSK, Novartis, MSD, and UCB. Prof Price is a board member for Aerocrine, Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, and Teva. He provides consultancy for Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Meda, Mundipharma, Napp, Novartis, Pfizer, and Teva. He has grants and grants pending from the UK National Health Service, British Lung Foundation, Aerocrine, AstraZeneca, Boehringer Ingelheim, Chiesi, Eli Lilly, GSK, Meda, Merck, Mundipharma, Novartis, Orion, Pfizer, Respiratory Effectiveness Group, Takeda, Teva, and Zentiva. He has received payments for lectures/speaking/manuscripts/educational materials from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GSK, Kyorin, Meda, Merck, Mundipharma, Novartis, Pfizer, SkyePharma, Takeda, and Teva. He owns shares in AKL Ltd., which produces phytopharmaceuticals and owns 80% of Research in Real Life Ltd. and its subsidiary social enterprise, Optimum Patient Care. He has unrestricted funding for investigator-initiated studies from Aerocrine, AKL Ltd., Almirall, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, Orion, Takeda, Teva, and Zentiva.
Acknowledgements: Writing assistance was provided by Dr Nicola Ray apothecom scopemedical.
Support: Medical writing assistance was funded by Novartis. The views and opinions expressed are those of the authors as expressed during the symposium and not necessarily of Novartis.
Citation: EMJ Respir. 2014;2:28-32.

MEETING SUMMARY

The meeting discussed the current understanding of the role of immunoglobulin E (IgE) in asthma, and anti-IgE strategies in the treatment of severe asthma. Prof Gary Anderson provided an overview of the integral role of IgE in the inflammatory pathways involved in the pathogenesis of severe asthma and the development of omalizumab (Xolair®), an anti-IgE therapy. Prof William Busse presented some of the clinical findings on the use of omalizumab for virus-provoked asthma. Prof Jan Lötvall discussed how phenotyping could improve the development of patient-targeted treatment strategies in asthma. Finally, Prof David Price discussed how changes to the clinical management of patients with severe asthma could improve patient outcomes.

Chair's Opening Comments

Professor Roland Buhl

There is a widespread and growing prevalence of asthma, with 300 million cases worldwide.[1] In Europe, asthma causes 15,000 deaths[2] and accounts for 5 million disability-adjusted life-years annually.[1] One study revealed that patients who continue to experience asthma symptoms despite using inhaled corticosteroids (ICS), as well as long-acting β_2-agonists (LABA), can achieve guideline-defined control of asthma by increasing ('stepping-up') their use of these medications.[3] However, this study also revealed that a significant number of asthma patients can remain uncontrolled despite very high doses of ICSs and LABAs.

Severe asthma has been defined by an ERS/American Thoracic Society-led task force[4] as a disease that requires treatment with high-dose ICSs plus a second controller and/or systemic corticosteroids, or a disease that remains uncontrolled despite this therapy. Severe asthma should be distinguished from difficult-to-treat asthma, which includes patients with poor treatment compliance and/or persistent exposure to environmental allergens. Using this definition, European prevalence estimates of severe asthma range between 5-10%.[4]

The 2014 Global Initiative for Asthma guidelines[1] recommend increasingly high dosages of ICSs and LABAs when asthma symptoms persist, until they are brought under control. If medium-to-high doses of these fail, anti-IgE treatments are suggested in those with a history of allergies.[1] Analysis of The German Severe Asthma Registry[5] found that >50% of patients with severe asthma had a positive skin-prick test (SPT) against common allergens and asthma symptoms that correlate with allergen exposure. A further 15% also have a positive SPT, but without clear correlation between symptoms and allergen exposure.[6] For these reasons, it seems logical to discuss treatment strategies that target severe allergic asthma, thereby reducing symptoms and improving quality of life (QoL) in these patients.[7]

IgE: The Whole Story

Professor Gary Anderson

There is an established link between IgE levels and the risk of asthma.[8] Our understanding of this link has previously assumed that T-helper Type 2 (Th2) cells interact with B lymphocytes to induce IgE production. An elevated level of IgE was then assumed to promote inflammation when sensitised mast cells degranulate and thereby cause changes in lung function and increase asthma symptoms. Omalizumab was therefore developed to reduce the allergic response by blocking the high-affinity IgE receptor (FcεRIβ) present on mast cells. However, current understanding of asthma is much more sophisticated, and recognises that many different endotypes exist that are defined by distinct pathological mechanisms.[9]

While the mode of action of omalizumab – to bind and neutralise IgE without triggering high affinity IgE receptors – is understood in exact molecular detail, its efficacy in different disease endotypes is less clear. However, investigation of the impact of omalizumab on the cellular and molecular markers that contribute to the immune response has provided new insights. For example, analysis of airway mucosa of individuals with asthma and taking omalizumab revealed effective removal of IgE from both high and low-affinity IgE receptors,[10] and this was, in turn, associated with a marked reduction in the expression of the high-affinity IgE receptor. Decreased receptor density after omalizumab treatment has also been shown in other studies,[11,12] and its therapeutic benefit may derive from an overall reduction in sensitivity to IgE.

When the immune response is reduced, the propensity for exacerbations should also decrease. Eosinophils are key cells within the immune system that may determine the risk of exacerbations in asthma. Furthermore, it has been established that ICS treatment titrated entirely by eosinophil sputum levels, rather than asthma control, can reduce the risk of exacerbations.[13] A second known risk for exacerbations is reduced Type 1 anti-viral interferon levels. A key source of Type 1 interferons are the plasmacytoid dendritic cells (pDCs). If the high-affinity IgE receptor located on these cells is bound by IgE, there is a resulting decreased production of protective Type 1 interferons. Omalizumab both reduces eosinophil levels[10,14] and downregulates the high affinity receptor on pDCs,[15] which may account for the clinically proven ability of omalizumab to reduce the forward risk of exacerbations.[16-22]

In summary, IgE is intimately related to asthma risk, working through multiple pathways. Omalizumab profoundly reduces blood IgE levels, reducing the sensitivity of the system and therefore the T2

immune response. The risk of exacerbations might also be reduced with omalizumab by decreasing eosinophil levels and increasing production of Type 1 anti-viral interferons.

Clinical Benefits of IgE Blockade

Professor William Busse

Viral respiratory infections, particularly the common cold virus, rhinovirus, are a major cause of asthma exacerbations. Not every patient with asthma experiences an exacerbation with a respiratory infection. Conversely, not every respiratory infection leads to an asthma exacerbation, even in high-risk patients. A number of risk factors have been identified, including allergic sensitisation. This association points to IgE as also being involved in exacerbations. Clinical research has also indicated the importance of IgE-sensitisation as a risk for an asthma exacerbation with a rhinovirus respiratory infection. A large study conducted in Costa Rica by the University of Virginia[23] recruited three groups: children with asthma and exacerbation, children with asthma but without exacerbation, and normal controls. They found that the level of IgE to house dust mite was a risk factor for wheezing. However, the risk for wheezing was markedly enhanced by the presence of a rhinovirus respiratory infection, suggesting a link between wheezing with a rhinovirus infection and the IgE-allergic sensitisation process.

The link between asthma and altered anti-viral responses has been investigated by Sebastian Johnston and colleagues at Imperial College, London, UK.[24] They obtained bronchial epithelial cells from children with asthma and normal subjects. Bronchial epithelial cells from asthmatic patients generated less interferon-β and interferon-λ production in response to rhinovirus. This suggests that the anti-viral response to rhinovirus may be impaired in asthma. Previous work has also shown that pDCs from patients with asthma have a diminished interferon response (i.e. interferon-α) when incubated with influenza or rhinovirus.[25]

It is also known that asthma exacerbations have a seasonal variation, with a marked increase in hospitalisations occurring in September, when children return to school.[26] At this time of year, as well as children returning to school, and therefore increasing their proximity to one another, it is also a time of increased environmental allergen exposure. This study raises the possibility that the likelihood of an asthma exacerbation is enhanced when respiratory infections occur in the presence of heightened allergic symptoms.

In a randomised trial comparing omalizumab and guideline-directed care, omalizumab reduced exacerbations and virtually eliminated the exacerbations of asthma during the fall.[27] Following these results, the PROSE study[28] was designed to determine whether omalizumab might be beneficial if used preventatively, immediately prior to children returning to school. PROSE has recently been completed, and the results are being reviewed.

Does Phenotyping Matter?

Professor Jan Lötvall

The term 'phenotype' can be defined as the 'observable, physical characteristics' of an organism that enables it to be classified within a group, and distinguished from others. Sally Wenzel[29] brought forward the idea that we should distinguish between phenotypes of asthma patients in order to be able to better understand their individual disease-related characteristics. She described three phenotype characteristics that should be considered, including 'clinical physiology', 'environmental triggers', and 'pathology/inflammation'. Since then, five different phenotypic clusters have been described in several studies, which are based on age of onset and severity of symptoms, lung function, and medication use.[30] However, there is much overlap between these phenotypes, leading us to propose a classification system based on 'endotypes' of disease. This aims to understand distinct molecular mechanisms of subsets of disease.[31] From the available data, these endotypes may be separated either on Th2-associated or Th2-independent processes.

Anti-IgE therapy has historically been applied to patients with an allergic phenotype, but these may not fully represent the severe asthma group. Therefore, while omalizumab should be prescribed in individuals with high IgE levels or a positive SPT, phenotyping will become ever more important for the development of future mechanism-targeted therapies.

Improving the Severe Asthma-Patient Journey

Professor David Price

The goals for the treatment of severe asthma are to prevent death, minimise symptoms, and reduce exacerbations. A UK-based review of asthma-related deaths revealed that these remain disappointingly high.[32] 43% of people who had died were managed in secondary or tertiary care during the 12 months prior to their death, and at least 21% had been seen at A&E in the previous year, suggesting that opportunities to intervene had been missed, and patients are not getting the appropriate care even when the warning signs are present. In addition, many patients remain symptomatic and have frequent exacerbations in spite of high-dose combination therapy.

For patients with severe asthma, it is recognised that anti-IgE treatment should be the preferred option, rather than long-term use of oral steroids. High-dose ICS and oral steroids can be lifesaving, but there is a potential for side-effects to arise when taken for prolonged periods. For example, there is increasing evidence of metabolic side-effects of higher dose ICS and frequent oral steroid use.[1] Therefore, a further goal in the management of severe asthma should be to reduce the use of oral steroids and possibly high-dose ICS. To achieve this, we need to communicate better with patients in order to get a more accurate representation of asthma control, and to use better decision-making processes. For example, before stepping-up a patient's therapy, the International Primary Care Respiratory Group[33] recommend considering other options, such as checking that the patient is not being exposed to avoidable external allergens in their home.

An evaluation of the real-world effectiveness of omalizumab was recently published.[34] Patients using omalizumab achieved a reduction in exacerbations that increased over time so that, at 24 months, at least a 67% reduction was achieved. Long-term improvements in QoL were also observed. Furthermore, oral corticosteroid use was reduced.

There are still hurdles to overcome in improving the care of patients with severe asthma. For instance, many patients who are potentially eligible for omalizumab are being referred to centres specialising in severe asthma. It is possible that patients are not being assessed appropriately because their asthma is controlled with frequent use of rescue oral corticosteroids. It should perhaps be recommended that people using two or more courses of steroids in a year should be referred for further assessment so that it can be determined whether omalizumab is an appropriate option. If we can address these issues of referral, patient journeys can be altered and outcomes can improve.

Chair Summary

Professor Roland Buhl

In summary, Prof Roland Buhl made clear that IgE has a central role in severe and allergic asthma, but maybe also in the non-allergic phenotype. He suggested that clinicians should look more carefully at patients with asthma so that anti-IgE therapy is used more, when appropriate. Furthermore, he further suggests that we should move on to evaluate the role that anti-IgE can play in other diseases, such as urticaria, a disease that is totally unrelated to the allergic phenotype, and yet anti-IgE therapy seems to work very well.

Panel Discussion

In considering whether non-allergic asthmatics would benefit from anti-IgE therapy, Prof Lötvall expressed the view that testing for allergies is imperfect due to fluctuating environmental allergen levels, so the more important consideration should be whether or not they respond to anti-IgE therapy. Prof Busse pointed out that the best results of anti-IgE are achieved in those with diagnosed allergies. Prof Price proposed that any patient with problematic asthma should be tested for allergies. He also later indicated that patients with raised eosinophils, but without allergy, might respond to anti-IgE therapy. Another candidate patient group – those with elevated exhaled nitric oxide – was suggested by Prof Busse.

Responding to a question regarding the role of neutrophils in asthma, and whether they should be targeted by treatment, Prof Anderson suggested that while there is a lot of evidence suggesting that reducing eosinophils can improve asthma symptoms, it is less clear that targeting neutrophils would be beneficial.

In a discussion around the specific use of medication for different asthma phenotypes, Prof Lötvall pointed out that certain groups of asthma patients do not respond well to ICSs, but are still offered these in combination with other medications. It is possible that this contributes to an overuse of ICS. However, those with significant disease respond very clearly to ICSs, and we do not have long-term studies that can guide the specific treatment of patients with different phenotypes.

Asked how to best differentiate between severe asthma and chronic obstructive pulmonary disease, Prof Price pointed out that there is a validated questionnaire capable of differentiating between the two conditions. The most important features of the questionnaire were related to evidence of allergies and duration of disease.

REFERENCES

1. 2014 Global Initiative for Asthma (GINA) guidelines. Available at: http://www.ginasthma.org/.

2. ERS - Respiratory health and disease in Europe. Available at: http://www.erswhitebook.org/.

3. Bateman ED et al; GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Am J Respir Crit Care Med. 2004;170:836–44.

4. Chung KF et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43:343–73.

5. German Asthma Net e.V. Available at: http://www.german-asthma-net.de/en.

6. Korn S et al. Allergic and eosinophilic phenotypes in the German severe asthma registry. Abstract A1297. American Thoracic Society, San Diego, California, USA, 16–21 May, 2014.

7. Bousquet J et al. Predicting and evaluating response to omalizumab in patients with severe allergic asthma. Respir Med. 2007;101:1483–92.

8. Burrows B et al. Association of asthma with serum IgE levels and skin-test reactivity to allergens. N Engl J Med. 1989;320:271–7.

9. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. Lancet. 2008;372:1107–19.

10. Djukanović R et al. Effects of treatment with anti-immunoglobulin E antibody omalizumab on airway inflammation in allergic asthma. Am J Respir Crit Care Med. 2004;170:583–93.

11. MacGlashan D Jr et al. In vitro regulation of FcepsilonRIalpha expression on human basophils by IgE antibody. Blood. 1998;91:1633–43.

12. MacGlashan DW Jr et al. Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. J Immunol. 1997;158:1438–45.

13. Green RH et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Lancet. 2002;360:1715–21.

14. van Rensen EL et al. Eosinophils in bronchial mucosa of asthmatics after allergen challenge: effect of anti-IgE treatment. Allergy. 2009;64:72–80.

15. Prussin C et al. Omalizumab treatment downregulates dendritic cell FcepsilonRI expression. J Allergy Clin Immunol. 2003;112:1147–54.

16. Humbert M et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy. 2005;60:309–16.

17. Ayres JG et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. Allergy. 2004;59:701–8.

18. Vignola AM et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. Allergy. 2004;59:709–17.

19. Busse W et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol. 2001;108:184–90.

20. Solèr M et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. Eur Respir J. 2001;18:254–61.

21. Holgate ST et al; Omalizumab 011 International Study Group. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. Clin Exp Allergy. 2004;34:632–8.

22. Bousquet J et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. Allergy. 2005;60:302–8.

23. Soto-Quiros M et al. High titers of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus. J Allergy Clin Immunol. 2012;129:1499–1505.e5.

24. Edwards MR et al. Impaired innate interferon induction in severe therapy resistant atopic asthmatic children. Mucosal Immunol. 2013;6:797–806.

25. Gill MA et al. Counterregulation between the FcepsilonRI pathway and antiviral responses in human plasmacytoid dendritic cells. J Immunol. 2010;184:5999–6006.

26. Johnston NW et al. The September epidemic of asthma hospitalization: school children as disease vectors. J Allergy Clin Immunol. 2006;117:557–62.

27. Busse WW et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med. 2011;364:1005–15.

28. National Institute of Allergy and Infectious Diseases (NIAID). Preventative omalizumab or step-up therapy for severe fall exacerbations (PROSE). NCT01430403. https://clinicaltrials.gov/ct2/show/NCT01430403?term=PROSE&rank=6.

29. Wenzel SE. Asthma: defining of the persistent adult phenotypes. Lancet. 2006;368:804–13.

30. Moore WC et al; National Heart, Lung, and Blood Institute's Severe Asthma Research Program. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med. 2010;181:315–23.

31. Lötvall J et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. J Allergy Clin Immunol. 2011;127:355–60.

32. Royal College of Physicians. National Review of Asthma Deaths. Available at: https://www.rcplondon.ac.uk/projects/national-review-asthma-deaths.

33. International Primary Care Respiratory Group (IPCRG). Difficult to Manage Asthma. Available at: https://www.theipcrg.org/display/DIFFMANAST/Home+-+Difficult+to+manage+asthma.

34. Braunstahl GJ et al. The eXpeRience registry: the 'real-world' effectiveness of omalizumab in allergic asthma. Respir Med. 2013;107:1141–51.