Therapeutics and Clinical Risk Management

Dovepress
open access to scientific and medical research

Open Access Full Text Article

EDITORIAL

Anticholinergics in asthma: are we utilizing asthma therapies effectively?

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management

Christian Vogelberg

Department of Pediatric Pulmonology and Allergy, University Hospital Carl Gustav Carus, Technical University of Dresden, Dresden, Germany

Data have shown that asthma is the most prevalent chronic respiratory disease, affecting 358 million people worldwide in 2015.[1] While data show that the age-standardized asthma-related death rate decreased by 58.8% from 1990–2015,[1] asthma still represents a significant burden in terms of morbidity.[2] As such, there is an important role for utilizing add-on therapy options. The focus of this review series is on the use of long-acting anticholinergic add-on therapy to reduce asthma morbidity.

In the first article of this review series, Dr Kevin Gruffydd-Jones reviews the unmet needs in the diagnosis, management, and treatment of asthma. There is no universally accepted, gold-standard diagnostic test for asthma, so diagnosis relies on assessing the probability of a patient's symptoms being due to asthma and using objective tests.[3,4] As a result, under-, over-, and misdiagnosis of asthma are common, with one study finding no evidence of asthma in one-third of participants who had previously received a physician's diagnosis of asthma, and another prospective study in an adolescent cohort showing that one-third of the diagnosed asthma patients had previously been undiagnosed.[5,6] In addition, a high proportion of patients with asthma are classified as having guideline-defined uncontrolled asthma, and experience symptoms despite the availability of different treatment options and guidelines.[7] A move toward precision medicine so as to provide more individualized treatment will go some way to meeting the unmet needs in asthma diagnosis and management; however, for most patients with asthma, this approach remains a long way off. Long-acting anticholinergics such as tiotropium are an effective add-on therapy across a broad spectrum of severity and age groups and are therefore helping to meet some of these unmet needs.

These add-on treatments are particularly important because many patients remain uncontrolled with inhaled corticosteroids (ICS) and long-acting β_2-agonists (LABAs).[8,9] In line with the Global Initiative for Asthma (GINA) strategy, there are several add-on therapy options in patients who are uncontrolled despite medium- to high-dose ICS/LABA at GINA Step 4, such as tiotropium delivered via Respimat®, a soft-mist inhaler.[3] In Professor Christine Jenkins' article "Barriers to achieving asthma control in adults: evidence for the role of tiotropium in current management strategies", she explores the interesting question of whether add-on therapy options are being utilized effectively in clinical practice, with a focus on the extensive evidence for tiotropium add-on therapy in current management strategies for adults with asthma. GINA recommends regular reviews as part of the cycle of management and the stepwise approach to care;[3] this includes considering add-on therapy options to provide safe and efficacious treatment according to individual patient needs.[3] Furthermore, this regular review opens up the opportunity for dialog between patients and health care

Correspondence: Christian Vogelberg
Department of Pediatric Pulmonology and Allergy, University Hospital Carl Gustav Carus, Technical University of Dresden, Fetscherstrasse 74, 01307 Dresden, Germany
Email christian.vogelberg@uniklinikum-dresden.de

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/TCRM.S190363

professionals, encouraging patients toward self-management. Treatment adherence remains problematic in asthma management, yet studies have shown that interventions that aid dialog, such as professionals undergoing communication skills training, can improve patient adherence.[10] Regular reviews also allow for ongoing inhaler technique training, as many studies show loss of technique when it is only demonstrated once.[11,12] Professor Jenkins concludes that health care professionals should actively implement this cycle of asthma management in regular reviews, and patients should be empowered with their health care provider to be involved in their own care.

The 2018 GINA report also recommends tiotropium as add-on therapy in patients aged ≥12 years with a history of asthma exacerbations at Steps 4 and 5 of the stepwise approach.[3] In addition, approvals in patients aged ≥6 years were recently granted by the US Food and Drug Administration and the European Medicines Agency.[13,14] In light of this, Professor Stanley Goldstein reviews the use of anticholinergics in pediatric asthma, including the various challenges for selecting appropriate endpoints in future clinical trials in a pediatric population. For example, traditional endpoints such as forced expiratory volume in 1 second and peak expiratory flow do not correlate well with asthma severity in children. Alternative endpoints, such as forced expiratory flow between 25% and 75% of forced vital capacity, can be more sensitive measures of small airway obstruction in a pediatric population. Of particular note is the focus on the safety of anticholinergic therapies in pediatric patients. Four phase III and one phase II/III clinical trials in adolescents and pediatric patients have shown that tiotropium has a similar safety and tolerability to placebo.[15–19]

In the next article in the series, I review asthma in preschool children. Over half of asthma cases develop before the age of 3 years, and 80% before the age of 6 years, and yet there remain challenges in recognizing and treating asthma at this age. Frequently cited complications include the maturity of the respiratory and immune systems, the natural history of the disease, lack of reliable and reproducible tests, difficulty in delivering treatment, unpredictable responses to treatment, and underestimation of disease severity by parents, guardians, and patients. These difficulties with diagnosis also mean that there are limited treatment options available and few clinical trials investigating potential treatments in this age group. While pediatricians are familiar with short-acting anticholinergics, especially in the context of treating acute asthma attacks in young children,[20] there is only very recent data on long-acting anticholinergics in this age group. A recent trial assessing tiotropium vs placebo in preschool children demonstrated a comparable safety and tolerability profile.[19] However, further trials are needed to establish the efficacy of tiotropium in this very young patient population.

So, what can be done to improve utilization of asthma therapies? One approach is the selection of appropriate inhaler devices and improvements in inhaler technique. This is explored in Dr Omar Usmani's article "The importance of inhalation devices in the management of asthma and COPD", in which he recommends a tailored and personalized approach to choosing an inhaler. This should be based not only on achieving better clinical control and improved quality of life but also on factors such as pulmonary function,[21,22] device handling[23] and patient preferences.[24] It is important to note that both the patient and the health care practitioner should receive training and education on inhaler technique. Advances in electronic and digital health are likely to provide additional support to inhaler use in obstructive airway diseases.

Finally, we look toward the future of asthma therapy. With the increasing number of biologic agents entering the asthma treatment armamentarium, where do current treatments such as tiotropium sit? Professors Roland Buhl and Eckard Hamelmann assess the future position of anticholinergics – in particular tiotropium – for asthma treatment in adults and children. The heterogeneous nature of asthma means that patients can respond differently to the same treatment. This makes the concept of precision medicine an attractive approach in asthma, although it should be noted that, currently, we do not have all the tools to implement this in clinical practice.[25] Newer biologic therapies such as dupilumab have shown improved outcomes in adults with severe asthma.[26] However, use of these newer biologic therapies will need to be subjected to cost–benefit analysis, taking into account the additional costs of patient phenotyping and biomarker analysis.[27] Data have shown that tiotropium is efficacious in adults with asthma, irrespective of baseline characteristics such as allergic status.[28] This means that tiotropium can be administered without the need for patient phenotyping, which will make it relatively easy and cost-effective to incorporate into routine clinical practice. As an add-on therapy, tiotropium can also provide a steroid-sparing alternative for patients who are uncontrolled with ICS/LABA who would otherwise require higher ICS doses.[29] The review makes the important point that utilizing tiotropium effectively can help to reduce the burden of asthma and improve patient outcomes, as shown by extensive clinical trial data. Further data from real-world studies of tiotropium add-on therapy in asthma should add additional insight.

This series of reviews raises many interesting questions – from how to ensure effective implementation of guidelines, why training and regular dialog with patients is so important, to the future position of long-acting anticholinergics in asthma therapy.

Acknowledgments

Medical writing assistance in the form of the preparation and revision of the draft manuscript was supported financially by Boehringer Ingelheim and provided by Helen Moore, PhD, of MediTech Media, under the author's conceptual direction and based on feedback from the author. Boehringer Ingelheim was given the opportunity to review the manuscript for factual accuracy only.

Disclosure

The author has participated as a lecturer and speaker in scientific meetings and courses under the sponsorship of ALK Abello, Allergopharma, Boehringer Ingelheim, Engelhard Arzneimittel, HAL Allergy, Infectopharm, Merck Sharp & Dohme, and Novartis and as a member of the advisory board for ALK Abello, Boehringer Ingelheim, Engelhard Arzneimittel, Merck Sharp & Dohme, Stallergenes, and Novartis. He was an investigator on the pediatric tiotropium studies. The author reports no other conflicts of interest in this work.

References

1. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med*. 2017;5(9):691–706.
2. Asthma UK. Annual Asthma Survey: 2016 report. Available from: https://www.asthma.org.uk/globalassets/get-involved/external-affairs-campaigns/publications/annual-asthma-care-survey/annualasthmasurvey2016final.pdf. Accessed June 19, 2017.
3. Global Initiative for Asthma. GINA report: global strategy for asthma management and prevention. Available from: http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed March 8, 2018.
4. McCormack MC, Enright PL. Making the diagnosis of asthma. *Respir Care*. 2008;53(5):583–590.
5. Aaron SD, Vandemheen KL, Fitzgerald JM, et al. Reevaluation of diagnosis in adults with physician-diagnosed asthma. *JAMA*. 2017;317(3):269–279.
6. Siersted HC, Boldsen J, Hansen HS, Mostgaard G, Hyldebrandt N. Population based study of risk factors for underdiagnosis of asthma in adolescence: Odense schoolchild study. *BMJ*. 1998;316(7132):651–657.
7. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J*. 2000;16(5):802–807.
8. Demoly P, Annunziata K, Gubba E, Adamek L. Repeated cross-sectional survey of patient-reported asthma control in Europe in the past 5 years. *Eur Respir Rev*. 2012;21(123):66–74.
9. Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL Study. *Am J Respir Crit Care Med*. 2004;170(8):836–844.
10. Zolnierek KB, Dimatteo MR. Physician communication and patient adherence to treatment: a meta-analysis. *Med Care*. 2009;47(8):826–834.
11. Resnick DJ, Gold RL, Lee-Wong M, Feldman BR, Ramakrishnan R, Davis WJ. Physicians' metered dose inhaler technique after a single teaching session. *Ann Allergy Asthma Immunol*. 1996;76(2):145–148.
12. Basheti IA. The effect of using simulation for training pharmacy students on correct device technique. *Am J Pharm Educ*. 2014;78(10):177.
13. Boehringer Ingelheim Pharmaceuticals Inc. Highlights of prescribing information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021936s007lbl.pdf. Accessed December 14, 2017.
14. Boehringer Ingelheim. Asthma: expanded indication for SPIRIVA® Respimat® for people 6 years and older. Available from: https://www.boehringer-ingelheim.com/press-release/expanded-asthma-indication-spiriva-respimat-eu. Accessed March 20, 2018.
15. Hamelmann E, Bateman ED, Vogelberg C, et al. Tiotropium add-on therapy in adolescents with moderate asthma: a 1-year randomized controlled trial. *J Allergy Clin Immunol*. 2016;138(2):441–450.
16. Hamelmann E, Bernstein JA, Vandewalker M, et al. A randomised controlled trial of tiotropium in adolescents with severe symptomatic asthma. *Eur Respir J*. 2017;49(1):1601100.
17. Szefler SJ, Murphy K, Harper T, et al. A phase III randomized controlled trial of tiotropium add-on therapy in children with severe symptomatic asthma. *J Allergy Clin Immunol*. 2017;140(5):1277–1287.
18. Vogelberg C, Engel M, Laki I, et al. Tiotropium add-on therapy improves lung function in children with symptomatic moderate asthma. *J Allergy Clin Immunol Pract*. Epub 2018 May 08.
19. Vrijlandt E, El Azzi G, Vandewalker M, et al. Safety and efficacy of tiotropium in children aged 1–5 years with persistent asthmatic symptoms: a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med*. 2018;6(2):127–137.
20. Rodrigo GJ. Anticholinergics for asthma: a long history. *Curr Opin Allergy Clin Immunol*. 2018;18(1):38–43.
21. Normansell R, Kew KM, Mathioudakis AG. Interventions to improve inhaler technique for people with asthma. *Cochrane Database Syst Rev*. 2017;13(3):CD012286.
22. Bonini M, Usmani OS. The importance of inhaler devices in the treatment of COPD. *COPD Res Pract*. 2015;1(1):9.
23. Lavorini F, Fontana GA, Usmani OS. New inhaler devices – the good, the bad and the ugly. *Respiration*. 2014;88(1):3–15.
24. Dekhuijzen PN, Lavorini F, Usmani OS. Patients' perspectives and preferences in the choice of inhalers: the case for Respimat(®) or HandiHaler(®). *Patient Prefer Adherence*. 2016;10:1561–1572.
25. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J*. 2016;47(2):410–419.
26. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet*. 2016;388(10039):31–44.
27. Chang A, Bossé Y. Targeting single molecules in asthma benefits few. *Trends Mol Med*. 2016;22(11):935–945.
28. Kerstjens HA, Moroni-Zentgraf P, Tashkin DP, et al. Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway obstruction, and allergic status. *Respir Med*. 2016;117:198–206.
29. Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med*. 2010;363(18):1715–1726.