CHEST

Use of Biological Agents in Asthma

Pharmacoeconomic Lessons Learned From Omalizumab

Steven Draikiwicz, MD
John Oppenheimer, MD
Newark, NJ

Despite advances in asthma initiatives, there continues to be a large population of patients with severe asthma whose condition remains uncontrolled despite the use of inhaled combination corticosteroids and long-acting beta-agonist treatment.[1] For this population, which may include as many as one-third of all patients with asthma, biological therapy is often a treatment consideration in specialist clinics.[2] In contemporary asthma care, and in the scope of this paper, the term "biological agent" indicates the use of a monoclonal antibody. In an attempt to avoid the side effects of oral corticosteroid therapy, specialists often feel obligated to add this therapeutic option. With an anticipated influx of monoclonal antibody therapies soon to come to market, the necessity of appropriately stratifying patients prior to initiating such therapy is of paramount necessity. It is important to recognize that following accepted prescribing criteria does not necessarily equate to anticipated clinical response. Omalizumab provides a prime example in which, based on current prescribing criteria, as many as one-half of the patients who are administered the medication may be poor responders.[3] Postmarket studies of omalizumab suggest that other phenotypic markers such as exhaled fractional nitrous oxide, periostin, and blood eosinophil levels better define predicted response to therapy.[3]

Use of biological agents is further complicated when considering what a sufficient clinical response would be to justify the continuation of therapy in practice. Because of the severity of baseline symptoms, many providers may not discontinue therapy even when only marginal benefit has been seen. The pharmacoeconomic ramifications of physicians initiating inefficacious or marginally effective biological therapy are daunting and likely are not sustainable. We evaluate the cost efficacy of omalizumab prescription in patients with asthma as a model of the use of biological agents in uncontrolled asthma. Despite the fact that omalizumab has been available since 2003, there is a surprising paucity of data supporting the cost-effectiveness of this therapy. Nonetheless, it is worthwhile to examine the limited data available in an effort to explore the potential economic impact of incumbent pipeline biological agents for which similar studies are unavailable.

The economic consequences of therapy with omalizumab are significant, with each vial of omalizumab in the United States priced at $> \$900$.[4] It can be estimated that on a per-patient basis, the average direct cost of annual prescriptions for omalizumab are within the range of \$15,000 to \$44,000.[5] In a study by Lafeuille et al,[6] a mean of one less emergency department visit per year in a best-case scenario was found attributable to omalizumab therapy. In the same cohort, the mean number of hospitalizations was reduced from 0.79 to 0.48 per annum in a best-case scenario. It is unclear whether the magnitude of change observed is sufficient to justify continuation of therapy.[6] A study by Sullivan et al[7] suggests a corresponding increase in average annual cost of care from \$14,071 to \$34,887 despite improved asthma control. While not part of prescribing guidelines, it has previously been suggested that only patients who are hospitalized $\geq$ five times or $\geq$ 20 days per year be candidates for omalizumab from a pharmacoeconomic basis.[8]

There remains conflicting data when considering the impact of omalizumab on quality of life from a cost perspective. Multiple models have demonstrated the cost burden of omalizumab at $>$ \$100,000 quality adjusted

AFFILIATIONS: From the Division of Allergy and Immunology, New Jersey Medical School.

FINANCIAL/NONFINANCIAL DISCLOSURES: The authors have reported to *CHEST* the following: J. O. receives consulting fees from Glaxo, Myelin, and Meda; adjudication fees from Quintiles; fees for research from AstraZeneca, Genetec, Sanofi, and Glaxo; legal consultation fees for malpractice defense; reviewer fees from Up-to-date, Annals of Allergy and Immunology, and American Board of Allergy and Immunology. None declared: S. D.

CORRESPONDENCE TO: John Oppenheimer, MD, 8 Saddle Rd, No. 101, Cedar Knolls, NJ 07927; e-mail: nallopp@optonline.net

DOI: http://dx.doi.org/10.1016/j.chest.2016.06.033

life-years (QALY), with some ranging as high as $800,000/QALY.[9,10] The addition of omalizumab resulted in improved QALY but with increased direct medical costs and a poor incremental cost-effectiveness ratio (ICER).[11] An improved but still significant ICER was found when selecting patients with more aggressive uncontrolled baseline asthma resulting in multiple exacerbations and hospitalizations.[12] The National Institute for Health and Care Excellence guidelines acknowledge that many assumptions need to be made regarding the cost-effectiveness of omalizumab in children and adults, with use being acceptable in select individuals.[13]

In comparison, a recent Cochrane review suggested that omalizumab administration in patients with uncontrolled asthma receiving moderate- to high-dose inhaled combination corticosteroids resulted in a reduced absolute risk of hospitalization rate from 3% to 0.5%.[14] Data are available from Europe that approximate the use of omalizumab, with €30,000 to €40,000 QALY when considering asthma mortality after hospitalization or a study-based questionnaire end point.[15,16] A small cohort in Ireland also found overall savings in health-care costs following 7 months of omalizumab therapy due to the reduction in hospitalized days, overall hospitalizations, and the use of oral corticosteroids.[17] A confounding factor when broadly applying the results of these studies is the disparity in prescribing costs of therapy when comparing Europe and the United States.

It is also important to recognize that cost savings solely focusing on health-care use ignore other potential benefits of therapy, such as the improvement in patient quality of life, as well as absenteeism and presenteeism. One study estimated that uncontrolled asthma may account for approximately $200 per week in productivity loss.[18] Reduced mortality and disability are also significant contributors to indirect cost savings.[19] Unfortunately, these effects are difficult to quantify in direct relation to omalizumab therapy.

Recognizing these concerns, it remains clear that there is a significant population of patients in whom omalizumab is both indicated and beneficial. Yet it needs to be acknowledged that anticipated clinical response is not necessarily predicted based on current accepted criteria for initiation of omalizumab therapy. Furthermore, in an economically burdened health-care system, any consideration of indirect cost savings and quality-adjusted life benefits of omalizumab must pay homage to the increased direct medical costs of therapy. Accepted QALY and ICER standards for asthma therapy may need to be reevaluated. With the inception of increasing numbers of clinically available monoclonal antibodies in asthma management, comparison of head-to-head cost savings may be of equal import to other clinically reported end points. From a systems perspective, the cost of attempting antibody therapy and failing is prohibitive; pharmacoeconomic guidelines for these agents are required. Prescription of these agents requires improved understanding of surrogate markers of asthma phenotypes, which allows for optimal patient stratification in an attempt to maximize cost-effectiveness. Ultimately, biological agents should not be used reflexively because of a failure of other agents. Their use should be limited to select patients in whom a specific phenotype has been identified that is predicative of response.

References

1. Moore WC, Bleecker ER, Curran-Everett D, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol*. 2007;119(2):405-413.
2. Bateman ED, Boushey HA, Bousquest 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.
3. Hanania NA, Wenzel S, Rosen K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med*. 2013;187(8):804-811.
4. http://www.goodrx.com/xolair?drug-name=xolair. Accessed February 14, 2016.
5. Belliveau PP, Lahoz MR. Evaluation of omalizumab from a health plan perspective. *J Manag Care Pharm*. 2005;11(9):735-745.
6. Lafeuille MH, Dean J, Zhang J, Duh MS, Gorsh B, Lefebvre P. Impact of omalizumab on emergency-department visits, hospitalizations, and corticosteroid use among patients with uncontrolled asthma. *Ann Allergy Asthma Immunol*. 2012;109(1):59-64.
7. Sullivan PW, Campbell JD, Ghushchyan VH, Globe G. Outcomes before and after treatment escalation to Global Initiative for Asthma steps 4 and 5 in severe asthma. *Ann Allergy Asthma Immunol*. 2015;114(6):462-469.
8. Oba Y, Salzman G. Cost-effectiveness analysis of omalizumab in adults and adolescents with moderate-to-severe allergic asthma. *J Allergy Clin Immunol*. 2004;114(2):265-269.
9. Zelger RS, Schatz M, Dalal AA, et al. Utilization and costs of severe uncontrolled asthma in a managed-care setting. *J Allergy Clin Immunol Pract*. 2016;4(1):120-129.
10. Wu AC, Paltiel AD, Kuntz KM, Weiss ST, Fuhlbrigge AL. Cost-effectiveness of omalizumab in adults with severe asthma: results from the Asthma Policy Model. *J Allergy Clin Immunol*. 2007;120(5):1146-1152.
11. Campbell JD, Spackman DE, Sullivan SD. The costs and consequences of omalizumab in uncontrolled asthma from a USA payer perspective. *Allergy*. 2010;65(9):1141-1148.
12. Norman G, Faria R, Paton F, et al. Omalizumab for the treatment of severe persistent allergic asthma: a systemic review and economic evaluation. *Health Technol Assess*. 2013;17(52):1-342.

13. Diaz RA, Charles Z, George E, Adler A. NICE guidance on omalizumab for severe athma. *Lancet Respir Med*. 2013;1(3):189-190.

14. Normansell R, Walker S, Milan SJ, Watlers EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev*. 2014;131:CD003559.

15. Van Nooten F, Stern S, Braunstahl GJ, Thompson C, Groot M, Brown RE. Cost-effectiveness of omalizumab for uncontrolled allergic asthma in Netherlands. *J Med Econ*. 2013;16(3):342-348.

16. Faria R, McKenna C, Palmer S. Optimizing the position and use of omalizumab for severe persistent allergic asthma using cost-effectiveness analysis. *Value Health*. 2014;17(8):778-782.

17. Costello RW, Long DA, Gaine S, McDonnell T, Gilmartin JJ, Lane SJ. Therapy with omalizumab for patients with severe allergic asthma improves asthma control and reduces overall healthcare costs. *Ir J Med Sci*. 2011;180(3):637-641.

18. Sadatsafavi M, Rousseau R, Chen W, Zhang W, Lynd L, FitzGerald JM. The preventable burden of productivity loss due to suboptimal asthma control: a population-based study. *Chest*. 2014;145(4):787-793.

19. Stock S, Redaelli M, Luengen M, Wendland G, Civello D, Lauterbach KW. Asthma: prevalence and cost of illness. *Eur Respir J*. 2005;25:47-53.