

Pharmacoeconomics of Biologic Therapy



Don A. Bukstein, MD^{a,b,*}, Allan T. Luskin, MD^{c,1}

KEYWORDS

- Severe asthma • Biologic therapy • Pharmacoeconomics • Health care resource use
- Oral corticosteroid • Personalized medicine

KEY POINTS

- Pharmacoeconomics in immune therapy with biologics involves comparing the costs of an intervention with the change in health status to establish value of an intervention.
- Accurate assessments require measuring all disease costs before and after the intervention, including direct disease costs, costs of related comorbidities, and indirect costs.
- Indirect costs include absenteeism, presenteeism, and quality of life of the patient and family/caregivers.
- Proper policy decisions demand that the cost of the intervention be compared with the cost of the lack of the intervention or alternative interventions.
- Costs of lack of the intervention or alternative therapies include both direct and indirect costs, and the direct costs should include the costs of complications of uncontrolled disease and long-term side effects medications such as corticosteroids.

The good physician treats the disease; the great physician treats the patient who has the disease.

—Sir William Osler

INTRODUCTION

Recent years have witnessed tremendous progress in the therapeutic approach to immune-related diseases, such as rheumatoid arthritis, psoriasis, inflammatory bowel disease, and asthma. The introduction of novel biologic agents, including antibodies

Disclosure Statement: D.A. Bukstein has served as a speaker for Merck, Genentech, Novartis Pharmaceuticals, AstraZeneca, Aerocrine, Teva Pharmaceuticals, Meda Pharmaceuticals, and Circassia. He has received honoraria from AstraZeneca, Schering-Plough, Merck, Meda Pharmaceuticals, Alcon, and Aerocrine and has commercial interests in Altus Minicampus and the PBL Institute. A.T. Luskin has served as a speaker for Genentech.

^a Allergy, Asthma & Sinus Center, Madison, WI, USA; ^b Allergy, Asthma & Sinus Center, Milwaukee, WI, USA; ^c Healthy Airways, Madison, WI, USA

¹ Present address: 10 Tower Drive, Sun Prairie, WI 53590.

* Corresponding author. 11 Glen Arbor Way, Fitchburg, WI 53711.

E-mail address: donabukstein@gmail.com

Immunol Allergy Clin N Am 37 (2017) 413–430

<http://dx.doi.org/10.1016/j.iac.2017.01.011>

0889-8561/17/© 2017 Elsevier Inc. All rights reserved.

immunology.theclinics.com

and cytokine inhibitors, has allowed clinicians to achieve improved outcomes for their patients. An important factor that has affected the utilization of novel therapies is their acquisition costs, which far exceed those for older drugs. Nevertheless, these are serious chronic conditions, which can cause substantial morbidity and accelerated mortality for affected individuals. Alternative therapeutic choices often involve the use of agents such as systemic corticosteroids with potentially costly side effects. Both undertreatment with uncontrolled disease and treatment with alternative therapies have severe economic consequences to patients and their families as well as to society. Therefore, appropriate pharmacoeconomic analyses demand we take into account all relevant costs, not only of the treatments but also of the disease itself and that of alternative treatments. In this way, the value of therapies can be correctly estimated.

Previous articles have emphasized the clinical burden of severe asthma. The authors summarize the pharmacoeconomic data obtained for biologic agents in patients with inadequately controlled severe persistent allergic asthma despite high-dose inhaled corticosteroids (ICSs) plus a long-acting β -agonist (LABA) and discuss the cost-effectiveness evidence published for biologic agents in this patient population. Although there is a great deal of evidence highlighting the health, economic, and societal burden of asthma, the evidence is highly skewed toward patients with severe uncontrolled asthma, particularly when asthma is inadequately controlled. In patients who do not respond to traditional therapy but do respond to biologic therapy, the cost-effectiveness of biologics often compares well with other treatments for chronic illness in the long terms of costs.

Costs are a measure of resources consumed. By assessing costs, pharmacoeconomic studies complement studies of efficacy and safety, helping to determine the relationships of treatment and outcome. Costs are divided into 3 categories: direct costs, or costs attributable to the intervention; indirect costs, or costs resulting from reduced productivity; and intangible costs, which are incurred from pain and emotional suffering. Insurance companies, patients, doctors, and society each have different perspectives with respect to costs. The authors review different types of cost analyses and their use in studies of asthma as a model. Cost studies influence clinicians', policy makers', and third-party payers' decisions regarding the implementation of particular therapies or programs. Collection of all relevant cost data needs to be facilitated and evaluated along with clinical trials to facilitate these decisions.

This article attempts to provide a more clinically useful perspective on the pharmacoeconomics of new biologics in the treatment of immune diseases, particularly in the area of asthma. Biologics are a cornerstone of personalized medicine but are inherently costly. Therefore—especially for those with the greatest economic burden—a cost-sensitive approach to improve the health of persons who have or are at the highest risk for uncontrolled asthma and other immune disorders must be developed.

Pharmacoeconomic evaluation encompasses a collection of methods that assesses the costs and consequences of comparative health care interventions. **Table 1** summarizes types of pharmacoeconomic evaluation. Evaluating the health and economic impacts of these interventions has been a topic of long-standing interest among clinicians.¹ Such evaluation involves a variety of issues and methods and additionally has major policy implications. This review discusses the main types of pharmacoeconomic evaluation used to assess the use of biologics in asthma and immune disease and will be achieved by analyzing studies to demonstrate how pharmacoeconomic evaluation has been used for asthma care strategies using biologics. Also discussed are the challenges in the practical application of pharmacoeconomic evaluation and related policy implications. This review is designed for clinicians caring for

Table 1
Types of pharmacoeconomic analyses

Type	Description	Comparison (X:Y)
Cost minimization (CMA)	Compares cost in monetary terms of treatment with identical outcomes	Dollars: Outcome unit varies but equivalent in comparatory groups
Cost-effectiveness (CEA)	Compares cost in monetary terms with outcomes in natural units	Dollars: Natural units such as years, blood glucose, LDL, cholesterol
Cost utility (CUA)	Compares cost in monetary terms and outcomes in terms of years of life	Dollars: QALY quality of life-years
Cost benefit (CBA)	Compares costs and outcomes in monetary terms	Dollars: dollars

Abbreviation: LDL, low-density lipoprotein.

individuals with asthma and other immune diseases to assist with understanding and evaluating published economic analyses, and identifying the key costs and benefits associated with their own clinical practices.¹

Why Should Caregivers, Insurance Companies, Payers, and Society Be Concerned About the Pharmacoeconomics of Immune Diseases?

Health care costs are increasing, and the focus of both government and private insurance on spending places demands on health care providers to reduce costs yet improve outcomes.² Although new medical interventions can substantially improve health outcomes, these often come at considerable cost to both the health care system and patients. In order to efficiently use limited health care resources, beyond the standard evaluations of safety and efficacy, it is necessary to also evaluate the relative cost-effectiveness of new medical technologies. First the inflammatory immune disease asthma is discussed as an example one area of medicine that is grappling with the challenge of applying biologic therapies.

ASTHMA

Asthma is considered a high-burden inflammatory disease of the lungs, affecting an estimated 17.7 million adults and 6.3 million children in the United States.³ Approximately 1 in 2 asthma sufferers, 10.7 million people, reported having at least one asthma attack, and 3651 casualties were a result of asthma in 2014.³ In 2010, asthma in the United States resulted in 439,435 hospitalizations, 1.8 million emergency department (ED) visits, and 14.2 million physician office visits.^{3,4} Although its health implications are frightening enough, asthma's cost burden is astounding as well. Asthma is associated with an estimated \$50 billion (2009 dollars) in total direct incremental costs annually.⁴ Furthermore, productivity loss related to the illness accounts for an additional \$3.8 billion, and productivity loss from mortality accounts for another \$2.1 billion.⁵

Typically, physicians take a three-pronged approach to allergy care: minimize exposure to allergens, reduce symptoms with pharmacologic therapy, and alter the immune response with immunotherapy. For severe asthma, physicians have the option to improve control with either biologics or thermoplasty.⁶ Although this 3-pronged method has been adopted by most specialty physicians for asthma

treatment, to form an overall management strategy that maximizes positive patient outcomes, asthma treatment needs to be a shared decision-making process (SDM) between the patient, clinician, and payer. Each of the main stakeholders, physician, health care delivery system, employer, patient, and society as a whole, have different areas of emphasis.

Physician perspective

- How can I help these patients control asthma symptoms and prevent comorbidities and exacerbations?
- What type and mix of medical care services will achieve control, balancing benefit and risk?
- For managed-care patients:
 - How can I achieve clinical objectives of Accountable Care Organizations (ACOs), satisfy patient preference, and minimize costs?
 - How can I adhere to mandated guidelines (Pay For Performance [P4P]) and ACOs?

Health care delivery system perspective

- How can direct costs be contained? Managing insurance premiums across groups and maximizing the number of insured patients.
- How will we reduce exacerbation? Exacerbation is associated with mortality and likely higher direct costs than chronic daily symptoms.⁷
- How do we meet guidelines or regulated performance requirements, such as Healthcare Effectiveness Data and Information Set and the Affordable Care Act (ACA)?
- How can I use P4P to reduce costs?
- How do we keep plan members satisfied?
- How do we keep asthma off of our list of concerns?

Employer perspective

- How do I reduce medical costs?
- How do I maintain a productive workforce?
 - Ensure a satisfied workforce
 - Reduce workforce absenteeism
 - Reduce workforce presenteeism
 - Reduce workforce turnover

Patient Perspective

- How do I limit out-of-pocket costs?
- How do I improve my quality of life (QOL)?
- How do I prevent exacerbations and avoid going to the ED?

Societal perspective

- What are the societal costs of asthma?
- How do we control these costs in a non-Orwellian world? (ie, a mandate such as *"Get rid of the cat"* or *"Quit smoking" is not an option!*)
- What is the impact of the disease on family, friends, work or school, and the community?
- How do we sustain public programs?
- What is the cost-effectiveness and lifetime impact of a preventive intervention?

These various stakeholders weigh various costs differently. Health care systems place more importance on direct costs, whereas patients and employers may value indirect costs. Although all of these parties have high concerns with cost, it is vital

to note that value does not equate to cost. It is important then that we define what we mean by quality value in health care and how this may outweigh any dollar costs that many fear. Value in health care is generally defined as quality/cost. More specifically, physicians have refined it to the following:

$$\frac{\text{Change in health status} + \text{Satisfaction}}{\text{Cost}}$$

The cost of a biologic intervention equates to the following:

$$\text{Cost} = \text{Cost of drug} - \text{Direct Costs} - \text{Positive Change in QOL} - \text{Change in Patient Productivity}$$

Accurate evaluation of the equation demands that all costs be measured. These costs are hidden direct costs including the costs of asthma, side effects, medications, and comorbid disease. Furthermore, comorbid disease might be favorably affected either directly by medication, such as in the case of allergic rhinitis, or indirectly by improved control, such as in the case of gastroesophageal reflux disease or obstructive sleep apnea.

Therefore, cheaper is not always less expensive when other elements are measured. As clinicians, we need to learn how to develop an understanding of the true pharmacoeconomic value of biologics, so that we can accurately convey this to health care organizations, the government, and, most importantly, patients. The evaluation depends not solely on drug acquisition costs but also on the costs of the disease itself, from short- and long-term side effects of the drug to alternative treatment costs. The most difficult cost to calculate is the change in productivity. This change in productivity is the cost generated by uncontrolled disease resulting in the loss of personal parental and spousal/family productivity. Also challenging to estimate is the long-term societal cost that is generated from the lack of education because of the effect on school performance as well as underemployment of a patient and their family. The different costs listed in the equation above will vary based on the population receiving the biologic and will depend on identifying the patients who are able to respond and those who are able to do so. The Refractory Asthma Stratification Programme in the United Kingdom (RASP-UK) points out that some patients have poorly controlled asthma simply because they are not taking their medicines correctly.⁸ Identifying those patients is important, but there is another group that RASP-UK investigators hope to identify: patients with severe asthma characterized by high eosinophil or periostin levels who are taking their medicines correctly yet fail to respond to medication. Even within this group of asthma sufferers who do have the right biomarker profile, physicians may have difficulty determining which patients should receive which biologic.^{8,9} The biomarkers linked to each medicine tend to go up and down together, so a patient might have a high eosinophil count in addition to high periostin levels.⁹⁻¹²

WHEN IS BIOLOGIC THERAPY COST-EFFECTIVE?

There are many ways to analyze cost data, and cost-effectiveness is a commonly used method ([Table 1](#)). A biologic therapy is deemed to be a cost-effective strategy when the outcome is worth the cost relative to competing alternatives. In other words, it is a cost-effective strategy when scarce resources are used to acquire the best value on the market considering all alternatives.¹³

Average cost-effectiveness is calculated as:

Cost of drug

Resulting effect = Cost per unit of effect achieved

What is the incremental cost-effectiveness of a biologic in comparison with all other treatment options?

$$\frac{\text{Cost}(\text{Option B}) - \text{Cost}(\text{Option A})}{\text{Effect}(\text{Option B}) - \text{Effect}(\text{Option A})} = \text{Cost to achieve one unit of effect}$$

Previous articles have discussed many of the efficacies of data variables, or what product (effect) can be consistently expected from the use of drug or health service, which was determined from clinical trials. They seek a direct relationship to morbidity and mortality such as survival/death or, as per the asthma example, asthma exacerbations avoided. These efficacy outcomes may rely on surrogate measures such as the Asthma Control Test, pulmonary function tests, fractional exhaled nitric oxide, or use of oral steroids. A randomized controlled clinical trial is the gold standard for deriving this efficacy data, but observational studies can also add insight into the real-world costs of a biologic.^{14,15}

HOW AND WHAT VARIABLES SHOULD WE MEASURE?

What resources are consumed to produce one unit of the effect? There are drug product acquisition costs, drug preparation and administration costs, drug monitoring costs, treatment costs of adverse effects, and indirect institutional costs (discounting other drugs).

In order to draw the most valid conclusion about costs generated over time to achieve an effect in the future, it is necessary to consider that there is a time preference associated with money. The concept of time-value of money states that the amount of money in your hand at this moment is worth more than the same amount in the future. Therefore, future costs must be adjusted to reflect present value. For example, a \$1000 cost 1 year from now requires only \$930 in hand today assuming a 7% return on investment.

Sensitivity analysis (SA) is another important tool used to assess the cost-benefit ratio of biologics. Basically, by altering important variables and then recalculating the results, we can test the validity of conclusions.¹⁴ SA becomes increasingly important because assumptions are often made without proper analysis.

For example, SA could be used for questions like:

- Would Agent A still be most cost-effective if the effect of Agent B was greater than measured in a clinical trial?
- Would Agent A still be most cost-effective if the monitoring costs of Agent B were actually lower to a much greater degree?

As an example, although oral steroids are the least costly method in terms of initial dollars for asthma treatment, they may actually be costly in the long run, due to the common health complications they cause for the patient.^{16–20} Steroid complications place not only an excessive emotional burden on patients but also a financial one, because they will then be forced to pay for additional hospitalization and also potentially for more drugs for treatment. Therefore, clearly physicians need to look deeper.

THE ADOPTION OF BIOLOGICS

Since biologics were brought into the picture, oral steroid use has decreased by 5%, and clinically significant ulcer complications were reduced by 50%.²⁰ When

questioning whether to adopt biologics, the risk of asthma attacks and exacerbations needs to be looked at. Although biologic treatment has shown to prevent these, it is also important to recognize that not all asthma patients have an equal risk of developing an exacerbation.

This then leads to several questions, including the following:

- Is paying extra for exacerbation protection justified in all patients?
- How much can the risk of asthma exacerbation be altered by using biologics?
- What value is really purchased for the extra cost?

All of these factors must be analyzed for each and every patient to determine the most effective treatment option.

What Are the Real-World Practical Applications of Pharmacoeconomics of Biologics to Shared Decision Making?

One must first collect all the data available, and that includes the true costs of medications, copays, deductibles, and prior authorizations at point of service in order to adequately partake in SDM with patients. Risk reduction for complications seen with oral steroids with biologics is unlikely to offset their increased cost in the management of average-risk patients with asthma with no or little history of exacerbations and without the TH-2 phenotype. Clinical decision making and attempts at risk reduction for other complications seen with biologics are unlikely to offset their increased cost in the management of average-risk patients with asthma-control problems with no history of frequent exacerbations and use of oral steroids.

Decreased monitoring costs of biologics and the attenuated risk of future complications with these agents do result in cost-effective care.²¹ Thus, the real issue is who is at risk for steroids' adverse events currently cannot be identified, and there is no consistent method of measurement. The higher acquisition cost may then be justified.

Treating the patient on an outpatient basis creates the best value. Better outcomes are achieved at a lower overall cost: the best possible situation.^{21–23} Time and money can only be spent once; choice is inevitable. Whether done unconsciously or with a consistent process, health care professionals are constantly evaluating patient care choices and acting on them.

Pharmacoeconomics and outcomes research can enhance the quality of the practice by strengthening the evaluation process and increasing the probability that better value is delivered in patient care.²²

Will Establishing General Disease Phenotype Influence the Pharmacoeconomic Choice of a Biologic?

There are many reviews on these topics,^{24–27} and in principle, it is generally accepted that therapeutic agents should be used when there is a favorable balance between their benefits and potential risks. Examples from other fields suggest that pharmacogenetic data can help predict both the benefit and the toxicity of particular drugs in individual patients.²³ The general use of disease endotypes for allergies and asthma and correct selection of the responder patient population with defined biomarkers remain essential unmet needs in the clinical settings.²⁴

Whether it will be possible to define subtypes of patients with asthma who might benefit from more cost-effective, personalized management plans remains to be determined. In the area of profiling, ideally one would be able to use a limited number of reasonably inexpensive tests to predict responses to various forms of treatment rather than to rely on comprehensive analyses of the subject's response to biologics and other medications (trial of 1), waiting until exacerbation costs skyrocket, or until

one can search the entire genome, metabolome, and microbiome. The same point can be made with respect to what type of testing would be needed for effectively monitoring and assessment of treatment responses.^{24–27}

What Does a Decision Maker (eg, Patient, Physician, Health Maintenance Organization Pharmacy and Therapeutics Committee, Government Agency) Need to Know in Selecting the Most Cost-Effective Management Approach for a Patient?

Although the potential cost of personalized or precision medicine has been widely discussed, the costs to individual patients and health systems will vary by country, and in countries with private health care options, costs will vary further based on one's type of health insurance.^{24–28} No matter who is assessing the cost-effectiveness of an intervention, they should ideally consider all of the costs and benefits of the decision, placing values on such important outcomes as long-term wellness and enhanced QOL, cost of time lost at school or work, and reductions in long-term economic productivity.

Hood²⁵ has emphasized the importance of involving patients, and in the case of children, their guardians, in making decisions about their health care. This participatory aspect of medicine constitutes the fourth “P” of P4 medicine, where the 4 Ps are predictive, preventive, personalized, and participatory.

It might be possible to devise approaches using biometric and other data, including data about one's genetic profile and personal environment, to identify more accurately if those patients with asthma or other immune diseases will or will not respond favorably to treatment with expensive biologics and to assess the likely effectiveness of diverse interventions. It might also be possible to define constellations of biometric and other individual characteristics that could change the trial-and-failure approach currently often used to move from first- to second- to third-line therapeutic approaches. An approach in which the caregiver, in consultation with the patient (and/or her or his guardians), can more quickly select a treatment, which is in some cases biologic, will likely result in a higher probability of success for that person. Such precision care approaches not only will permit health care resources to be used in a more cost-effective manner, but more importantly, would result in improved satisfaction of patients and their families with their management and treatment, along with producing favorable social and economic effects by improving attendance and performance in school or at work. If we can overcome the significant impediments to establishing such new approaches, then we will be able to offer a much brighter future to those subjects at risk of allergic diseases and to those patients who already have them.²⁴ This is the basis for the process of initiating patient activation, and possibly improved adherence to biologic therapy.^{29–31}

We cannot remain stuck in the past. Even if a study done in 2010 says a biologic is not very cost-effective, the criteria available then do not mean in the near future with improved phenotyping and patient selection, that biologic will not be extremely cost-effective in 2017.²⁴

Which of the Potential Biologic Agents Will Be the Most Pharmacoeconomically Realistic and Valuable Choice? In Asthma? What Do We Use?

The past decade has been marked by the introduction and expanding use of biologic therapies for the induction and maintenance of response in patients with asthma and other immune diseases. Traditional cost analyses had shown that biologics and medication costs contributed minimally toward the overall costs associated with the disease; however, these studies were all conducted before the introduction of biologic therapies. At that time, a small minority of patients accounted for a disproportionately

large percentage of the overall costs.^{17,32,33} This suggested that cost savings could be realized if interventions decreased the utilization of health care resources and associated costs. More recent studies have been heterogeneous in their design and findings. Some have suggested that cost savings realized, due to a decrease in the utilization of health care services, may partially offset the higher costs of biologic agents. Incorporation of data on indirect cost savings and QOL improvements into ongoing and future analyses is required to allow for more accurate analyses of overall costs and cost savings.

Uncontrolled diseases, like asthma, are costlier than controlled diseases, regardless of severity. To appropriately stratify the uncontrolled population, we need not only additional medications but also an improved guide to SDM to make sure the specific biologic is appropriate for the underlying phenotype. Without stratification of uncontrolled asthma for anticipated clinical and economic benefit, the pharmacoeconomics of specific biologics are unclear. Data are conflicting regarding the cost-effectiveness of omalizumab, despite the drug being used on patients for over a decade.^{34,35} It has been proposed that omalizumab is a cost-saving option only if given to patients who are predicted to be hospitalized 5 or more times, or 20 days, per year, despite maximal medical management.³⁵ However, these studies evaluated patients only on severity of disease, not the patients most likely to respond, and thus are fatally flawed.

One commonly used approach in cost-effectiveness analyses is to calculate the incremental cost-effectiveness ratio (ICER), in the form of cost per quality-adjusted life-years (QALY). QALY is an index of survival that is weighted or adjusted by the patient's QOL during the survival period.³⁶ QALY is particularly useful because it allows for comparisons between interventions and across different conditions. For example, the cost-effectiveness of a therapy for asthma can be compared with one for rheumatoid arthritis.^{37,38}

In order to provide estimates of ICER, economic modeling is often necessary. Although general methodological guidelines exist offering helpful modeling principles, evaluating treatments for autoimmune disorders remains challenging.^{37,38}

What About Gains in Quality-Adjusted Life-Years with the Use of Biologics?

A recent model suggests that omalizumab may cost as much as \$117,000 per QALY, compared with standard therapy with ICS/LABA at a much lower cost of \$15,000 per QALY.^{39,40} Of course, failure of ICS/LABA therapy administered according to Global Initiative for Asthma guidelines is the criterium used to define the patient who might benefit from biologics used in asthma therapy. There are almost no data at this time on the 2 other biologics mepolizumab and reslizumab, and the price for 1 year of mepolizumab is estimated to be more than \$32,500.⁴¹ Although often of minimal importance to the patient, these costs certainly put into question the long-term sustainability of these high costs on the health care system. Omalizumab has recently been reviewed by the National Institute for Health and Care Excellence and is recommended as an option for treating severe persistent allergic asthma as an add-on to optimized standard therapy in patients who need continuous or frequent courses of oral corticosteroids (OCSs).⁴²

Points to consider:

- How long must a patient stay on this biologic therapy before they are considered a treatment failure⁴³?
- What is the timeframe until we see efficacy and the plateau of that efficacy?

- Before initiating and continuing biologic therapy, SDM needs to take place on these issues, but without studies, this is difficult to quantify.
- Rational use in consideration of the underlying phenotype and with real assessment of costs, risks, and benefits, both long and short term, is the basis for rational decision making on biologic use in asthma rather than experimenting until something appears to work.
- Is there a better way of predicting exacerbations⁴⁴?

The significant progress in asthma therapy with the arrival of omalizumab and use of the new biological drugs has increased the focus on the economic aspects because of the very large price tag related to those treatments. Several more recent economic evaluations suggest that current expensive biologics as compared with pharmacotherapy might be cost-effective for asthma therapy in patients who remain uncontrolled per asthma guidelines. To date, the cost-effectiveness of biologics for comorbid allergic problems has not been investigated.^{39–56}

Because of the short amount of time mepolizumab has been on the market, there are limited data on its costs. Early reports estimate a cost per year of treatment from \$10,000 to \$15,000 per patient.⁴⁶ After US Food and Drug Administration approval, the real cost is \$32,500 per year per patient and approximately \$2700 for a single 4-week injection.⁴⁶ To the authors' knowledge, the only real cost-effectiveness analysis was recently conducted and published by the Institute for Clinical and Economic Review Group, which was based on a simulation model of asthma outcomes and costs in a representative population of suitable patients to mepolizumab therapy.⁴¹ The investigators evaluated the incremental cost-effectiveness of mepolizumab, applying drug costs obtained from current prices and estimates of reductions in asthma exacerbations and OCS use from available clinical literature data. In a scenario analysis, it was determined that the price of mepolizumab that would produce cost-effectiveness results at willingness-to-pay thresholds of \$50,000 per QALY, \$100,000 per QALY, and \$150,000 per QALY, respectively. At the moment, based on current purchase prices, the cost-effectiveness estimates are not affordable. To obtain a value correlated with the clinical benefit, a discount of two-thirds to three-quarters from the current acquisition costs of mepolizumab would be necessary. According to the authors of this report, mepolizumab should have a value-based cost between \$7800 and \$12,000 per year, whereas the full list price per patient in the United States is \$32,500 per year. Other doubts arise from the lack of clinical trials evaluating benefits in the long term.

Another group of researchers⁴⁷ conducted a study with the aim to evaluate the cost-effectiveness of the newest strategies for the treatment of severe refractory asthma, such as biologic drugs (omalizumab and mepolizumab), as well as bronchial thermoplasty. The investigators used a theoretic model based on the US health care perspective, with a cohort of 10,000 adult patients affected by refractory asthma in an annual cycle and 10-year time horizon. The addition of bronchial thermoplasty to biologic treatment in responder patients was found to not be cost-effective. However, in biologic nonresponders, bronchial thermoplasty remained a cost-effective option as an add-on treatment. Mepolizumab without bronchial thermoplasty was the most cost-effective option for biologic responders, with a 10-year per-patient cost of \$116,776 and 5.46 QALYs gained (Institute for Clinical and Economic Review: \$21,388). Bronchial thermoplasty is a cost-effective treatment option only in the nonresponders group to biologic treatment (\$33,161 per QALY).

A recent draft guidance of the National Institute for Health and Care Excellence does not recommend mepolizumab as an add-on therapy for severe refractory eosinophilic

asthma. This is most certainly due to the fact that the costs of mepolizumab compared with usual asthma treatments are above the range usually considered to be a cost-effective use of National Health Service resources.⁴⁷

In the authors' opinion, because it occurred in the past for omalizumab, the increase in the number of eligible patients evaluated in clinical trials may dispel doubts about the real cost-effectiveness ratio of mepolizumab in clinical practice. Cost-effectiveness and pharmacoeconomics of the currently available, extremely expensive biologics approved for use in uncontrolled severe asthma (mepolizumab, reslizumab, and benralizumab) are not well-established figures. Studies in the future should be aimed at defining real-life usefulness of these drugs, and establishing their correct position in treatment guidelines. Pharmacoeconomic studies carried out so far are controversial, but it is likely that they will be necessary to work toward a reduction of purchase costs to extend the availability of these promising therapeutic options.

If Biologics Are Used for Asthma, What Is Their Duration of Benefit?

With respect to clinical benefits, economic evaluations of biologics as compared with pharmacotherapy have indicated that the cost-effectiveness of biologics primarily depends on the duration of the clinical benefit of biologics following treatment cessation.⁴⁸ For instance, one study showed that a reduction in the time horizon of the analysis had a negative impact on the cost-effectiveness of the biologic therapy omalizumab.⁵² Data on the duration of the clinical benefit of biologics used in economic evaluations were derived from clinical trials, observational studies, expert opinion literature, or authors' assumptions. Although assumptions were informed by clinical trials, the quality of the clinical evidence can be questioned, and uncertainty surrounds the quantitative estimate of the duration of clinical benefit following cessation of biologics.^{57–59} Data from the XPORT trial suggest that almost 50% of patients can be successfully withdrawn from omalizumab after 5 years of therapy. Factoring this into the pharmacoeconomic models would make omalizumab appear a much more favorable therapy.^{57–59}

What Is the Cost Benefit of Biologics Compared with Pharmacotherapy in Asthma Treatment?

With respect to costs, the cost-effectiveness of biologics as compared with pharmacotherapy depends on the break-even point of cumulative costs between treatment alternatives (ie, the point in time when cumulative costs of biologics equal cumulative costs of pharmacotherapy). Biologics (plus drugs as needed) tend to be more expensive during the first years of treatment, but cumulative costs of pharmacotherapy start to exceed those associated with biologics (if pharmacotherapy is able to be decreased or stopped altogether) at a later stage when biologics has stopped, but its clinical benefit is maintained. Although steps down in therapy after control is maintained is suggested, it is rarely practiced. The break-even point tends to differ between economic evaluations and cannot be transferred given that, for instance, cost estimates reported in economic evaluations are specific to the study setting, and is unlikely to be generalizable.⁶⁰

No economic evaluation has involved a direct comparison of biologics with the combination of biologics with subcutaneous immunotherapy^{61–64} except for one study that did not give a conclusive answer because of methodological limitations.⁶⁴ Therefore, the question of the cost-effectiveness of biologics versus biologics plus immunotherapy has not been resolved to date. The literature does suggest that any future economic evaluation needs to consider such aspects as safety profile, compliance rate, and administrative costs, which may affect the cost-effectiveness of sublingual versus subcutaneous

immunotherapy.⁶⁴ Also, where the biologic is given—intravenously or subcutaneously in a medical facility or subcutaneously at home—needs to be considered.

The literature on the cost-effectiveness of biologics consists of studies conducted in Europe and in the United States. The results of these studies should be interpreted with care when assessing their generalizability to another country because the patient population and the specific biologics and administrative costs used are likely to vary between countries, as well as the funding, organization, regulation, and real-life practices governing biologic use in asthma.

Existing economic evaluations have used a variety of outcome measures, such as the peak expiratory flow rate, symptom scores, the number of symptom-free days, the number of patients free from symptoms, and the number of exacerbations. This makes it difficult to compare cost-effectiveness results between studies. Existing economic evaluations of respiratory allergy have shown that improvement in these outcome measures resulting from biologics translate into better QOL.⁶⁵ However, there is a need for additional economic evaluations that consider QOL by means of instruments such as the EQ-5D (QOIL scale used in Europe Don).⁶⁶ This instrument can be used to calculate QALYs and to express the cost-effectiveness of immunotherapy in terms of the additional costs per QALY gained as compared with the alternative. Comparing it with the threshold value set by the health care industry, the payer can then assess the cost-effectiveness of asthma biologics. For instance, the National Institute for Health and Clinical Excellence in England and Wales uses a threshold value of £20,000–£30,000 per QALY⁴² that determines which health technologies will be recommended for use by the National Health Service. Economic evaluations of biologics like immunotherapy for asthma should be carried out with real world clinical studies. Thus, cost-effectiveness can be based on randomized controlled trials to provide a degree of internal validity, whereas analyses based on observational studies reflect real-life practice. Alternatively, the use of modeling techniques that critically depend on the study design and the quality of data that are extracted from the literature or other sources are used as input in the cost-effectiveness model.⁶⁵

Some economic evaluations included direct health care costs from the perspective of the third-party payer or the health care system. As a result, these studies focused on the costs of biologics and examined the cost impact of biologics on the use of medicines, physician consultations and hospitalization, ED visits, and exacerbations.⁶⁵ The central outcome of exacerbations and use of OCSs most often determines biologic use in asthma. OCS use is the way most physicians determine the number of exacerbations in a patient. This exacerbation history is most often not based on pharmacy data of oral steroid use but on patient history. However, data suggest that relying on patient history could miss as many as 58% of patients who have had 3 or more exacerbations in the past year.⁴⁴ Identifying these patients can result in additional interventions that would further reduce their risk for future exacerbations, so a review of pharmacy refill data for OCS bursts, rather than patient history alone, should become a routine component of comprehensive care for asthma patients. Also, although OCS may help control asthma and manage exacerbations, it must be considered that OCS side effects may result in additional health care resource use and costs, highlighting the need for OCS-sparing asthma therapies.^{19,20}

A central and extremely important issue is that biologic use is predicated on the number of asthma exacerbations, which for most physicians involves asking the patient how many bursts of OCS they have been on in the past year. The issue is that this is often not a reliable number and may underestimate OCS use.⁴⁴ Although OCS are economical from a drug-cost and acquisition perspective, OCS have been associated with dose- and duration-dependent debilitating adverse events, including bone fractures, diabetes mellitus, infections, hypertension, and cataracts. Thus,

evidence related to the economic costs attributable to OCS-related side effects has the potential to inform health care insurance company about the tradeoffs of OCS use versus trial of biologic for improved asthma control. Thus, it is high-OCS users with possible OCS-related side effects that are more likely to use health care services than those without such side effects.⁶⁵

EMBRACING QUALITY HEALTH CARE IN THE UNITED STATES

There is pressure on medical providers to embrace payment reform models that give incentives to provide the right care, to the right patient, at the right venue, at the right time, and at the right cost. The United States is at the core of multiple experiments aimed to shift care delivery from a volume-based to a value-based system. On April 16, 2015, President Obama signed into law H.R. 2, the Medicare Access and CHIP Reauthorization Act, a bill that ushers in a new era in physician payment for Medicare. Under either the Merit-based Incentive Payment System (MIPS) or alternative payment models, health care providers will assume some level of financial risk for their clinical decisions. On April 27, Centers for Medicare and Medicaid Services published proposed rules on MIPS implementation and the process and requirements Alternative Payment Models must meet in order to be classified as Advanced Alternative Payment Models. Although fee-for-service is all about volume and reinforces work in silos with little incentive to integrate, the new emphasis for physician reimbursement is on value, with the triple aim of improving quality, enhancing the patient consumer experience, and most importantly, constraining cost growth.

There are huge problems with the current pharmacoeconomic analysis of the costs of biologics in asthma and other immune diseases. Because of fragmented, inefficient, and unorganized delivery of care, extreme variability in treatment practices without apparent benefits, misalignment of incentives, lack of transparency in pricing and costs, and inadequate pharmacoeconomic data to assess value (ie, interaction of quality, cost and patient satisfaction, and experience), biologics and asthma treatment costs are on an unsustainable course. Until some of these issues are addressed and repaired, cost-effective utilization of biologics may remain a mystery.

So What Can Insurance Companies, Society, and Caregivers Do to Move the Study of Pharmacoeconomics of Biologics in the Right Direction? Furthermore, How Can Pharmacoeconomics Enhance the Physicians' and Patients' Outcomes and Reduce Direct Costs, Indirect Costs, and Long-Term Complication Costs?

Improvements in the study of pharmacoeconomics are an aid to decision making with strong potential to:

- Mitigate the influence of marketing
- Help put physicians in the driver's seat
- Enhance the position of allergists from payer's perspective
- Help set practice priorities
- Affect Medicare plans to decrease payout to stem the tide of budget deficits
- Help private payers actively develop quality report cards

POTENTIAL PROBLEMS INTERPRETING PHARMACOECONOMIC DATA

1. The cost of uncontrolled asthma and immune disease is significant and increasing.
2. The cost of an intervention is only partly reflected in drug acquisition costs, and a great deal of the accuracy of pharmacoeconomic evaluations depends on ability to measure change in total disease costs.

3. The pharmacoeconomic equation changes based on the variation in importance of the various costs to user of the data. The individual and family will place more importance on sleep and cough, the employer and perhaps society on productivity, and the ACO on direct costs only without full appreciation for QOL or presenteeism.
4. Drug acquisition data have often been obtained from studies of all comers, completely contrary to personalized medicine, and if personalized therapy is the goal, the pharmacoeconomic data of relevance are the cost-benefits in that population. For example, what are the pharmacoeconomic data for anti-IL-5 biologic therapies in all patients versus patients with blood eosinophil levels of 150, 300, and 400 cells per microliter? The equations will look quite different.
5. Only models that look at responders, with discontinuation of drug in nonresponders, is appropriate. Models looking at 5- or 10-year costs with a drug continued is clinically irrelevant.
6. Models must account for all costs. Hidden direct costs are often overlooked. Indirect costs are difficult to measure and typically ignored but are extremely important to many users of pharmacoeconomic data.
7. Most importantly, pharmacoeconomic data are most appropriately evaluated not using drug versus no drug, but drug versus alternative therapy.
8. That leads to the importance of evaluating all costs of alternative therapy, including the costs of side effects. Because alternative therapy is typically OCSs, it is critical to better understand the costs of side effects of OCSs, both medical and psychiatric.
9. The hidden direct costs and indirect costs, including the ability to put a cost on QOL, are critical for evaluating omalizumab for hives and dupilumab for atopic dermatitis, in which direct costs may not be as great as with respiratory disease.
10. The omalizumab pediatric indication and upcoming dupilumab atopic dermatitis approval make it even more important to understand the costs of disease on parents and caregivers. This is almost invariably overlooked.

SUMMARY

Poorly controlled, therapy-resistant asthma negatively impacts QOL and health care costs. Medication adherence, socioeconomic factors, and other factors complicate asthma biologic treatments. Cost-effective models of biologic use commonly evaluate the benefit of treatments using QALYs that incorporate both the quantity and the quality of life. Cost-effectiveness information on biologic use can thus assist decision makers in evaluating the overall value of a new treatment or new technology. Long-term savings to the health care system do not always result in short-term patient or payer savings. Pharmacoeconomics and outcomes research can enhance the quality of the practice by strengthening the evaluation process and increasing the probability that better value in patient care is delivered. More of the costs in biologics will be borne by the patients in the future because these patients already have high indirect costs. The international literature suggests that biologics may be cost-effective as compared with pharmacotherapy for certain asthma phenotypes. One economic evaluation has suggested that biologics as compared with pharmacotherapy is unlikely to be cost-effective for asthma. The reader should note that this evidence originated from a limited number of economic evaluations that suffered from several methodological shortcomings. The question of the cost-effectiveness of biologics versus pharmacotherapy has not been resolved to date. No economic evaluation has examined the cost-effectiveness of biologics in asthma taking into account the comorbidities that

the biologic also improves. Time and money can only be spent once, so choice is inevitable. Whether done unconsciously or with a consistent process, health care professionals are constantly evaluating care choices and acting on them.

REFERENCES

1. Eisenberg JM. Clinical economics: a guide to the economic analysis of clinical practices. *JAMA* 1989;262:2879–86.
2. Trueman P, Drummond M, Hutton J. Developing guidance for budget impact analysis. *Pharmacoeconomics* 2001;19:609–21.
3. Centers for Disease Control and Prevention. Most recent asthma data. In: CDC website. 2016. Available at: http://www.cdc.gov/asthma/most_recent_data.htm. Accessed June 30, 2016.
4. Centers for Disease Control and Prevention. Asthma facts: CDC's National Asthma Control Program Grantees. In: CDC website. 2013. Available at: http://www.cdc.gov/asthma/pdfs/asthma_facts_program_grantees.pdf. Accessed November 18, 2015.
5. Bahadori K, Doyle-Waters MM, Marra C, et al. Economic burden of asthma: a systematic review. *BMC Pulm Med* 2009;9:24.
6. Reddel HK, Bateman ED, Becker A, et al. A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J* 2015;46:622–39.
7. Healthcare Cost and Utilization Project (HCUP). Chronic Condition Indicator (CCI) for ICD-9-CM. In: HCUP website. 2016. Available at: <http://www.hcup-us.ahrq.gov/toolssoftware/chronic/chronic.jsp>. Accessed July 8, 2016.
8. Heaney LG, Djukanovic R, Woodcock A, et al. Research in progress: medical research council United Kingdom refractory asthma stratification programme (RASP-UK). *Thorax* 2016;71(2):187–9.
9. Nair P, Pizzichini MM, Kjarsgaard M, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;360:985–93.
10. Haldar P, Brightling CE, Hargadon BN, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360:973–84.
11. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;371:1198–207.
12. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014;371:1189–97.
13. Cangelosi MJ, Ortendahl JD, Meckley LM, et al. Cost-effectiveness of bronchial thermoplasty in commercially insured patients with poorly controlled, severe, persistent asthma. *Expert Rev Pharmacoecon Outcomes Res* 2015;15(2):1–8.
14. Einarson TR, Bereza BG, Nielsen TA, et al. Systematic review of models used in economic analyses in moderate-to-severe asthma and COPD. *J Med Econ* 2016;19(4):319–55.
15. Antonova E, Trzaskoma B, Omachi TA, et al. Poor asthma control is associated with overall daily activity impairment: 3-year data from the EXCELS study of omalizumab. *J Allergy Clin Immunol* 2016;137(2 Suppl 1):AB14.
16. Morishima T, Ikai H, Imanaka Y. Cost-effectiveness analysis of omalizumab for the treatment of severe asthma in Japan and the value of responder prediction methods based on a multinational trial. *Value Health Reg Issues* 2013;2:29–36.
17. Barnett SBL, Nurmagambetov TA. Costs of asthma in the United States: 2002–2007. *J Allergy Clin Immunol* 2011;127(1):145–52.

18. Rowe B, Spooner C, Ducharme F, et al. Corticosteroids for preventing relapse following acute exacerbations in asthma. *Cochrane Database Syst Rev* 2007;(3):CD000195.
19. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol* 2013;9(1):30.
20. Luskin AT, Antonova E, Broder MS, et al. Healthcare resource use and costs associated with possible side effects of high oral corticosteroid use in asthma: a claims-based analysis. Presented at: Academy of Managed Pharmacy NEXUS 2015. Orlando (FL), October 26–28, 2015.
21. Dominguez-Ortega J, Phillips-Angles E, Barranco P, et al. Cost-effectiveness of asthma therapy: a comprehensive review. *J Asthma* 2015;52:529–37.
22. 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;4:120–9.
23. Diaz RA, Charles Z, George E, et al. NICE guidance on omalizumab for severe asthma. *Lancet Respir Med* 2013;1:189–90.
24. Galli SJ. Toward precision medicine and health: opportunities and challenges in allergic diseases. *J Allergy Clin Immunol* 2016;137:1289–98.
25. Hood L. Systems biology and P4 medicine: past, present, and future. *Rambam Maimonides Med J* 2013;4(2):e0012.
26. Ferkol T, Quinton P. Precision medicine: at what price? *Am J Respir Crit Care Med* 2015;192:658–9.
27. Joyner MJ, Paneth N. Seven questions for personalized medicine. *JAMA* 2015; 314:999–1000.
28. Akdis CA, Akdis M. Advances in allergen immunotherapy: aiming for complete tolerance to allergens. *Sci Transl Med* 2015;7:280ps6.
29. Marcum ZA, Sevick MA, Handler SM. Medication nonadherence: a diagnosable and treatable medical condition. *JAMA* 2013;309(20):2105–6.
30. Goldberg EL, Dekoven M, Schabert VF, et al. Patient medication adherence: the forgotten aspect of biologics. *Biotechnol Healthc* 2009;6(2):39–42, 44.
31. Bender BG. Overcoming barriers to nonadherence in asthma treatment. *J Allergy Clin Immunol* 2002;109(6 Suppl):S554–9.
32. Cisternas MA, Blanc PD, Yen IH, et al. A comprehensive study of direct and indirect costs of adult asthma. *J Allergy Clin Immunol* 2003;111:1212–8.
33. Colice GJ, Wu EQ, Birnbaum H, et al. Healthcare and workloss costs associated with patients with persistent asthma in a privately insured population. *Occup Environ Med* 2006;48:794–802.
34. Norman G, Faria R, Paton F, et al. Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation. *Health Technol Assess* 2013;17(52):1–342.
35. Humbert M, Beasley R, Ayres J, 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(3):309–16.
36. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;313:275–83.
37. Maetzel A, Tugwell P, Boers M, et al. Economic evaluation of programs or interventions in the management of rheumatoid arthritis: defining a consensus-based reference case. *J Rheumatol* 2003;30:891–6.

38. Economics Working Group report. a proposal for a reference case for economic evaluation in rheumatoid arthritis. *J Rheumatol* 2003;30:886–90.
39. Oba Y, Salzman G. Cost-effectiveness analysis of omalizumab in adults and adolescents with moderate-to-severe allergic asthma. *J Allergy Clin Immunol* 2004; 114:265–9.
40. Zafari Z, Sadatsafavi M, Marra CA, et al. Cost-effectiveness of bronchial thermoplasty, omalizumab, and standard therapy for moderate-to-severe allergic asthma. *PLoS One* 2016;11(1):e0146003.
41. Tice JA, Ollendorf D, Campbell JD, et al. Mepolizumab (Nucala, GlaxoSmithKline plc.) for the treatment of severe asthma with eosinophilia: effectiveness, value and value-based benchmarks: final report. Boston: Institute for Clinical and Economic Review; 2016.
42. National Institute for Health and Care Excellence (NICE). Omalizumab for treating severe persistent allergic asthma. In: NICE website. 2013. Available at: <https://www.nice.org.uk/guidance/ta278>. Accessed July 10, 2016.
43. Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systemic review. *Chest* 2011;139:28–35.
44. Bukstein D, Steven G, Luskin A. Pharmacy data more reliable at predicting asthma exacerbations. Presented at: American College of Allergy, Asthma and Immunology (ACAAI) annual meeting. Baltimore (MD), November 7–11, 2015. [abstract: 72].
45. UK Medicines Information. New drugs online report for mepolizumab. In: UK Medicines Information website. Available at: http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID4675. Accessed March 6, 2016.
46. Institute for Clinical and Economic Review (ICER). ICER draft reports on Nucala® (mepolizumab) for asthma and Tresiba® (insulin degludec) for diabetes posted for public comment edit. In: ICER website. 2015. Available at: <http://www.icer-review.org/icer-draft-reports-on-nucala-mepolizumab-for-asthma-and-tresiba-insulin-degludec-for-diabetes-posted-for-public-comment>. Accessed March 5, 2016.
47. Bogart M, Roberts A, Wheeler S. Cost-effectiveness of refractory asthma treatment strategies: a decision tree analysis. *Value Health* 2015;18:A174.
48. Kuprys-Lipinska I, Piotr Kuna P. Loss of asthma control after cessation of omalizumab treatment: real life data. *Postepy Dermatol Alergol* 2014;31(1):1–5.
49. Molimard M, Mala L, Bourdeix I, et al. Observational study in severe asthmatic patients after discontinuation of omalizumab for good asthma control. *Respir Med* 2014;108(4):571–6.
50. Nopp A, Johansson SG, Adedoyin J, et al. After 6 years with Xolair: a 3-year withdrawal follow-up. *Allergy* 2010;65:56–60.
51. Bonifazi F, Jutel M, Bilo BM, et al. EAACI Interest Group on Insect Venom Hypersensitivity. Prevention and treatment of hymenoptera venom allergy: guidelines for clinical practice. *Allergy* 2005;60:1459–70.
52. Turner SJ, Nazareth T, Raimundo K, et al. Impact of omalizumab on all-cause and asthma-related healthcare resource utilization in patients with moderate or severe persistent asthma. *Am J Respir Crit Care Med* 2014;189:A6580.
53. Bégin P, Dominguez T, Wilson SP, et al. Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using Omalizumab. *Allergy Asthma Clin Immunol* 2014;10(1):7.

54. Schneider LC, Rachid R, LeBovidge J, et al. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. *J Allergy Clin Immunol* 2013;132:1368–74.
55. Pauwels B, Jonstam K, Bachert C. Emerging biologics for the treatment of chronic rhinosinuitis. *Expert Rev Clin Immunol* 2015;11(3):349–61.
56. Umetsu DT. Targeting IgE to facilitate oral immunotherapy for food allergy: a potential new role for anti-IgE therapy? *Expert Rev Clin Immunol* 2014;10(9):1125–8.
57. Busse WW, Trzaskoma B, Omachi TA, et al. Evaluating omalizumab persistency of response after long-term therapy (XPORT). Presented at the Annual Meeting of the American Thoracic Society (ATS). San Diego (CA), May 16–21, 2014. [abstract: A31].
58. Busse W, Trzaskoma B, Omachi TA, et al. Evaluating omalizumab persistency of response after long-term therapy (XPORT). Presented at the Annual Meeting of the European Respiratory Society (ERS). Munich (Germany), September 6–10, 2014. *Eur Respir J* 2014;44(Suppl 58):P3485.
59. Antonova J, Trzaskoma B, Raimundo K, et al. Longitudinal change in asthma symptom control in patients who continued vs discontinued omalizumab: results from the XPORT study. Presented at the 71st American College of Allergy, Asthma & Immunology (ACAAI) annual scientific meeting. Atlanta (GA), November 8–11, 2014.
60. Campbell JD, McQueen RB, Briggs A. The “e” in cost-effectiveness analyses: a case study of omalizumab efficacy and effectiveness for cost-effectiveness analysis evidence. *Ann Am Thorac Soc* 2014;11(Suppl 2):S105–11.
61. Larenas-Linnemann D, Wahn U, Kopp M. Use of omalizumab to improve desensitization safety in allergen immunotherapy. *J Allergy Clin Immunol* 2014;133(3):937–937.e2.
62. Kamin W, Kopp MV, Erdnuess F, et al. Safety of anti-IgE treatment with omalizumab in children with seasonal allergic rhinitis undergoing specific immunotherapy simultaneously. *Pediatr Allergy Immunol* 2010;21(1 Pt 2):e160–5.
63. Casale TB, Stokes JR. Future forms of immunotherapy. *J Allergy Clin Immunol* 2011;127:8–15.
64. Casale TB, Busse WW, Kline JN, et al. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2006;117:134–40.
65. Sullivan PW, Campbell JD, Ghushchyan VH, et al. Characterizing the severe asthma population in the United States: claims-based analysis of three treatment cohorts in the year prior to treatment escalation. *J Allergy Clin Immunol* 2014;133(Suppl 2):AB41.
66. Pickard AS, Wilke C, Jung E, et al. Use of a preference-based measure of health (EQ-5D) in COPD and asthma. *Respir Med* 2008;102(4):519–36.