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Rapid Review

Bronchial thermoplasty and biologic agents as proposed targeted therapies for the treatment of severe uncontrolled asthma

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Summary

Although a small minority of patients with asthma has severe disease, it accounts for a majority of the morbidity related to the illness. Severe asthma represents a heterogeneous group of phenotypes. Targeted therapies for these phenotypes represent a major advance in the management of severe asthma. Omalizumab, a monoclonal antibody to IgE, significantly improves control in patients with a predominant allergic phenotype. Monoclonal antibodies targeted to IL-4 α and IL-5 have shown substantial benefit in patients with the eosinophilic asthma phenotype and to IL-13 in patients with a T2 phenotype. A new device to reduce airway smooth muscle, bronchial thermoplasty, has been shown to improve symptoms and reduce exacerbations in patients with severe uncontrolled asthma and the chronic airflow obstruction phenotype. While awaiting comparative trials between these treatments, we can now use a targeted approach with these phenotypes using the best evidence to guide our selection. This rapid review will focus on the latest developments in these newer therapies and inform the clinician on how to select the appropriate patient for these treatments.

Although most asthma patients can be adequately treated with current medical therapies, there are 5 to 10 percent of asthmatics with limited therapeutic options and substantial morbidity due to the severity of their illness.^{1,2} Once the diagnosis of asthma has been confirmed and comorbidities addressed, the European Respiratory Society (ERS) and American Thoracic Society (ATS) defines severe asthma as requiring management with high dose inhaled corticosteroids in addition to a second asthma controller, including the potential use of systemic corticosteroids. This regimen must be required to prevent symptoms from being uncontrolled or the symptoms are uncontrolled despite that therapy.² It is now evident that severe asthma represents a heterogeneous group of phenotypes rather than one disease entity.^{1,3} This can partly be explained by several mechanisms that contribute to the pathophysiology of the illness (referred to as “endotypes”).⁴ Some of those etiological factors include airway inflammation, increased mucous production, chronic airflow obstruction, and airway smooth muscle hyperresponsiveness.^{5,6} Along with these clinical characteristics, molecular, cellular, and structural elements play a role in the categorization of specific phenotypes.

Treatment for severe asthma is now focusing on tailoring to particular phenotypes driven by the endotypes.² Over the last three decades, therapeutic strategies have focused on the use of anti-inflammatory and bronchodilator drugs for the treatment of severe asthma. Recent advances in therapeutics have now given us new strategies to modulate the smooth muscle with bronchial thermoplasty (BT) or block eosinophilic driven disease with biologic therapy. This *Rapid Review* will focus on the latest developments in these areas and how clinicians could potentially select the right patient for these treatments.

Asthma Phenotypes

Unbiased analysis of rich data sets with clinical, physiologic and biologic variables have identified new phenotypes to better understand the heterogeneity of asthma. The Severe Asthma Research

Program [SARP] cluster analysis⁷ identified five distinct clinical phenotypes. Clusters 1 and 2 consisted of mostly younger, female patients with early onset atopic asthma and normal baseline lung function or lung function that reversed to normal. In contrast, cluster 3 included older women with a higher body mass index and late onset asthma with a more restrictive physiology. Patients in the last two clusters had a longer duration of disease and a severe reduction in baseline lung function. However, those in Cluster 4 tended to reverse to near normal lung function while the other cluster did not (fixed obstructive defect). Another group from Leicester using a similar unbiased analysis included sputum eosinophil counts.⁸ They found similar early onset atopic-asthma, an obese non-eosinophilic asthma, an early onset symptom predominant-asthma, and a later onset eosinophilic predominant asthma. Therefore these cluster analysis begin to identify potential endotypes that are driving these phenotypes.

When considering a molecular basis for asthma phenotypes (Figure 1), the degree of type 2 [T2] inflammation can be a distinguishing feature.^{9,10} T2 inflammation is mediated by interleukin-4 [IL-4], interleukin-5 [IL-5], and interleukin-13 [IL-13] released from lymphocytes, basophils and mast cells. T2-high and T2-low are two distinct groups identified by gene expression analysis.¹¹ These groups exhibited significant differences in eosinophil count in the airway and blood, serum immunoglobulin E (IgE), and expression of IL-5 and IL-13. Although T2-high asthma patients responded to inhaled corticosteroids with an improvement in lung function, this response was not evident in the T2-low patient population. Newer therapies targeting those specific inflammatory cytokines have been developed and will be reviewed. However, these biologic agents are limited to specific phenotypes, likely those which would fall into the T2-high category. Asthma that is non-T2 high, non-eosinophilic or pauci-granulocytic driven represents an important subgroup of patients with severe disease that has not been well defined as an endotype and no specific therapy exists for these patients besides inhaled corticosteroids and bronchodilators.

Severe allergic asthma is associated with high serum IgE levels, high eosinophils, and high fractional expired exhaled nitric oxide (FeNO).^{3,12} Therapy targeted towards inhibiting IgE, IL-4, IL-13, and the IL-4 receptor can be applied to this group. Aspirin sensitive asthma and aspirin exacerbated respiratory disease (AERD) is also associated with high blood eosinophils, FeNO and elevated urinary LTE₄ and therapy targeting leukotrienes, aspirin desensitization and IL-5 appear to be effective in this endotype.^{13,14} Severe non-atopic asthma is also often associated with evidence of eosinophilic airway inflammation. Treatments targeted to IL-4, IL-5, IL-13, and the IL-4 α receptor are options in this subset.¹⁵⁻¹⁸

There is a subset of severe asthma patients that have decreased sensitivity to corticosteroids. They may exhibit increased neutrophils in sputum, but specific associations to this phenotype have not been established. Macrolides have been studied and may be more effective in non-eosinophilic patients¹⁹, but there is no strong evidence to support their use as a targeted therapy.²⁰

Some severe asthma patients that do not respond to corticosteroids have also been found to have persistently elevated sputum eosinophil counts.²¹ Bronchial epithelial cells release eosinophil chemotactic factors, such as CCL26 that activate eosinophils. Larose et al have shown that IL-13 induces selective production of CCL26 and that sputum CCL26 levels correlate with the severity of asthma and sputum eosinophil counts.²² Further research is needed to determine if CCL26 may be a valuable biomarker to categorize the corticosteroid insensitive eosinophilic phenotype.

Chronic airflow obstruction is likely due to increased airway wall thickness from airway remodeling due to a variety of mechanisms including epithelial thickening, subepithelial fibrosis, smooth muscle hypertrophy, inflammatory cell infiltration, and goblet cell hyperplasia.^{5,23} Multidetector CT [MDCT] has been used to quantify the degree of remodeling by measuring airway wall thickness. Patients with severe asthma had a greater wall thickness when compared to healthy patients and those with mild to moderate disease.²³ Wall area and wall thickness were inversely

related to baseline FEV₁ percent predicted and positively correlated with responses to bronchodilators. Biologic therapies may provide an opportunity to reverse this remodeling process using quantitative wall thickness as a biomarker but to date it only has been shown in one small pilot with anti-IL5 therapy.²⁴ Although this study showed a significant decrease from baseline of the airway wall area measured by CT scan in the group treated with mepolizumab, this does not allow for determining the specific mechanisms involved. BT also represents a promising therapy to reverse airway remodeling.

Bronchial thermoplasty (BT)

BT aims to reduce airway smooth muscle mass in an effort to treat smooth muscle hypertrophy as its contraction may worsen bronchoconstriction and bronchial hyperreactivity (Figure 2).^{25,26} BT is delivered by the Alair Bronchial Thermoplasty System [Boston Scientific] and consists of a radiofrequency controller and a catheter. After insertion of the catheter through a compatible bronchoscope, thermal energy is delivered through the catheter to the walls of airways from the distal 3 mm airways to the proximal mainstem bronchi. Three separate bronchoscopies are completed approximately three weeks apart. In 2010, the FDA approved BT for the treatment of severe asthma adults with uncontrolled symptoms despite inhaled corticosteroids and long-acting bronchodilators.

Three randomized trials support the use of BT as a treatment modality for uncontrolled asthma with long-term follow-up now available out to 5 years.^{25,27-30} Although there was an increase in adverse events in the BT group during the treatment period in all three trials, there was an improvement in asthma symptoms in the BT group compared with the control group in the post-treatment period. The Asthma Research Intervention [AIR] trial, a randomized, multi-centered trial that included patients with moderate to severe persistent asthma, showed fewer mild exacerbations, improvement in symptom free days and asthma control and improved quality of life in the BT

treatment group at 3 and 12 months.²⁵ The Research in Severe Asthma [RISA] trial, a randomized, multi-centered trial for severe asthma demonstrated a significant reduction in rescue inhaler use and improvement in asthma control, pre-bronchodilator FEV₁ and quality of life at 22 weeks post treatment.²⁹ A limitation of the AIR and RISA trials was that they were non-blinded which may contribute to a significant placebo effect. However, the subsequent trial known as the AIR-2 trial was a sham-controlled, randomized, multi-centered, trial showing an improvement in quality of life, fewer days lost from work, and a reduction in severe exacerbations and healthcare utilization.²⁸ A limitation of this trial was that the sham group also had an improvement in their quality of life. However, this could be attributed to the attention given to participants by the study staff and the preconceived expectations of this new, promising therapy. Both the RISA and AIR 2 trial patients had up to 5 year follow up evaluations. Subsequent 5-year follow-up of patients treated in these trials have shown no change in lung function and a sustained reduction in exacerbations and healthcare utilization.^{30,31} There were no structural changes in the airways from BT based on review of CT scans 5 years later compared with baseline.^{27,30} It is important to note that all clinical trials of BT recruited patients with evidence of variable airflow obstruction as indicated by marked bronchodilator reversibility, a low methacholine PC₂₀, and/or a prompt deterioration after withdrawal of LABA. Some caution is needed in extrapolating clinical benefits beyond this population. It is also important to note that patients with an FEV₁ of less than 50 percent predicted and greater than three exacerbations per year were excluded from these trials.

Recent data demonstrates that BT works in part by reducing airway smooth muscle. At least two different groups have demonstrated reduction in airway smooth muscle following BT by 60+%.³²⁻³⁴ This reduction in smooth muscle appears to occur in a few weeks after the treatment with effects on adjacent untreated airways also noted. In addition to the reduction in airway smooth muscle, there has been a reduction in subepithelial fibrosis, another important component of airway remodeling.³³

Denner et al found that this was accompanied by a reduction in transforming growth factor- β_1 , CCL5 and eosinophils in the bronchoalveolar lavage.³² Lastly, data from an abstract by Aubier and colleagues suggests that this reduction in smooth muscle is also accompanied by a reduction in nerve cell receptors.³⁵ While these insights into the pathophysiologic mechanisms involved with BT have been helpful, further work is needed to assess the long term impact on airway remodeling as measured by quantitative CT. Given the long term follow up data from these randomized controlled trials, it appears we now have a therapy for the treatment of severe asthma that is truly disease modifying.

In an effort to develop predictors of BT response, lung function parameters, asthma control and quality of life, healthcare utilization, and demographic data were presented in an abstract of forty two patients undergoing BT at baseline and up to twelve months post BT.³⁶ Baseline chest MDCT was analyzed to measure wall area percentage in segmental airways and lung density to evaluate air trapping. A shorter duration of asthma and more frequent exacerbations in the year prior was predictive of an improvement in asthma control and quality of life. Less air trapping on MDCT was associated with a trend towards predicting BT response. Patients with a higher baseline oral corticosteroid dose, lower quality of life, and older age had significant subsequent reduction in oral corticosteroid and/or inhaled corticosteroid dose. Further studies are needed to determine phenotypes of BT response.

Biologic agents

Anti-Immunoglobulin E

Because IgE plays a major role in the pathophysiology of asthma, therapies targeted to IgE mediated pathways have been shown to be beneficial (Figure 2). IL-4 and IL-13 promote B lymphocytes to produce IgE and most patients with asthma have elevated IgE levels.³⁷ After B cells are stimulated and mature into plasma cells, they secrete IgE specific to various allergens and bind to

receptors on mast cells and basophils. Activation of these cells causes mediators to be released that result in bronchoconstriction. Omalizumab is an IgG1k monoclonal antibody that has a high affinity to IgE. Binding of the agent to IgE creates complexes that prevent its interaction with receptors on mast cells, basophils, and other cell lines.¹² Omalizumab is approved for use in adolescents and adult patients with moderate to severe persistent asthma and symptoms that are uncontrolled with inhaled corticosteroids. Patients must also demonstrate positive allergen skin testing and a total serum IgE level between 30-700 (U.S.) or -1500 (E.U.) international units/mL. A Cochrane database review concluded that in patients with moderate or severe asthma receiving inhaled corticosteroid therapy, omalizumab significantly reduced hospitalizations and asthma exacerbations compared to placebo.³⁸ While most of the trials were done in patients with moderate asthma, there is recent evidence to support its benefit in patients with severe disease. A randomized, multicenter trial that included patients with uncontrolled asthma despite treatment with LABAs plus high dose inhaled corticosteroids showed a significant reduction in asthma exacerbations (~25%) and ability to decrease corticosteroid dose with omalizumab.³⁹ This data is supported by the recent ERS/ATS guidelines that recommend a therapeutic trial of omalizumab should be considered in patients with severe allergic asthma.² The clinician should assess response to treatment by considering factors such as quality of life, frequency of exacerbations, and healthcare utilization. If no improvement is observed after four months of therapy, it is not likely that further treatment will provide benefit. A *post hoc* analysis of omalizumab trials suggests it may work in T2 predominant asthma and that the blood eosinophil count and FeNO are better biomarkers of response than IgE.⁴⁰ There is also growing evidence of a response to omalizumab in non-atopic patients with eosinophilic asthma. However, prospective confirmation of these findings is needed. Those patients with severe asthma with a less allergic component should be considered for BT. Those patients with a predominant severe eosinophilic phenotype should be considered for therapy directed against IL-5 and the IL-5 receptor.

Anti-Interleukin-5

Patients with the eosinophilic asthma phenotype have an increased frequency of exacerbations and this has been compellingly linked to eosinophilic airway inflammation.⁴¹ IL-5 is a cytokine that is directly involved in the activation and recruitment of eosinophils (Figure 2). Biologic agents that inhibit IL-5 and subsequently reduce blood and airway eosinophil counts have been shown to improve asthma control and decrease the rate of exacerbations¹⁵. Mepolizumab is a recently FDA-approved monoclonal antibody directed against IL-5 that reduces sputum and blood eosinophils. Several randomized controlled trials have documented the benefit of mepolizumab^{15, 28, 29} in patients with uncontrolled eosinophilic asthma (blood eosinophils >150 cells/ μ l) by reducing exacerbations (Dose Ranging Efficacy And safety with Mepolizumab [DREAM] trial)⁴², reducing oral corticosteroid dose (²¹, Steroid Reduction with Mepolizumab Study [SIRIUS] trial⁴³ and improving asthma control (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma [MENSA] trial¹⁸. Less consistent effects in improving FEV₁ with mepolizumab have been found⁴², perhaps due to incomplete clearance of airway eosinophils. Mepolizumab 100 mg subcutaneously (SC) should be considered in patients with uncontrolled eosinophilic asthma, especially those with prior exacerbations and on chronic oral corticosteroids.

Reslizumab is an IgG4k monoclonal antibody targeted to IL-5, preventing it from binding to eosinophils. A randomized, placebo-controlled study to evaluate the impact of reslizumab on the patients with uncontrolled eosinophilic (blood eosinophils >400 cells/ μ l) asthma despite high-dose inhaled corticosteroid use showed a significant decrease in sputum eosinophils, improvement in lung function and trend towards improved asthma control in the treatment group.⁴⁴ The effect of reslizumab was even greater in those with nasal polyps likely reflecting the effect of anti-IL 5 on the eosinophilic infiltration noted in these polyps. A larger subsequent randomized controlled trial

demonstrated a marked reduction in exacerbations (~50-60%) with an associated improvement in lung function (~220 ml) in those treated with reslizumab.⁴⁵ Reslizumab (3 mg/kg intravenously every month) should be considered in patients with uncontrolled eosinophilic asthma, especially those with prior exacerbations, reduced lung function or nasal polyposis.

Unlike these other anti-IL5 agents, benralizumab is an IgG1k monoclonal antibody that targets the human IL5-receptor alpha expressed on basophils and eosinophils and depletes eosinophils through antibody-dependent cell-mediated cytotoxicity. When patients with eosinophilic uncontrolled asthma were treated, benralizumab was found to decrease eosinophils in sputum and blood⁴⁶ while decreasing exacerbations and improving asthma control.¹⁷ Patients with a blood eosinophil count of at least 300 cells per uL had a significant decrease in asthma exacerbations (40-60%) when treated with benralizumab at 20 mg and 100 mg SC every month. Further studies to examine the exact dose of benralizumab to be used in larger populations are being conducted.

The efficacy of treatment with anti-IL-5 monoclonal antibodies is strongly associated with both the prior exacerbation history and the blood eosinophil count. High exacerbation rates and blood eosinophil counts are associated with a better response. The blood eosinophil count appears to be a better biomarker of response than more direct measures of eosinophilic airway inflammation such as FeNO and sputum eosinophils suggesting that a reduction in circulating eosinophils is the main treatment target.⁴² The optimum cut point of blood eosinophil count for a response to anti-IL-5 remains to be defined and will depend to some extent on the expected benefit of treatment. However, clear evidence of efficacy is apparent with all of the above agents at a blood eosinophil count of >300-400 cells/mm³. Traditional measures of asthma such as lung function and symptom scores are not predictive of a response to treatment and are less responsive to treatment than exacerbations. The differential effect of treatment on different outcomes emphasizes that morbidity in severe asthma is the result of more than one independent pathway. This has important implications for how we

monitor the response to treatment with anti-IL-5 as a symptom or lung function based approach is unlikely to be sufficient.

Anti-Interleukin-4/Interleukin-13

IL-13 induces production of a protein, periostin that is implicated in airway remodeling (Figure 2). Lebrikizumab is an IgG4 monoclonal antibody that targets IL-13, inhibiting its function. A randomized trial including asthma patients with uncontrolled symptoms despite ICS use showed that patients in the treatment arm had an improvement in FEV₁.¹⁶ The improvement in lung function was more significant in patients with a higher serum periostin level.⁴⁷ This suggests that serum periostin can serve as a T2 biomarker to identify patients that will respond to anti-IL13 therapy. FeNO levels are increased in asthma as a result of IL-13-induced induction of nitric-oxide synthase in the airway epithelium. FeNO is also strongly associated with a response to lebrikizumab.

IL-4 activates the type I receptor which controls Th2 cell differentiation and is located mainly on lymphocytes. The type II receptor is expressed by several cell lines, including myeloid cells and is activated by IL-13 in addition to IL-4. Antibodies such as dupilumab that target the alpha subunit of IL-4 receptor can inhibit both cytokines. A randomized, multi-centered phase 2A trial was conducted to evaluate the safety and efficacy of dupilumab in asthma patients with increased eosinophil counts and uncontrolled moderate-to-severe disease.¹⁵ When ICS and LABAs were withdrawn, dupilumab treated patients had fewer exacerbations, decreased levels of T2 inflammatory markers such as eotaxin 3 (CCL26), and an improvement in lung function. Inhibition of both cytokines may prove to be more effective than blocking either one alone although confirmatory studies are needed.

Future targeted biologic and BT therapies

Recent studies have explored the role of IL-33, thymic stromal lymphopoietin [TSLP], and IL-25 in the pathogenesis of asthma.⁴⁸ IL-33 is a cytokine of the IL-1 family that is expressed on Th2 cells and promotes the production of cytokines associated with Th2 such as IL-5 and IL-13. Increased levels of IL-33 have been found in the airways of adults with asthma and in blood and sputum samples in children with asthma^{41,49} Respiratory viral infections may stimulate production of IL-33 in patients with chronic obstructive lung disease. TSLP, an IL-7 like cytokine, has been shown to be increased in bronchial lavage samples and endobronchial biopsies in patients with asthma. A recent trial demonstrated that an anti-TSLP monoclonal antibody decreased bronchoconstriction induced by allergens in patients with mild asthma.⁵⁰ IL-25 has been implicated in the pathogenesis of the T2-high asthma population. A recent study of IL-25 high asthma patients demonstrated greater improvement in lung function in response to ICS when compared to the IL-25-low subset.⁵¹ Though these therapies appear promising as new targeted phenotypes, future studies are needed in severe asthma.

Newer imaging techniques may allow for BT image-guided localized therapy. Hyperpolarized helium or xenon MR imaging is being used to investigate segmental lung ventilation by utilizing high-spatial-resolution ventilation images in patients with severe asthma.⁵² In these patients, the median whole lung ventilation defect percentage was significantly greater in those with severe asthma compared with mild disease.⁵³ Use of this imaging technique before and after BT has demonstrated a short-term increase in ventilation defects with a significant decrease in ventilation defects several months post BT. This observation likely correlates with short-term increase in bronchial wall edema following BT that is subsequently reversed. Current studies are underway to evaluate if imaging with MR or quantitative CT as a biomarker prior to BT can guide those segments that could be treated with one session of BT as opposed to the current technique which requires three.

Conclusion

When should we consider a biologic therapy versus BT? This question will be easier to answer when comparative trials are available. Currently, we must depend upon a targeted approach in those phenotypes with the greatest evidence (Figure 1). Other phenotypes such as T2-low, paucigranulocytic, and neutrophilic asthma are not well defined to recommend specific therapy at this time. In those patients with severe uncontrolled asthma on ICS plus a second controller with a predominant allergic component, anti-IgE therapy should be considered. In those patients with severe uncontrolled asthma on ICS plus a second controller with a predominant eosinophilic component (blood eosinophils >300-400 cells/ μ l), anti-IL5 therapy should be considered. Future studies with anti-IL-4 α and -13 are needed to understand the optimal phenotype for these drugs and efficacy profile in severe asthma. In those patients with severe uncontrolled asthma on ICS plus a second controller with a predominant chronic airflow obstruction component (\pm reversibility) or those who fail to respond or are not candidates for anti-IgE or anti-IL5, BT is a therapeutic option. The need for biweekly or monthly injections with a biologic, concern regarding the bronchoscopy for BT, and cost of treatment should be considered. BT may be more appealing to some patients given that it is completed in three sessions compared to chronic life-long therapy required for biologic agents. When compared to standard therapy and omalizumab, recent studies suggested that BT could be a cost-effective option.^{54,55} Clinicians should incorporate patient preferences into the treatment decision, especially in those subjects with overlapping features across these phenotypes (e.g. high blood eosinophil count and allergic phenotype).

Search strategy and selection criteria

The authors searched PubMed for peer reviewed research from January 1990 to November 2015 published in English using the search terms “asthmatic phenotypes,” “bronchial thermoplasty,” “biologic agents in severe asthma.” These references were used in addition to the cumulative publications, research, and clinical experiences of the authors in the field of asthma.

KEY POINTS

- In selected phenotypes of severe asthma, newer therapies targeting specific patient populations have demonstrated much greater efficacy with acceptable safety.
- Omalizumab is a monoclonal antibody to IgE that benefits patients with severe uncontrolled asthma on ICS plus a second controller with a predominant allergic component,
- Anti-IL5 therapy (mepolizumab, reslizumab) and anti-IL5 receptor therapy (benralizumab) benefits patients with severe uncontrolled asthma on ICS or oral CS plus a second controller with a predominant eosinophilic component (blood eosinophils >300-400 cells/ μ l).
- Future studies with anti-IL-4 α and -13 are needed to understand the optimal phenotype for these drugs and efficacy profile in severe asthma.
- Bronchial thermoplasty reduces airway smooth muscle and provides benefits to patients with severe uncontrolled asthma on ICS plus a second controller and should be considered in those who fail to respond or are not candidates for anti-IgE or anti-IL5.

Conflict of Interest

AT has no conflicts of interest. In the last 5 years IDP has received speaker's honoraria for speaking at sponsored meetings from Astra Zeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, and GSK and a payment for organising an educational event from AZ. He has received honoraria for attending advisory panels with Almirall, Genentech, Regeneron, Astra Zeneca, Boehringer Ingelheim, GSK, MSD, Schering-Plough, Novartis, Dey, Napp and Respivert. He has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, Astra Zeneca and Napp. MC reports grants to the University from NIH and ALA and from industry: Amgen, Boston Scientific, Genentech, Gilead, GSK, Invion, Johnson&Johnson, KalaBios, Medimmune, Merck, Novartis, Pfizer, Sanofi-Aventis, Teva, Vectura; personal fees from Boehringer-Ingelheim, Boston Scientific, Genentech, GSK, Hoffman LaRoche, Holaria, Sanofi-Aventis, Teva, Vectura; royalties from Elsevier; and stock options from Sparo, Inc.

Contributors

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