

Original Article

Estimation of Health and Economic Benefits of Clinic Versus Home Administration of Omalizumab and Mepolizumab

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What is already known about this topic? Biologic therapy for asthma and urticaria is safe and effective for most patients, but anaphylaxis risk has historically limited access to at-home administration.

What does this article add to our knowledge? For most patients, at-home administration of omalizumab and mepolizumab is a cost-effective option. The in-clinic mitigation of therapy-related anaphylaxis risk is offset by increased risk of automobile-related fatality.

How does this study impact current guidelines? Home administration may be an appropriate consideration for many patients receiving omalizumab or mepolizumab. This is associated with lower overall risk to the patient, lower costs, and increased access to these therapies.

BACKGROUND: Biologic therapy is a paradigm-shifting management strategy for many patients with asthma and chronic urticaria, but concerns for therapy-associated anaphylaxis may limit access to these therapies for patients unable to travel to medical clinics.

OBJECTIVE: To characterize the cost-effectiveness of in-clinic versus at-home biologic therapy with omalizumab and mepolizumab.

METHODS: Economic evaluation using microsimulations was performed from societal and health care sector perspectives for patients with asthma or chronic spontaneous urticaria receiving omalizumab or mepolizumab in an allergy clinic, primary care provider (PCP) office, or at home over a 1-year time horizon (12 injections per year in each base case with sensitivity analysis to 24 injections per year). Travel times and distances were applied to a population attending a tertiary care allergy clinic in

Northern New England receiving omalizumab or mepolizumab, using a willingness-to-pay value of \$10 million per death prevented and in-clinic administration reducing anaphylaxis fatality and hospitalization 10- to 100-fold. Deterministic and probabilistic sensitivity analyses were performed.

RESULTS: One-way allergy clinic travel distances significantly exceeded local PCP offices (49 miles, 95% CI, 42-56, vs 12 miles, 95% CI, 10-15). In the omalizumab societal analysis, annual PCP and allergy clinic administration cost \$1369.14 (mean) ± \$51.33 (SD) and \$1916.68 ± \$40.86, respectively. Small reductions in medication-related fatalities with in-clinic administration were offset by the potential increase in automobile fatalities resulting from traveling to the allergy clinic (14.6 ± 15.0 per million person-years for this strategy). Compared with at-home administration, in-clinic omalizumab administration was not cost-effective, with an incremental cost-effectiveness ratio of

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Conflicts of interest: M. Shaker has a family member who is CEO of Altrix Medical and is a member of the Joint Taskforce on Allergy Practice Parameters. J. Oppenheimer is involved in research/adjudication with AstraZeneca (AZ), GlaxoSmithKline (GSK), Sanofi, and Novartis; works as a consultant for GSK, AZ, and Sanofi; is associate editor of *Annals of Allergy Asthma Immunology*, Allergy-Watch; is section editor of *Current Opinion of Allergy*; receives royalties from Up to Date; is board liaison American Board of Internal Medicine for American Board of Allergy and Immunology; and is member of the Joint Taskforce on Allergy Practice Parameters. M. Greenhawt is supported by the Agency for Healthcare Quality and Research (grant no. 5K08HS024599-02); is an expert panel and coordinating committee member of the National Institute of Allergy and Infectious Diseases—sponsored Guidelines for Peanut Allergy Prevention; has served as a consultant for the Canadian Transportation Agency, Thermo Fisher, Intromune, and Aimmune Therapeutics; is a member of physician/medical advisory boards for Aimmune Therapeutics, DBV Technologies, Sanofi/Genzyme, Genentech,

Nutricia, Kaleo Pharmaceutical, Nestle, Aquestive, Allergy Therapeutics, Allergen, Aravax, Protia, Glaxo Smith Kline, and Monsanto; is a member of the Scientific Advisory Council for the National Peanut Board; has received honorarium for lectures from Thermo Fisher, Aimmune, DBV, Before Brands, multiple state allergy societies, the American College of Allergy, Asthma, and Immunology, and the *European Academy of Allergy and Clinical Immunology*; is an associate editor for the *Annals of Allergy, Asthma, and Immunology*; and is a member of the Joint Taskforce on Allergy Practice Parameters. The rest of the authors declare that they have no relevant conflicts of interest.

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*Abbreviations used**ED- Emergency department**ICER- Incremental cost-effectiveness ratio**PCP- Primary care provider*

\$500,648,430 (PCP), and with allergy clinic administration dominated by higher costs and automobile-related fatalities. Routine mepolizumab clinic administration was dominated by at-home administration unless anaphylaxis rates or self-administration teaching costs were high.

CONCLUSIONS: For many patients, at-home administration of omalizumab or mepolizumab may be a cost-effective strategy. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: Omalizumab; Mepolizumab; Biologic; Asthma; Urticaria; Home administration; Anaphylaxis; Cost-effectiveness analysis; Fatality; Simulation

INTRODUCTION

In 2007, the Omalizumab Joint Task Force established a series of recommendations on the basis of a review of Genentech omalizumab clinical trial and postapproval surveillance data, which advised the administration of omalizumab to be limited to physicians working in clinical settings.¹ This recommendation was established in response to the 0.09% risk of anaphylactic reactions following administration of omalizumab noted in clinical trial data, as well as the black box warning being placed on the package.² Subsequently, continued observation of post-marketing reports suggested that the estimated frequency of omalizumab-related anaphylaxis was at least 0.2%, and the product insert language has been updated.² Although in-clinic administration of omalizumab may allow for observation for development of anaphylaxis and improved reaction management, the opportunity cost and travel-related risks associated with administration of omalizumab and similar biologics in a clinical setting have not been defined (Table I).²⁻⁷ However, delayed anaphylaxis may occur despite in-clinic observation.^{8,9} Recently, the European Commission approved omalizumab self-administration across all indications,¹⁰ a practice facilitated with the availability of omalizumab prefilled syringes.¹¹ European guidance suggests that omalizumab may be administered by trained lay-caregivers from the fourth dose onward, if deemed appropriate by the treating physician.¹⁰ Similarly, the recent approval of mepolizumab for home administration illustrates an evolving paradigm of risk management and health care delivery (with other biologics following suit).^{3,12}

The approach of mandated clinic observation instituted for some biologics may require patients to frequently travel long distances to specialty clinics, often with limited or absent evening and weekend access. Given that evidence suggests that lay-caregivers are able to successfully perform home administration,¹³ the cost-effectiveness of clinic biologic administration is an important unanswered question. We therefore undertook this cost-effectiveness analysis of clinic-observed biologic administration to clarify the health and economic benefits of this practice.

METHODS

Decision model

TreeAge Pro (Williamstown, Mass) was used to develop a decision model (Figure 1) to evaluate Monte-Carlo microsimulations of hypothetical patients ($n = 100,000$ per arm) receiving at-home versus in-clinic administration of omalizumab or mepolizumab, with comparisons of both allergy and primary care provider (PCP) clinic administration of biologic therapies. Microsimulations were performed to estimate anaphylaxis and hospitalization rates. To isolate the effect of in-clinic versus at-home administration with respect to therapeutic costs and benefits of biologic therapies, a 1-year time horizon was used, which assumed equivalent effectiveness between at-home and in-office administration. The threshold for cost-effective care was set at \$10 million per death prevented.¹⁴ Because the effect of at-home administration on adherence is uncertain (home availability could increase or decrease adherence rates), this variable was not included in the base-case analysis; however, sensitivity analyses did include additional costs of home teaching and adherence monitoring. This analysis conformed to the Consolidated Health Economic Evaluation Reporting Standards guideline¹⁵ and was approved by the Dartmouth College Committee for the Protection of Human Subjects.

Clinic travel

Deidentified travel distances and travel times for the population of patients traveling to the Dartmouth-Hitchcock Medical Center Allergy Clinic for omalizumab and mepolizumab were collected from September 1, 2016, to October 7, 2018. For each patient identified, the city and state of residence was used to record travel time and distance using Google Maps. Travel time and mileage to the allergy clinic and the patient's PCP of record were recorded.

Costs

Table II details model assumptions. Direct costs of in-clinic administration were estimated from health care claims data compiled and maintained by FAIR Health, Inc, after permissions for data use were obtained (the authors are solely responsible for research and conclusions reflected in this article and FAIR Health is not responsible for the conduct of the research or for the opinions expressed in this article).¹⁶ Costs of in-clinic injections (code 96372) included the primary medical procedure and hospital outpatient facility fee. Total in-network costs of medication administration were used in the base-case model. Average automobile fuel price and economy were incorporated into the model,^{18,19} in addition to average hourly wage to reflect indirect costs associated with clinic biologic administration.²⁰ All patients experiencing anaphylaxis assumed costs of emergency department (ED) evaluation, and those with severe anaphylaxis assumed additional costs of hospitalization. Patients receiving injections at home and at primary care sites also experienced costs of emergency transport to the ED; however, because the Dartmouth-Hitchcock Medical Center Allergy Clinic (Lebanon, NH) is attached to an ED, medical center transportation costs were excluded from the allergy clinic (which we presume to be the case for most academic allergy practices similar to the one modeled in this analysis). The costs of ED visits and hospitalizations were derived from Clark et al²³ who reported data from 11,972 individuals with an ED visit or hospitalization from January 1, 2002, to December 31, 2008. All costs were expressed in January 2019 dollars,²⁰ with a midpoint conversion date of January 1, 2005, used for Clark et al.^{20,23}

TABLE I. Incidence of anaphylaxis with selected biologics

Biologic	Manufacturer	Mechanism of action	Incidence of anaphylaxis	In-clinic administration recommended on product labeling?
Dupixent (dupilumab)	Sanofi Genzyme	Inhibits IL-4 and IL-13	Not reported	No
Enbrel (etanercept)	Amgen	TNF- α inhibitor	<2%	No
Fasenra (benralizumab)	AstraZeneca	IL-5 antagonist	Not reported	Yes
Humira (adalimumab)	Abbvie	TNF- α inhibitor	~1%	No
Nucala (mepolizumab)	GlaxoSmithKline	IL-5 antagonist	Not reported	Optional
Xolair (omalizumab)	Genentech	Anti-IgE	$\leq 0.2\%$	Yes

Probabilities

Published literature was incorporated to represent risks of anaphylaxis, hospitalizations, and fatalities, with a *priori* risk reductions assumed for in-clinic administration ranging from 10-fold to 100-fold. The rate of occurrence of anaphylaxis related to omalizumab and mepolizumab administration was modeled at 0.2% and 0.1% per patient, respectively.^{2,3} Case-anaphylaxis fatality was estimated at 0.33%, on the basis of a population-based epidemiologic study of 3 national databases reported by Ma et al.²¹ The rate of severe anaphylaxis necessitating hospitalization was based on Clark et al²³ who reported that 22% of patients seen with anaphylaxis required hospitalization. Because the incremental health-state utility between in-clinic and at-home biologic administration is unknown, quality-adjusted life-years were not used as an outcome measure and instead the analysis evaluated cost per fatality prevented.

Sensitivity analyses

Base-case analyses were performed from the societal perspective with additional sensitivity analyses including the health care sector perspective (excluding fuel and job-related indirect costs). Additional sensitivity analyses were performed, with home teaching/adherence monitoring costs modeled at \$1500. Medication and in-clinic observation was estimated at 40 minutes in the base case, with sensitivity ranges modeled to 130 minutes. In the base case, 12 injections of each medication were assumed, with 24 injections of omalizumab evaluated in sensitivity analyses. In-clinic administration-related protection against anaphylaxis hospitalization and fatality was 10-fold in the base case, with 100-fold protection modeled in sensitivity analyses. Further analyses were performed across variable ranges by deterministic and probabilistic sensitivity analyses with modal triangular distributions. Triangular distributions were used to incorporate base assumptions as modal distributions with extreme value probabilities minimized, and were validated using alternative beta distributions for probabilities and fatalities, with gamma distributions for costs and times.

RESULTS

Travel times and distances

For both omalizumab and mepolizumab, travel times and distances to the allergy clinic exceed those to the PCP office by significant margins. For omalizumab, 1-way allergy travel distance was 49 miles (95% CI, 42-56 miles) compared with a distance to the PCP of 12 miles (95% CI, 10-15 miles), translating to 1-way travel time of 59 minutes (95% CI, 51-66) for allergy clinic versus 19 minutes (95% CI, 16-22) for the PCP office. Similar findings were observed for patients receiving mepolizumab (Allergy: 39 miles, 95% CI, 29-49 miles; 46 minutes, 95% CI, 37-56 minutes; PCP: 14 miles, 95% CI, 10-17 miles; 21 minutes, 95% CI, 16-25 minutes).

Cost-effectiveness

In the omalizumab analysis, the costs of either type of observed injection strategy were greater than those of the home injection strategy: Allergy clinic \$1916.68 (mean) $\pm$ \$40.86 (SD), PCP administration \$1369.14 $\pm$ \$51.33, and home injection \$7.47 $\pm$ \$213.66. Small reductions in medication-related fatalities were noted with in-clinic administration (fatalities per million person-years: home; 6.8 $\pm$ 149.6; PCP; 4.1 $\pm$ 15.0), but these were offset by increased automobile fatalities attributable to having to travel longer distances to the allergy clinic (fatalities per million person-years: 14.6 $\pm$ 15.0). In-clinic administration of omalizumab was not cost-effective, with an incremental cost-effectiveness ratio (ICER) of \$500,648,430 at a PCP office. Administration in the allergy clinic was dominated (eg, of all options compared, this resulted in the worst comparative health outcomes and highest cost), with both higher costs and fatalities attributable to automobile travel (Table III). Modeling an extreme scenario in a sensitivity analysis where in-clinic (either venue) administration was associated with a 100-fold reduction in the risk of anaphylaxis hospitalization and fatality risk still remained cost-ineffective, with PCP and allergy clinic ICERs above \$10 million per death prevented (PCP: \$463,456,793; Allergy: dominated). When evaluating fatality risk, patients living more than 24 miles from the clinic were at a higher risk of automobile fatality than anaphylaxis fatality.

Clinic administration of mepolizumab resulted in greater fatalities (from anaphylaxis and automobile accidents combined) whether patients traveled to PCP or allergy offices (per-strategy deaths per million persons at home: 3.1 $\pm$ 102.2; PCP office: 4.3 $\pm$ 10.2; allergy clinic: 11.4 $\pm$ 10.2). From a societal perspective, administration-related costs were greater in both the PCP and the allergy clinic (home: \$4.40 $\pm$ \$166.59; PCP office: \$1396.35 $\pm$ \$454.88; allergy clinic: \$1744.00 $\pm$ \$40.86). Clinic administration remained dominated in the PCP and allergy clinic models even assuming a 100-fold risk reduction for anaphylaxis hospitalization and fatality.

Sensitivity analyses

Additional microsimulation with 1 million subjects randomized to each strategy did not change overall results. Additional Monte-Carlo simulation with alternate random number seeding demonstrated similar findings, with a PCP versus home administration ICER of \$641,000,659. Multiple additional analyses were performed to determine critical levers where these practices could potentially attain cost-effectiveness. Increasing the degree of in-clinic protection to a 1000-fold fatality risk reduction still did not result in cost-effective care (omalizumab ICER \$426,098,636 for PCP vs home administration; allergy clinic administration dominated). Excluding wage costs, in-clinic

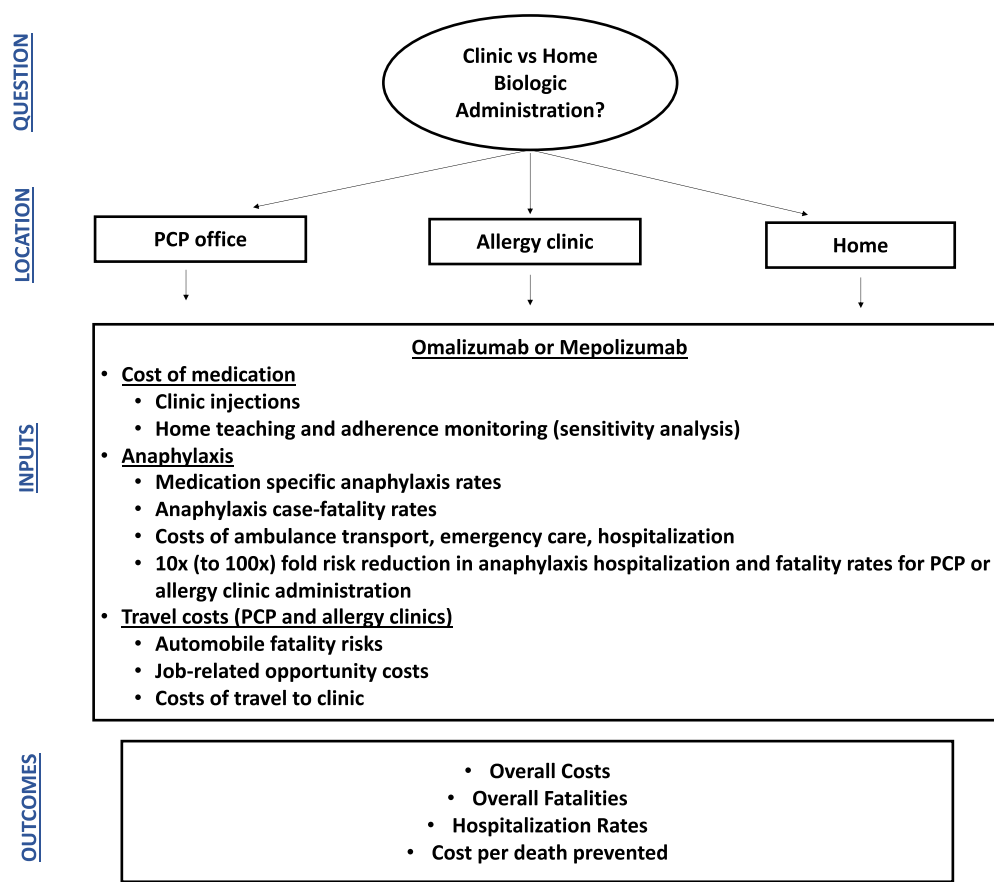


FIGURE 1. Evaluation of health and economic benefits of clinic vs home biologic administration.

administration remained cost-ineffective (omalizumab PCP vs home administration \$364,952,038 with allergy clinic administration dominated).

Omalizumab PCP-clinic administration became cost-effective as rates of anaphylaxis increased above 4.2%, anaphylaxis case-fatality rate exceeded 7.7%, or if additional teaching and adherence costs reached \$1336.29 (Figure 2), with an interaction seen between risk of anaphylaxis and case-fatality rate (Figure 3). Given longer travel distances to allergy clinic, this strategy was not cost-effective unless risks for omalizumab anaphylaxis reached 6.2%, case-fatality exceeded 11.3%, or teaching costs reached \$1988.66. Probabilistic sensitivity analysis ($n = 10,000$ simulations) demonstrated home administration to be the most cost-effective strategy of the 3 options in 91.7% of omalizumab simulations (Figure 4). Similar to the omalizumab analysis, PCP administration of mepolizumab could be cost-effective if the rate of mepolizumab anaphylaxis exceeded 4.4%, case-anaphylaxis fatality rate was 15.9%, or teaching/adherence costs reached \$1402.51. Probabilistic sensitivity analysis ($n = 10,000$ simulations) demonstrated home administration to be the most cost-effective strategy in 92.7% of mepolizumab simulations (Figure 4). Using alternative distributions without adherence costs, home administrations was the most cost-effective option in 99.9% of omalizumab simulations and 99.7% of mepolizumab simulations.

Evaluation of clinic-administered omalizumab from the health care sector perspective resulted in PCP and allergy strategy costs of $\$901.66 \pm \$75.96$ and $\$900.6 \pm \$66.72$, respectively, for a

PCP versus home strategy ICER of \$445,861,774. The allergy clinic strategy remained dominated by the home strategy, and mepolizumab was similarly dominated by home administration from this perspective.

DISCUSSION

Although recent changes in European practice have created an avenue for home administration of omalizumab, in the United States, current recommendations advocate for administration of omalizumab in a medical clinic. This is due in equal parts to previous lack of availability of a prefilled omalizumab syringe and the fact that this had to be reconstituted, as well as the aforementioned risk of anaphylaxis and black box warning from the Food and Drug Administration accompanying the drug. Allergy and pulmonary clinics serve as the most common setting of omalizumab administration; however, in many parts of the country, access to subspecialty care requires significant travel burdens compared with local primary care settings. Our study highlights this reality at a tertiary care medical center in Northern New England, where patients receiving omalizumab travel significantly longer distances for omalizumab administration in an allergy clinic relative to more proximal PCP offices (with an average additional distance traveled of 37 miles). Given the longer travel distances, patients experience significant risks of traffic accidents and fatalities, important variables that we may not readily consider when weighing recommendations for in-office administration of products to protect against small risks.

TABLE II. Model inputs and assumptions

Input	Value	Range	Reference
Cost of clinic injection, code 96372	<i>Primary medical procedure:</i> in-network price: \$42; out-of-network price: \$90; <i>Hospital outpatient facility fee:</i> in-network: \$33; out-of-network: \$94; <i>Total costs:</i> in-network: \$75; out-of-network: \$184 <i>Base assumption:</i> \$75	\$75-\$320	¹⁶
Automobile fatality rate	1.18 per 100 million vehicle miles traveled	0.118-1.18 per 100 million vehicle miles traveled	¹⁷
Automobile fuel price and economy	\$2.68 per gallon, regular 23 miles per gallon	\$1.98-\$3.50 per gallon (18-39 mpg)	^{18,19}
Omalizumab clinic travel (1-way)	Allergy miles: 49 (95% CI, 42-56); Allergy travel: 59 min (95% CI, 51-66); PCP miles: 12 (95% CI, 10-15); PCP travel: 19 min (95% CI, 16-22); No. of visits per year: 12-24	Allergy clinic: 24.5-98 miles (30-120 min); PCP: 6-19.5 miles (9.5-38 min)	Practice survey DHMC, n = 134
Mepolizumab clinic travel (1-way)	Allergy miles: 39 (95% CI, 29-49); Allergy time: 46 min (95% CI, 37-56); PCP miles: 14 (95% CI, 10-17); PCP time: 21 min (95% CI, 16-25); No. of visits per year: 12	Allergy clinic: 19.5-78 miles (23-92 min); PCP: 7-19.5 miles (10.5-42 min)	Practice survey DHMC, n = 36
Average hourly wage	\$27.83	\$0-\$100	²⁰
Omalizumab anaphylaxis	0.2%	0.2%-5%	²
Mepolizumab anaphylaxis	≤0.1%	0.1%-5%	³ ; K. Woodrow, written communication, October 2018
Anaphylaxis fatality	≤0.33%	0.33%-1.3%	²¹
Annual visits	12	12-24	Model assumption
Clinic wait time	40 min	30-130 min	Model assumption
Home teaching	\$0	\$0-\$1500	Model assumption
Clinic administration fatality risk reduction	10×	10×-100×	Model assumption
Anaphylaxis cost	Ambulance transport: \$470 (2007 USD); \$585 (2019 USD); ED evaluation (all): \$1152 (2005 USD); \$1521 (\$2019 USD); Hospitalization (22%): \$5652 (2005 USD); \$7460 (2019 USD)	Ambulance transport: \$400-\$1500; ED evaluation: \$900-\$2500; Hospitalization (5%-50%): \$2500-\$20,000	²²⁻²⁴

DHMC, Dartmouth-Hitchcock Medical Center.

Note: Triangular distributions were evaluated using the modal value of each variable bounded by the minimum and maximum ranges fitted to a triangle with maximum apical unit distribution at the mode and probability minimized at extreme values, and were validated by alternative beta distributions for probabilities and fatalities, and gamma distributions for costs and times.

Travel distances may vary by location, with greater or lesser disparities between allergist and PCP travel distances noted contextually. However, despite current practice standards being what they are, on the balance, requiring in-clinic omalizumab administration in the United States does not appear cost-effective, specifically with allergy clinic administration potentially leading to both greater costs and overall fatalities in the simulation reported here. Although administration at PCP offices is unusual (which we recognize is not a realistic option in many circumstances and was included only for cost comparison), even in this setting, mandated clinic-observed omalizumab administration is not cost-effective, with the ICER exceeding \$500 million per death prevented from a societal perspective.

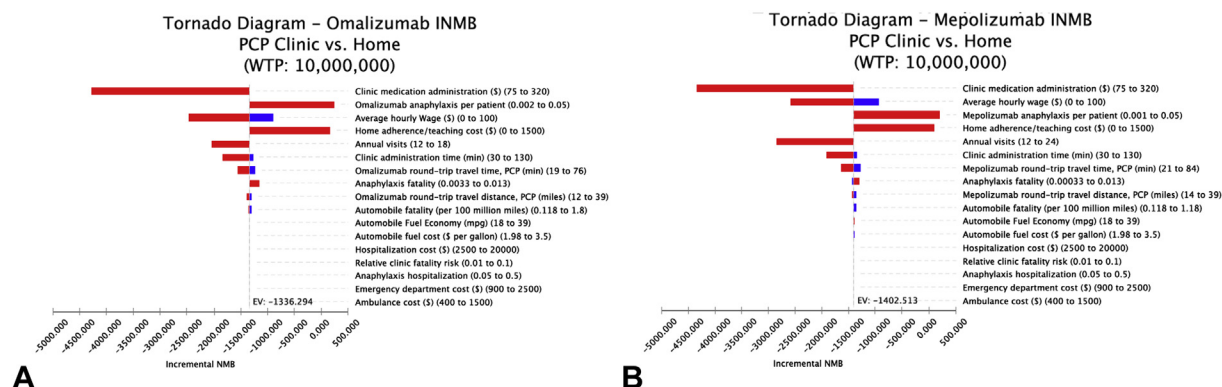
Our analysis suggests that patient-specific scenarios may exist to justify clinic-observed omalizumab administration. For example, if significant teaching costs or adherence concerns exist,

or if risk of anaphylaxis or case-fatality is high, clinic observation would be appropriate. However, in more rural setting such as ours, extended travel to subspecialty clinics to receive biologic therapy does not seem justified in most circumstances. Although preference data do not exist exploring this area as of yet, it is also presumable that this could represent a preference-sensitive care area for patients who value the in-office pathway, where shared decision making and use of a decision aid could also play a role. We could not model this as of yet, however.

Strengths of our analysis include incorporation of home education and adherence monitoring costs, because a legitimate concern of home biologic administration may be that adherence may fall without health care provider supervision. However, whether or not adherence would actually increase or decrease is unknown, because improved access to therapy for patients who no longer need to travel hours for therapy may actually offset a

TABLE III. Cost-effectiveness analysis of administration strategies by product

Strategy	Cost	Fatality (per million)	Net monetary benefit	Anaphylaxis	Hospitalization (per million)	ICER
Omalizumab, mean $\pm$ SD						
Home administration	\$7.47 $\pm$ \$213.66	6.8 $\pm$ 149.6	−\$75.45 $\pm$ \$1,666.28	0.2% $\pm$ 4.5%	420 $\pm$ 20,490	Dominant
PCP clinic	\$1,369.14 $\pm$ \$51.33	4.1 $\pm$ 15.0	−\$1,409.92 $\pm$ \$185.56		30 $\pm$ 5,480	\$500,648,430
Allergy clinic	\$1,916.68 $\pm$ \$40.86	14.6 $\pm$ 15.0	−\$2,062.25 $\pm$ \$159.78			Dominated
Mepolizumab, mean $\pm$ SD						
Home administration	\$4.04 $\pm$ \$166.59	3.1 $\pm$ 102.2	−\$35.72 $\pm$ \$1,156.85	0.1% $\pm$ 3.1%	270 $\pm$ 16,430	Dominant
PCP clinic	\$1,396.35 $\pm$ \$47.53	4.3 $\pm$ 10.2	−\$1,439.16 $\pm$ \$133.72		30 $\pm$ 5,480	Dominated
Allergy clinic	\$1,744.00 $\pm$ \$40.86	11.4 $\pm$ 10.2	−\$1,857.62 $\pm$ \$116.57			Dominated

**FIGURE 2.** Deterministic cost-effectiveness analyses are shown for omalizumab (A) and mepolizumab (B), with red bars indicating values above and blue bars those below the base-case analysis. Tornado diagrams of incremental net monetary benefit (INMB) are shown with PCP clinic strategy compared with home administration strategy, with prevented fatalities converted to dollars at a willingness-to-pay (WTP) value of \$10,000,000 per death prevented. Positive values are considered cost-effective. Expected value (EV) shows the base-case analysis.

decrease in home adherence. The incorporation of home adherence devices for biologic administration will be valuable to ensure home administration as prescribed. Such adherence monitors can effectively interact with medical devices and relay real-time information to providers and pharmacies through cloud computing.²⁵ The issue of ensuring adherence to home biologic therapy cannot be overstated, and in the end may be the most critical piece of the puzzle in improving asthma management.²⁶

Our analysis does have limitations. First, as a simulation it is dependent on strength of inputs used, and is an approximation of how “real life” may unfold, and as such this should be kept in perspective. Second, this is a novel concept that has exceptionally limited prior literature to help guide plausible assumptions. Third, our travel time and distances were derived from the clinic population of a rural tertiary care medical center in Northern New England, so it is quite possible that our travel times to allergy clinic may be less applicable to travel distances in a more urban setting, or in states with higher densities of other academic medical centers and we did not evaluate differential costs for pediatric versus adult patients. However, 1-way travel distances and times of 12 miles (19 minutes) to a PCP office may be more reflective of national median values. Although, as noted earlier, significant variation in travel distance may occur on the basis of geographic location. Sensitivity analyses were performed to address this limitation, with 1-way travel distances and times of

6 miles (9.5 minutes) to a PCP office modeled. Fourth, we intentionally did not model health state transitions, extended model horizons, costs associated with access barriers to biologics, lost opportunities to improve disease control, and their consequences in health care utilization. Although incorporating these aspects of care into more complex models could provide additional perspective on cost-effectiveness, the intent of this analysis was to specifically evaluate the practice of observed biologic administration. There may be a role for further investigation of models with longer time horizon, all-cause age-adjusted mortality, and health state transitions, but unless a large differential effect occurs with therapy adherence, these factors would not be expected to impact the model conclusions. Fifth, we excluded ED transport costs for allergy clinic anaphylaxis; however, the addition of these costs would only make this strategy less-cost-effective. Sixth, we did not specifically model the practice of home biologic administration in patients with previous episodes of anaphylaxis, and excluded patients with known hypersensitivity to omalizumab and mepolizumab from the respective analyses. Similar to patients with very poorly controlled asthma despite biologic therapy, a history of biologic anaphylaxis could increase risk for more severe anaphylaxis where home administration would be less desirable. Seventh, we did not evaluate differential cost of epinephrine autoinjectors (because it was assumed that there was no differential self-injectable epinephrine

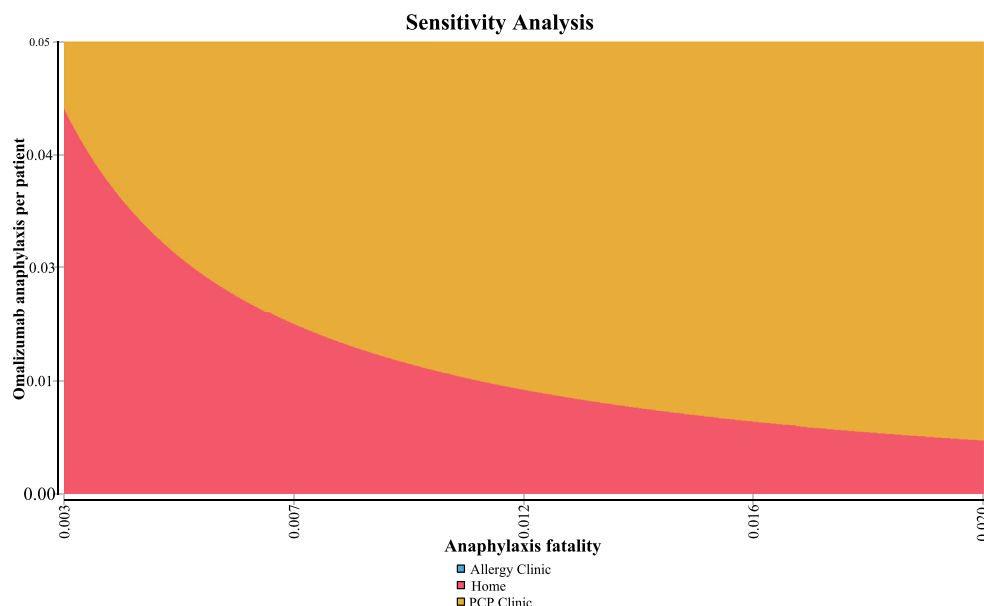


FIGURE 3. Sensitivity analyses of omalizumab anaphylaxis risk vs anaphylaxis fatality risk. Colors denote cost-effective care at a willingness-to-pay value of \$10,000,000 per death prevented.

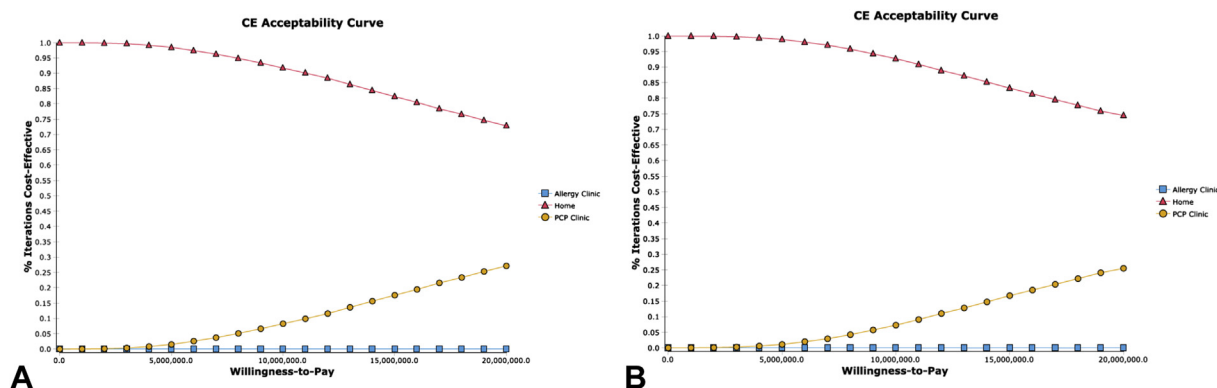


FIGURE 4. Probabilistic sensitivity analysis using modal triangular distributions for omalizumab (A) and mepolizumab (B) from a societal perspective demonstrated home administration to be most cost-effective in 91.7% of omalizumab and 92.7% of mepolizumab simulations ($n = 10,000$ each) at a willingness-to-pay value of \$10,000,000 per death prevented. *CE*, Cost-effectiveness.

preparedness between groups and because all patients would have one irrespective of where the biologic was administered) or patient-preference sensitive shared decision making regarding emergency medical care in the setting of resolved anaphylaxis at home. The potential delayed nature of anaphylaxis with omalizumab creates an indication for self-injectable epinephrine for all patients, which means that self-injectable epinephrine cost will be the same, because being monitored in the office does not remove all risk.⁹ Eighth, shared decision making should also have a role in the setting of biologic administration, and there may be a role for the development of formal decision aids to assist in this process, which could influence cost models. Ninth, it is important to note that home administration could shift coverage of biologic therapy by some insurers with difference in costs that could impact patients; however, from a societal perspective, these changes would not be expected to impact model conclusions. Tenth and finally, additional medication procurement costs, more extended lost-

productivity costs, and time away from school for clinic travel was not modeled, which could make in-clinic administration even more costly. However, the model did account for potential underemployment due to severe asthma with an analysis excluding wage costs. Medication procurement was not included in the model due to unknown variation between clinic and home administration in terms of in-home delivery, pharmacy travel distance, and frequency of medication pick-up.

In summary, routine administration of clinic-observed omalizumab or mepolizumab does not appear to be a cost-effective practice in most situations. The current analysis supports the recent label change for mepolizumab home administration, and suggests that the United States should explore the risks and benefits of adopting an approach similar to the Europe for omalizumab administration with the advent of prefilled omalizumab syringes. Although we as a field focus on patient safety related to medications in the office, and above all else are

cautious to protect against the risk of anaphylaxis, there should be consideration for the trade-offs we unintentionally ask our patients to assume in the risk related to automobile travel to the office, which may be the greatest risk a patient assumes that particular day.

REFERENCES

1. Cox L, Platts-Mills TA, Finegold I, Schwartz LB, Simons FE, Wallace DV, et al. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. *J Allergy Clin Immunol* 2007;120:1373-7.
2. Xolair (omalizumab) Highlights of Prescribing Information. South San Francisco, CA: Genentech; 2019.
3. Nucala (mepolizumab) Highlights of Prescribing Information. Research Triangle Park, NC: GSK; 2019.
4. Humira [package insert]. North Chicago, IL: Abbott Laboratories; 2019.
5. Dupixent [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2019.
6. Enbrel [package insert]. Thousand Oaks, CA: Amgen; 2019.
7. Fasenna [package insert]. Wilmington, DE: AstraZeneca; 2019.
8. Cox L, Lieberman P, Wallace D, Simons FE, Finegold I, Platts-Mills T, et al. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology Omalizumab-Associated Anaphylaxis Joint Task Force follow-up report. *J Allergy Clin Immunol* 2011;128:210-2.
9. Limb SL, Starke PR, Lee CE, Chowdhury BA. Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. *J Allergy Clin Immunol* 2007;120:1378-81.
10. Novartis. Novartis receives European Commission approval for self-administration of Xolair across all indications. Available from: <https://www.novartis.com/news/media-releases/novartis-receives-european-commission-approval-self-administration-xolair-across-all-indications>. Accessed June 16, 2019.
11. Novartis. Novartis announces FDA approval for Xolair (omalizumab) prefilled syringe formulation. Available from: <https://www.pharma.us.novartis.com/news/media-releases/novartis-announces-fda-approval-xolair-omalizumab-prefilled-syringe-formulation>. Accessed June 16, 2019.
12. GlaxoSmithKline. Nucala (mepolizumab) gains FDA approval for two new self-administration options. Available from: <https://www.gsk.com/en-gb/media/press-releases/nucala-mepolizumab-gains-fda-approval-for-two-new-self-administration-options/>. Accessed June 16, 2019.
13. Bel EH, Bernstein DI, Bjerner L, Follows R, Bentley JH, Pouliquen I, et al. Usability of mepolizumab single-use prefilled syringe for patient self-administration. *J Asthma* 2019;1-10.
14. US Department of Transportation. Economic values used in analysis. Available from: <https://www.transportation.gov/regulations/economic-values-used-in-analysis>. Accessed May 27, 2019.
15. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMJ* 2013;346:f1049.
16. Fair Health, Inc. Fair Health Consumer. Available from: www.fairhealthconsumer.org. Accessed June 15, 2019.
17. US Department and Transportation. Traffic safety facts 2016 data. Available from: <https://crashstats.nhtsa.dot.gov/Api/Public/ViewPublication/812554>. Accessed June 15, 2019.
18. Irving Gas. On the Road. Available from: www.theirving.com. Accessed June 15, 2019.
19. Cars.com Editors. Best and worst gas mileage 2018. Available from: <https://www.cars.com/articles/best-and-worst-gas-mileage-2018-1420698621218/>. Accessed June 15, 2019.
20. US Department of Labor. US Bureau of Labor Statistics. Available from: www.bls.gov. Accessed June 15, 2019.
21. Ma L, Danoff TM, Borish L. Case fatality and population mortality associated with anaphylaxis in the United States. *J Allergy Clin Immunol* 2014;133:1075-83.
22. Patel DA, Holdford DA, Edwards E, Carroll NV. Estimating the economic burden of food-induced allergic reactions and anaphylaxis in the United States. *J Allergy Clin Immunol* 2011;128:110-5.
23. Clark S, Wei W, Rudders SA, Camargo CA Jr. Risk factors for severe anaphylaxis in patients receiving anaphylaxis treatment in US emergency departments and hospitals. *J Allergy Clin Immunol* 2014;134:1125-30.
24. CPI inflation calculator. Available from: www.data.bls.gov. Accessed June 15, 2019.
25. Propeller Health. Available from: <https://www.propellerhealth.com>. Accessed June 16, 2019.
26. Barnes PJ. COUNTERPOINT: will new anti-eosinophilic drugs be useful in asthma management? No. *Chest* 2017;151:17-20.