

Prior authorization delays biologic initiation and is associated with a risk of asthma exacerbations

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ABSTRACT

Background: Biologics are effective treatments for patients with severe allergic disease. Impacts of delays in the prior authorization process on clinical outcomes has not been studied.

Objective: The objective was to quantify the times for approval and filling of biologics, and whether patients were at risk of exacerbations during this time frame.

Methods: The times for insurance approval and pharmacy filling of biologics (omalizumab, benralizumab, mepolizumab, dupilumab) in 80 subjects with severe asthma ($n = 60$) or urticaria ($n = 20$) from our clinic were reviewed. We compared the impact of clinical features, insurance, specialty pharmacy on fill times, and quantified exacerbations and prednisone use while awaiting biologic initiation.

Results: The mean $\pm$ standard deviation (SD) time (days) from submission of a prescription to the first dose available for injection was 44.0 ± 23.2 days. This was composed of the mean $\pm$ SD time for insurance approval (21.5 ± 19.6 days) and the mean $\pm$ SD time for a specialty pharmacy to fill the medication (22.8 ± 14.1 days). There was no significant difference between the times for diagnosis (asthma versus urticaria), specific biologic, or insurance. The “buy and bill” system was faster than filling via a specialty pharmacy (mean $\pm$ SD, 7.3 ± 8.5 days versus 23.3 ± 21.3 days, respectively, $p < 0.001$). Clinical features of patients with fast versus slow approval times was not significantly different. The subjects with asthma were at high risk of exacerbations and need for prednisone while awaiting initiation of the biologics; 28 of 59 patients (47%) required prednisone, with an mean cumulative dose of 483.2 ± 273.7 mg per person.

Conclusion: The prior authorization process for biologics was slow, and the subjects were at high risk of exacerbations during this time. The system needs to be improved to expedite approval and initiation of these medications.

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Asthma and allergic diseases are common causes of morbidity, particularly in patients with severe and/or difficult-to-treat disease. For instance, the $\sim 10\%$ of individuals with asthma who are diagnosed with severe treatment-refractory disease account for $>50\%$ of the costs and health care burdens associated with asthma.¹ These patients have a high risk of exacerbations, systemic corticosteroid use, and emergency department visits. Similarly, patients with treatment refractory urticaria or atopic dermatitis have a poor quality of life and the need for systemic corticosteroids or other immunosuppressants.² The emergence of biologic therapy within the past decade has dramatically changed our approaches to managing these patients.

There are five monoclonal antibodies that are approved by the U.S. Food and Drug Administration to treat allergic disease: omalizumab (Xolair, Genentech, Inc. South San Francisco, CA), benralizumab (Fasenra, AstraZeneca Pharmaceuticals, Wilmington, DE), mepolizumab (Nucala, GlaxoSmithKline LLC, Philadelphia, PA), reslizumab (Cinqair, Teva Respiratory, LLC; West Chester, PA), and dupilumab (Dupixent, Regeneron Pharmaceuticals, Inc. Tarrytown, NY). Omalizumab is approved for treatment of moderate-to-severe allergic asthma and antihistamine-refractory urticaria.^{3,4} Benralizumab, mepolizumab, and reslizumab are indicated for treatment of difficult-to-treat eosinophilic asthma.^{5–9} Dupilumab is indicated for the treatment of type 2 asthma, moderate-severe atopic dermatitis, and sinusitis with nasal polyps.^{10–13} Collectively, these targeted therapeutics are highly effective to reduce exacerbations and improve disease control.^{3,4,6,12–15} These medications have also been shown to decrease the need for systemic corticosteroids, by reducing the need for maintenance dosing and exacerbations.^{16–21}

The major factor that limits the use of biologics is the high cost. However, the majority of studies that examined the cost-benefit ratio of these medications demonstrated the cost-effectiveness of biologics, particularly

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when the specific biologic is phenotypically matched to patients with severe disease.²² Regardless, the high medication cost has led to the requirement of a prior authorization process, which anecdotally is a slow process, which may delay initiation of therapy. This process has not been well studied, and, to our knowledge, there are no reports in the literature related to the amount of time that it takes to obtain approval of biologics for allergic diseases. A previous study on the impact of a prior authorization policy for montelukast found that no significant adverse clinical outcomes or unintended consequences occurred.²³

However, we hypothesized that there would be a significant effect of the prior authorization process for biologics because these medications are used in patients with the most severe disease. We sought to quantify the amount of the time for insurance approval and administration of biologics, the time for specialty pharmacies to fill the medications, and whether patients are at risk of disease exacerbations while waiting for these approvals. We also sought to identify potential factors, such as the patient's insurance, the specialty pharmacy, and patient and disease characteristics, that could affect the approval times. These findings are discussed herein.

METHODS

Subjects

This study was approved by Mount Nittany Medical Center Institutional Review Board. We retrospectively collected data from patients with a new prescription of monoclonal antibody therapy in our allergy and immunology clinic between March 2014 and August 2019 ($n = 80$), with the majority between 2017 and 2019 ($n = 77$). We excluded one patient from the final analysis because the medication was denied because the patient was a current smoker. All other prescriptions were approved. Subjects were excluded if they transferred to our clinic already on a monoclonal antibody because we were unable to obtain documentation of the initial prior authorization process.

Our clinic records and tracks each step of the prior authorization process, including the time and dates of the following: submission of prior authorization, insurance approval, rejection, peer-peer review; communication with the insurance company and specialty pharmacy; shipment dates; communication with patients; and the first dose administration in our office. This information was used to track the time for insurers to make an approval decision (time from submission to insurance approval) and the time for a specialty pharmacy to fill the medication (the time from approval to shipment of the first dose).

Selection of Monoclonal Antibody Use

Subjects with chronic idiopathic urticaria were selected for omalizumab administration if they had urticaria ≥ 5

days a week despite 4 weeks of a combination of a second-generation antihistamine (taken twice a day) and a first-generation antihistamine (hydroxyzine or doxepin at bedtime).²⁴ All the subjects with asthma were classified as having severe persistent asthma based on the National Heart, Lung, and Blood Institute Expert Panel R3 asthma guidelines²⁵ and were treated with at least two controller medications (medium-to-high-dose inhaled corticosteroid plus a long-acting β -agonist, antileukotriene agent, or long-acting antimuscarinic agent). In patients with asthma, the therapy was selected based on blood eosinophil levels, allergy testing, total immunoglobulin E (IgE) level, and patient weight per published criteria.^{3,6,9,12,15,25} The treating clinician selected the most appropriate therapy based on these criteria, with patient preference with regard to frequency, route of administration, and home versus office administration included in the decision-making.

Statistical Analyses

Differences in continuous variables were determined by using the T-test for comparisons of two groups or analysis of variance with Tukey posttest analysis for comparisons of more than two groups. For categorical variables, the Fisher exact test was used to assess the differences between two groups, and the χ^2 test was used to compare the differences across more than two groups. A significance level of $p = 0.05$ was used for all analyses. All analyses were performed in GraphPad Prism V (GraphPad Software, San Diego, CA).

RESULTS

Demographics and Characteristics of the Study Population

Biologics were approved in 79 subjects ($n = 59$ asthma, $n = 20$ urticaria), with demographics presented in Table 1. The mean $\pm$ SD age was 51.2 ± 16.8 years (for asthma, mean $\pm$ SD age of 53.7 ± 15.2 years; for urticaria, mean $\pm$ SD age of 43.9 ± 19.4 years). The distribution of women and men was as follows: overall, 49 and 30; asthma, 32 and 27; and urticaria, 17 and 3, respectively. Other demographics and clinical information are listed in Table 1.

Time to Insurance Approval and Administration

We tracked the amount of time that it took for insurers to approve the medication and a specialty pharmacy to fill the medication. The sum of these values was listed as the "total time" and represented the number of days from submission of the prescription to the first dose arriving in our office. The mean $\pm$ SD total time for our cohort was as follows: 44.0 ± 23.2 days (45.8 ± 23.9 days for asthma and 40.6 ± 21.3 days for urticaria). There was no statistical difference in the times between the different biologics in asthma or urticaria ($p = 0.573$) (Table 1).

Table 1 Subject characteristics and approval times by biologic

Characteristic	Biologic					p
	Omalizumab Urticaria (n = 20)	Omalizumab Asthma (n = 24)	Mepolizumab (n = 7)	Benralizumab (n = 22)	Dupilumab (n = 6)	
Age, mean $\pm$ SD, y	43.9 $\pm$ 19.4	48.8 $\pm$ 14.5	67.1 $\pm$ 12.9	56.6 $\pm$ 14.1	46.3 $\pm$ 14.8	0.854
Sex, no. women/men	17/3	13/11	5/2	10/12	4/2	0.092
Race: W/B/A	19/0/1	21/3/0	7/0/0	21/1/0	6/0/0	0.492
BMI, mean $\pm$ SD, kg/ m ²	30.2 $\pm$ 9.2	32.6 $\pm$ 9.7	34.9 $\pm$ 4.5	34.6 $\pm$ 8.5	34.9 $\pm$ 4.5	0.452
Eosinophils, mean $\pm$ SD, cells/ μ L	N/A	367 $\pm$ 637	700 $\pm$ 154	630 $\pm$ 605	332 $\pm$ 245	0.3661
IgE level, kU/L	N/A	239.6 $\pm$ 211.6	184.1 $\pm$ 378.3	583.2 $\pm$ 900.9	359.4 $\pm$ 392.7	0.229
FVC % predicted	N/A	77.8 $\pm$ 13.8	73.0 $\pm$ 17.3	79.0 $\pm$ 14.6	67.3 $\pm$ 27.6	0.416
FEV1 % predicted	N/A	69.8 $\pm$ 17.5	65.3 $\pm$ 22.9	70.8 $\pm$ 16.2	62.2 $\pm$ 27.5	0.734
FEV1/FVC %	N/A	73.2 $\pm$ 7.7	68.0 $\pm$ 13.6	72.3 $\pm$ 9.0	69.5 $\pm$ 9.4	0.530
Number of subjects with exacerbations	1/20 (5%)	7/24 (29%)	4/7 (57%)	13/22 (59%)	4/6 (67%)	0.0015
Mean cumulative amount of predni- sone used during exacerbation pe- riod, mean $\pm$ SD, mg	590	380 $\pm$ 153	315 $\pm$ 170	556 $\pm$ 338	547 $\pm$ 190	0.284
ICS-LABA use, n/ total n (%)	N/A	24/24 (100)	7/7 (100)	21/22 (95)	6/6 (100)	0.634
LAMA use, n/total n (%)	N/A	12/24 (50)	4/7 (57)	13/22 (59)	4/6 (67)	0.869
Antileukotriene, n/ total n (%)	7/20 (35)	23/24 (96)	4/7 (57)	16/22 (73)	4/6 (67)	0.001
Total time, mean $\pm$ SD, days	40.6 $\pm$ 21.3	39.3 $\pm$ 22.5	46.4 $\pm$ 10.6	51.2 $\pm$ 26.7	41.2 $\pm$ 25.8	0.573
Insurance approval time, mean $\pm$ SD, days	18.9 $\pm$ 17.1	18.9 $\pm$ 16.7	22.1 $\pm$ 13.4	26.9 $\pm$ 25.6	18.3 $\pm$ 11.4	0.654
Pharmacy fill time, mean $\pm$ SD, days	21.6 $\pm$ 10.7	20.4 $\pm$ 12.7	24.3 $\pm$ 9.2	24.3 $\pm$ 16.7	22.8 $\pm$ 20.5	0.384

SD = standard deviation; BMI = body mass index; N/A = not applicable; IgE = immunoglobulin E; FVC = forced vital capacity; FEV1 = forced expiratory volume in the first second of expiration; ICS = inhaled corticosteroid; LABA = long-acting β -agonist; LAMA = long-acting muscarinic antagonist; W/B/A = White/Black/Asian.

The mean $\pm$ SD time for insurance approval (time from the date that the prior authorization was submitted to the date approved) was 21.2 $\pm$ 19.7 days for all the subjects. This corresponded to a mean $\pm$ SD of 22.6 $\pm$ 20.6 days for asthma and a mean $\pm$ SD of 18.9 $\pm$ 17.1 days for urticaria. There was no significance difference in the times for asthma versus urticaria or between the different monoclonals in asthma (Table 1). The shortest time to approval was 1 day and the longest time was 97 days.

To determine whether approval times got longer in more recent years, we compared approval times by year for 2016–2019 (we did not include 2014 and 2015

because we only had two or fewer submissions for these years). The mean $\pm$ SD approval times were as follows: 2016, 14.5 $\pm$ 14.8 days; 2017, 22.4 $\pm$ 20.1 years; 2018, 26.8 $\pm$ 21.4 days; 2019, 16.9 $\pm$ 16.0 days. The approval times by year were not statistically significant ($p=0.113$, analysis of variance with the Tukey posttest for multiple comparisons).

Comparison of Subject Characteristics in Short Versus Long Approval Times

We next sought to determine whether there were any trends that were associated with shorter or longer

Table 2 Comparison of short vs long approval times

	Approval Time		<i>p</i>
	Short	Long	
Age, mean $\pm$ SD, y	49.7 $\pm$ 17.5	54.1 $\pm$ 12.5	0.421
No. women/men	10/8	10/8	>0.900
Race: W/B/A	17/1/0	15/3/0	>0.900
BMI, mean $\pm$ SD, kg/m ²	29.8 $\pm$ 6.1	35.5 $\pm$ 10.1	0.064
Blood eosinophils, mean $\pm$ SD, cells/ μ L	350 $\pm$ 240	610 $\pm$ 700	0.169
IgE level, kU/L	243.9 $\pm$ 277	544 $\pm$ 923	0.647
FVC % predicted	78.7 $\pm$ 12.4	70.9 $\pm$ 18.9	0.173
FEV1 % predicted	69.2 $\pm$ 15.2	63.7 $\pm$ 18.8	0.359
FEV1/FVC %	69.2 $\pm$ 15.2	73.4 $\pm$ 7.3	0.135
Patients with exacerbations, <i>n</i> /total <i>n</i> (%)	7/18 (39)	9/18 (50)	0.738
Prednisone use during authorization period, mean $\pm$ SD, mg	477.1 $\pm$ 248.0	537.8 $\pm$ 277.2	0.548
ICS-LABA use, <i>n</i> /total <i>n</i> (%)	17/18 (94)	18/18 (100)	>0.900
LAMA use, <i>n</i> /total <i>n</i> (%)	14/18 (78)	9/18 (50)	>0.900
Antileukotriene, <i>n</i> /total <i>n</i> (%)	15/18 (83)	14/18 (78)	>0.900
No. prescriptions: benralizumab, dupilumab, mepolizumab, omalizumab	5, 3, 0, 10	10, 2, 1, 5	>0.900
Total time, mean $\pm$ SD, days	19.9 $\pm$ 8.2	73.6 $\pm$ 16.0	<0.001
Insurance approval, mean $\pm$ SD, days	8.0 $\pm$ 6.3	41.9 $\pm$ 23.6	<0.001
Pharmacy fill time, mean $\pm$ SD, days	11.9 $\pm$ 7.8	31.7 $\pm$ 18.0	<0.001

SD = standard deviation; BMI = body mass index; IgE = immunoglobulin E; FVC = forced vital capacity; FEV1 = forced expiratory volume in the first second of expiration; ICS = inhaled corticosteroid; LABA = long-acting β -agonist; LAMA = long-acting muscarinic antagonist; W/B/A = White/Black/Asian; 18/18 (100) = 18 in Short group and 18 in Long group).

approval times. We restricted this analysis to the (Table 2) asthma group because there was a larger sample size and more clinical heterogeneity that could have resulted in different approval times. We ranked approval times from shortest to the longest time and compared multiple variables in the top 30% of the subjects (shortest approval times) and the bottom 30% (longest approval times).

We did not find any statistical difference in insurance company, subject demographics, or clinical variables (lung function, controller medication use, total IgE value, blood eosinophil levels) in the subjects with shorter versus longer approval times. There was a trend toward a higher body mass index in the longer approval time group. This could be an important factor for omalizumab because dosing is based on the total IgE value and weight. However, there were only five prescriptions for omalizumab in the “longer time” group, and none of these subjects exceeded the dosing table values.

We then manually reviewed records to identify potential reasons for delays in approval of the biologics. Sixteen submissions were initially denied by the insurer, and these were due to multiple different reasons. Although a high-dose inhaled corticosteroid–long-acting β -agonist had been tried and failed in all the subjects, four claims were denied because the subject had not tried the specified brand(s) in the insurer-specific step therapy. There were seven cases in which the informa-

tion had to be re-Faxed or resubmitted two to three times because the denial letter stated that incomplete information was submitted.

Five submissions required peer-to-peer review to get insurance approval, most often because the subject did not meet spirometry criteria (a lack of a 12% improvement in the forced expiratory volume in the first second of expiration after bronchodilator [*n* = 3] or forced expiratory volume in the first second of expiration $\geq$ 80% predicted [*n* = 2]). All the rejections were subsequently approved, either after appeal or peer-to-peer review. There was only one complete rejection (for dupilumab because the subject was a current smoker), and this case was excluded from our analysis. We were unable to identify other factors that could have contributed to delays in approval of the medications.

Pharmacy Fill Times

We next analyzed whether there were delays in filling the medication after it was approved by the insurer, which could be due to barriers at the level of specialty pharmacies or our “buy and bill” system. In our workflow, our clinic contacts the insurer-preferred specialty pharmacy within a day of receiving insurance approval to coordinate and schedule shipment of the medication. The process typically involves a second round of approval of the medication by the specialty

pharmacy before it can be shipped. In the buy and bill system, the medication is purchased by our institution and billed to the insurance company after the patient receives the injection. Currently, our organization uses the buy and bill system only for patients with Medicare insurance.

Sixty-seven prescriptions were filled by a specialty pharmacy and 12 prescriptions by our hospital pharmacy (buy and bill). The mean $\pm$ SD pharmacy fill time was 22.8 ± 14.1 days for all biologics; 23.2 ± 15.1 days for asthma biologics and 21.6 ± 10.7 days for urticaria. There was no statistical difference between asthma versus urticaria or among each of the asthma biologics (Table 1). There was a significant difference between a specialty pharmacy and “buy and bill” times: mean $\pm$ SD, 23.3 ± 21.3 days versus 7.3 ± 8.5 days, respectively; $p \leq 0.001$. There was no difference in times among each of the specialty pharmacies. We also examined pharmacy fill times by year. There was no difference in the mean $\pm$ SD fill times between any year (2016–2019): 2016, 20 ± 5.6 days; 2017, 15.6 ± 12.3 days; 2018, 24.6 ± 14.7 days; and 2019, 19.3 ± 11.9 days; $p = 0.26$.

Exacerbations and Systemic Corticosteroid Use

Given the significant amount of time required to fill these medications, we hypothesized that our asthma population was at risk of exacerbations and in need of systemic corticosteroids during this time frame. In the period between submission of the prior authorization and specialty pharmacy filling the medications, 28 of the 59 subjects (47%) required systemic corticosteroids for asthma exacerbations. There was a total of 30 exacerbations (26 subjects with one exacerbation and 2 subjects with two exacerbations) and the duration of prednisone ranged from 5 days to 4 weeks. The mean cumulative dose of prednisone over this time frame was 483.2 ± 273.7 mg. Three subjects were admitted to the hospital for asthma while awaiting the first dose of biologic therapy, and one patient was admitted twice.

DISCUSSION

The emergence of biologic therapy has significantly increased our ability to treat severe allergic diseases. Unfortunately, the high cost of these medications has led to the requirement of a prior authorization process, which delays access to these medications. Our overall success rate in obtaining insurance approval was high (98.7% [79/80]), consistent with guideline recommendations²⁵ on the suitability of starting patients with severe disease on a biologic.

Despite this, we found that the time required to approve and fill these medications was excessive, with a mean time > 40 days. However, there was great variability in these times, and we sought to identify factors

that affected approval time. When comparing the subjects with short versus long approval times, there were no differences in insurance company, patient demographics, or clinical variables (lung function, controller medication use, total IgE level, blood eosinophil level). In addition, there were no trends related to specific biologic or diagnosis indication. It, therefore, seemed arbitrary why some prescriptions took longer to approve than others.

The submission that took 97 days for approval illustrated some of the gaps in the system. This prescription for benralizumab was initially denied because the subject had not tried and failed tiotropium, even though the subject had not responded to a different long-acting muscarinic antagonist, aclidinium. A peer-to-peer review was unsuccessful. Submission of a prescription for tiotropium was then rejected because it was not on the insurer’s formulary. We were able to provide a 4-week sample of tiotropium and the prior authorization was re-submitted after a lack of clinical improvement. It was again denied because there was not a record of an insurance claim for tiotropium. However, after another peer-to-peer review, benralizumab was approved.

It was surprising to find additional delays related to specialty pharmacies filling the medications. We hypothesized that this process would be relatively quick because the medication was already approved by the insurer by the time the prescription was sent to the specialty pharmacy. However, the amount of time required for the pharmacy to fill the medication (mean $\pm$ SD, 22.8 ± 14.1 days) was similar to the time it took for the insurer to approve the medication (mean $\pm$ SD, 21.5 ± 19.6 days). Although our nurses called the specialty pharmacies on a regular basis to check on the status (typically one to five times per week), we were not able to find any specific reasons for these delays.

It is likely that the specialty pharmacies need to take necessary steps to ensure that they receive payment for their services, given the high cost of the medications. The only significant factor related to fill times was the use of the buy and bill system, which was significantly shorter than the specialty pharmacy fill times. However, the use of the buy and bill system carries a risk of financial loss for practices, and we found that some patients had a higher copay when this system was considered. As a result, it is unlikely that our practice could adopt more widespread use of this method to reduce the time to fill these medications.

The impact of the delays in filling these medications on disease activity was potentially high because half of the subjects with severe asthma in our study had exacerbations that required one or more courses of prednisone while waiting for the biologic to be filled. The high cumulative dose of prednisone (mean $\pm$ SD, 483.2 ± 273.7 mg) was significant because our severe asthma clinic population was obese (mean BMI, 33.0 ± 8.8 kg/

m2), had diabetes (19% of patients with asthma), and had hypertension (32% of patients with asthma). These subjects, therefore, were at risk of not only adverse asthma-related outcomes but also adverse effects of prednisone on their comorbid conditions.

Our study did not address whether these subjects had reduction in exacerbations after starting therapy, so we could not say whether these exacerbations could have been prevented had the medications been approved quicker. However, the subjects' significant need for prednisone in this cohort underscored their high risk and disease instability, further emphasizing the need for rapid escalation of therapy.

The findings highlighted the crucial need to optimize the prior authorization process and reduce the amount of time to fill biologics. There are several interventions that could be optimized to streamline this process in clinics. These include standardizing the process to ensure that patients fit appropriate criteria before submission of the prior authorization, by confirming that factors such as previous medication use, lung function tests, and diagnostic criteria are met. However, this process is complicated by different requirements by different insurers. Our clinic has optimized our workflow to maximize pharmaceutical company resources, such as the Xolair starter program (<https://www.genentech-access.com/hcp/brands/xolair/learn-about-our-services/our-services.html>), AstraZeneca Access 360 (<https://www.myaccess360.com/home.html>), Gateway to Nucala (<https://www.gatewaytonucala.com/>), and Dupixent MyWay programs (<https://www.dupixenthcp.com/atopicdermatitis/access-support/dupixent-myway>).

The approval and fill times reflect our experience, even with maximum use of these resources; so, clearly, other changes are needed. We did not measure whether patient-specific copays delay filling medications. Patients with high copays may be eligible for financial assistance from pharmaceutical companies, and this application may be another source of delays in filling medications. We tried to identify patients with high copays as soon as the medication was approved by insurance companies, so that an application for financial assistance could be submitted as soon as possible. It is possible that there are additional opportunities to streamline this process.

CONCLUSION

Prior authorization of biologics delays therapy in patients with severe allergic disorders, and improvements in this process are needed. In addition to optimizing the application process on the physician and nurse side, we propose that changes need to occur at the level of the insurers and specialty pharmacies. There needs to be more standardization of approval criteria across insurers that reflect current consensus

guidelines. The process needs to be streamlined, simplified, transparent, and faster.

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