Elaborate biologic approval process delays care of patients with moderate-to-severe asthma

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Background: mAbs (biologics) are indicated in patients with poorly controlled moderate-to-severe asthma. The process of prior authorization and administration of a biologic requires exceptional commitment from clinical teams.
Objective: Our aim was to evaluate the process of approval and administration of biologics for asthma and determine the most common reasons associated with denials of biologics and delays in administration.
Methods: We examined the records of patients with asthma who were prescribed biologics from January 2018 to January 2020 at 2 centers, Montefiore Medical Center (Bronx, NY) and Scripps Clinics (San Diego, Calif). Demographics, insurance information, and details on the approval process were collected.
Results: After querying of electronic health records, the records of 352 and 70 patients with moderate-to-severe asthma were included from Montefiore and Scripps, respectively. Most patients at Montefiore (58.2%) were insured under Managed Care Medicaid (MC Medicaid), whereas most patients at Scripps (61.4%) had commercial insurance. The median times from prescription to administration of a biologic were similar: 34 days (interquartile range [IQR] = 18-63 days) and 34 days (IQR = 22.5-56.0 days) ($P = .97$) for Montefiore and Scripps, respectively. However, the median approval time for Montefiore was 6 days (IQR = 1-20 days) and that for Scripps was 22 days (IQR = 10-36 days) ($P < .001$). Approval times for prescriptions requiring appeals were significantly longer than for prescriptions approved after the initial submission: 23 days versus 2.5 days and 40.5 days versus 15.5 days (for Montefiore and Scripps, respectively [$P < .001$ for both]).
Conclusions: Lengthy appeals contribute to delays between prescribing and administering a biologic. Site-specific practices and insurance coverage influence approval timing of the biologics for asthma. (J Allergy Clin Immunol Global 2023;2:100076.)

Key words: *mAbs, asthma, omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, prior authorization*

According to the US Centers for Disease Control and Prevention, more than 20 million adults aged 18 years or older and 6 million children are affected by asthma in the United States.[1] There are several pharmacologic treatment options currently available for patients with asthma; they include inhaled corticosteroids with and without long-acting β-agonists, long-acting muscarinic receptor antagonists, leukotriene modifiers, systemic corticosteroids, and short-acting β-agonists. Patients with severe asthma account for 5% to 10% of the population of those whose asthma is inadequately controlled after using high-dose inhaled corticosteroids and long-acting β-agonist therapy.[2,3] Among those with asthma, 22.2% and 0.7% are diagnosed with moderate and severe asthma, respectively.[4] Even though moderate-to-severe asthma is less common, the direct and indirect costs associated with its treatment are 3 times higher than the costs of treating mild asthma.[4]

Six biologics that are currently approved for treatment of moderate-to-severe asthma in the United States. These mAbs are omalizumab, which binds IgE; mepolizumab and reslizumab, which target IL-5; benralizumab, which targets IL-5 receptor-α; dupilumab, which blocks IL-4 receptor-α signaling; and tezepelumab, which binds thymic stromal lymphopoietin (TSLP). Studies investigating the effectiveness of biologic treatments in severe asthma have shown reductions in exacerbations and systemic corticosteroid use as well as decreases in hospitalizations and emergency department visits.[5-9]

Nevertheless, a recent study based on commercial claims data showed low overall use of biologics by those with severe asthma.[10] In this study, the likelihood of biologic use was attributed to patients having a higher income and easier access to specialists.[10] In addition, a disproportionately lower use of biologics was reported among those who are publicly insured, who are also often the patients most affected by uncontrolled asthma.[11] Insurance carriers, such as federal versus commercial carriers, may influence approvals of biologic therapies.[11,12] One of the reasons for disparities in access to biologics is the high cost associated with

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Abbreviations used
ER: Emergency room
IQR: Interquartile range
MC Medicaid: Managed Care Medicaid

these treatments.[13-17] A recent review of the cost-effectiveness of the biologic therapy for asthma indicated that the wholesale acquisition costs of 5 biologics range from $31,000 to $39,000 per patient per year, which does not include administrative costs associated with their approval.[13] Biologic prescriptions require medical teams to be highly engaged in the process of biologic prescription, given the need for prior authorization. Lengthy prior authorization processes may put patients at risk for asthma exacerbations.[18]

The purpose of this study was to understand the logistics of approval and administration processes of biologics for asthma. We attempted to identify factors associated with the length of approval and administration of biologics. In addition, we investigated the common reasons for denials and delays in approvals and administration of biologics. We conducted this study at 2 US medical centers that differ in terms of geography, populations served, and insurance coverage: Montefiore Medical Center (Bronx, NY) and Scripps Clinics (San Diego, Calif).

METHODS

Patient cohort

Electronic health records were queried for patients for whom biologics were prescribed between January 2018 and January 2020 at Montefiore Medical Center, Bronx, NY (Montefiore) and Scripps Clinic, San Diego, CA (Scripps); both study sites used the EPIC electronic health records, which is a comprehensive electronic health record system. Patients who were prescribed a biologic for an indication other than asthma were excluded from the study. However, patients who were prescribed a biologic for another condition (eg, atopic dermatitis) but also had moderate-to-severe asthma were included.

Overall chart review

Demographic information, such as age at the time of prescription, sex, and race/ethnicity, was extracted from EPIC. Similarly, information on insurance, other allergic conditions, and the maximum eosinophil and serum total IgE values before biologic administration was recorded. Manual chart review was performed for all patients. We calculated approval rates, time intervals from prescription to approval and from prescription to medication administration, and the need for appeals. Appeals were defined as any interactions between health care providers and insurance in response to the initial denial of the biologic by insurance companies. This included letters of medical necessity provided by the physicians and provider calls to insurance carriers for a peer-to-peer review of treatment necessity. Tezepelumab was not US Food and Drug Administration–approved at the time of this study period and thus was not included in the analysis.

Detailed chart review

A subset of patients was randomly selected from the list at Montefiore for a detailed chart review. All of the prescriptions from Scripps were included for the detailed chart review. This additional review included identification of the common reasons for denials of biologic treatment approval by insurance and the reasons for discontinuation of a biologic. Emergency room (ER)/office visits and corticosteroid prescriptions associated with asthma were reviewed for the patients who continued biologic treatment for at least 6 months. Annualized rates of ER and office visits and corticosteroid prescriptions were calculated. The study was approved by the institutional review boards of Montefiore Medical Center/Albert Einstein College of Medicine and Scripps Clinics. Overall, the patient data were extracted for an additional 15 months beyond January 2020 (until April 2021) to assess discontinuations, frequency of ER and office visits, and steroid prescriptions.

Statistical analysis

All statistical analysis was performed in R software, version 3.6 (www.r-projecrt.org). In particular, R library lme4 was used for fitting generalized linear mixed effect models.[19] Wilcoxon rank sum tests were used to compare 2 medians. Fisher exact tests were used to test association between 2 categoric variables. Poisson mixed effect models were used to estimate the effect of biologics, with individuals as the random effects and the number of ER and office visits or the number of steroid prescriptions as the outcome, offset by the period of observation time. For the pretreatment outcome, we used the data from the 12 months before the treatment. For the posttreatment outcome, we used the data after the first 3 months of treatment.

RESULTS

Between January 2018 and January 2020, totals of 4634 and 1205 patients were seen for asthma at Montefiore and Scripps, respectively. Among these, 592 and 108 patients with moderate-to-severe asthma were prescribed biologics at Montefiore and Scripps, respectively. From Montefiore, a total of 352 patients (7.6% of all patients with asthma) were included in the study for basic chart reviews and 108 of them were randomly selected for the detailed chart reviews (Fig 1). From Scripps, 70 patients (5.8% of all patients with asthma) were included for both basic and detailed chart reviews (Fig 1).

Table I summarizes patient characteristics from both sites. The cohort from Scripps was older (median age 56 years) than the Montefiore cohort (median age 43.7 years). At both centers, more than 60% of the population was female. The Montefiore population had a higher percentage of Latinx and Black patients. The Scripps patients were predominantly White, followed by Asian. Although nasal polyps were more frequently diagnosed at Scripps (57.1% vs 27.6% at Montefiore), Montefiore had more patients diagnosed with aspirin-exacerbated respiratory disease (21.3% vs 15.7% at Scripps). Eczema or dermatitis was reported more commonly among the Scripps population (44.3% vs 26.4% at Montefiore [Table I]). At Montefiore, 58.2% of the individuals had Managed Care Medicaid (MC Medicaid) as their primary insurance, whereas at Scripps, commercial was the primary insurance type for 61.4% of the cohort. In addition to patients covered by commercial insurance and Medicare, Scripps had a small percentage of patients covered by Tricare (insurance for military personnel). There were no MC Medicaid–insured patients at Scripps.

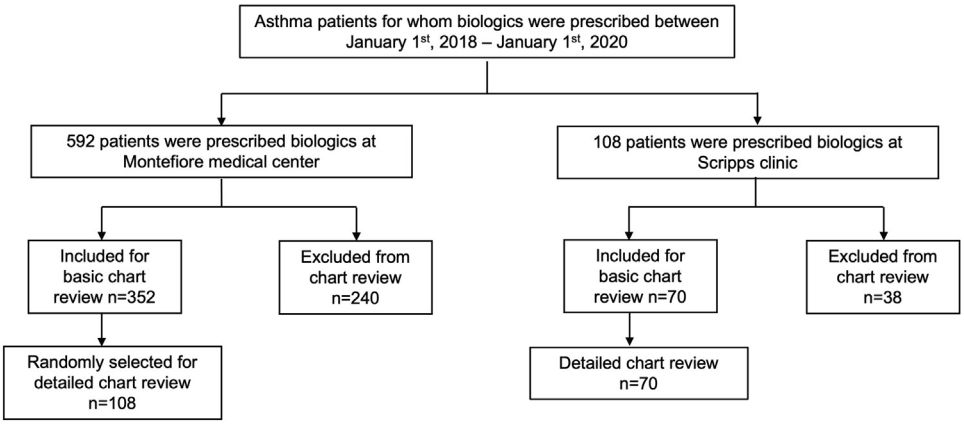

FIG 1. Schematic representation of the study design and patient inclusion at Montefiore Medical Center and Scripps Clinic. The exclusion criteria were as follows: the biologic was prescribed, approved, and administered before 2018, and the biologic was prescribed for an indication other than asthma.

TABLE I. Characteristics of patients taking biologics for asthma at Montefiore and Scripps from January 2018 to January 2020

Characteristic	Montefiore (n = 352)	Scripps (n = 70)
Demographics		
Age (y)		
Median (IQR)	43.7 (26.7-59.1)	56 (45.5-66.5)
Mean (SD)	41.9 (20.8)	56.31 (13.5)
Female sex, no. (%)	245 (69.6)	43 (61.4)
Race/ethnicity, no. (%)		
White	46 (13.1)	53 (75.7)
Black	104 (29.5)	2 (2.9)
Latinx	138 (39.2)	3 (4.3)
Asian	6 (1.7)	9 (12.8)
Other/unknown	58 (16.5)	3 (4.3)
Diagnosis		
Asthma, no. (%)	352 (100)	70 (100)
Nasal polyps, no. (%)	97 (27.6)	40 (57.1)
NSAID allergy, no. (%)	97 (27.6)	13 (18.6)
AERD, no. (%)	75 (21.3)	11 (15.7)
Chronic idiopathic urticaria, no.(%)	76 (21.6)	13 (18.6)
Eczema/dermatitis, no. (%)	93 (26.4)	31 (44.3)
Insurance		
MC Medicaid, no. (%)	205 (58.2)	-
Medicare, no. (%)	30 (8.5)	23 (32.9)
Commercial, no. (%)	117 (33)	43 (61.4)
Other, no. (%)	-	4 (5.7)
Biomarker		
Max eosinophil count recorded (k/uL), median (IQR)	0.3 (0.2-0.8)	0.3 (0.1-0.6)
Max IgE level recorded (IU/mL), median (IQR)	252.5 (95-697)	261 (78-568)

AERD, Aspirin-exacerbated respiratory disease; *max*, maximum; *NSAID*, nonsteroidal anti-inflammatory drug.

Prescription distribution, approval, and medication administration

Overall, for 352 patients at Montefiore, a total of 406 prescriptions of biologics were issued during the study period. For Scripps, 70 patients had 100 prescriptions; 54 and 27 patients at Montefiore and Scripps, respectively, were prescribed more than 1 biologic during the study with no known overlaps. The distribution of prescriptions was slightly different between the 2 sites ($P = .024$). Whereas dupilumab accounted for 37% and 42% of all prescriptions at Montefiore and Scripps, respectively, omalizumab prescriptions were slightly higher at Montefiore (at 33.7%) than at Scripps (at 18%) (Fig 2).

After exclusion of 52 patients with missing information, the overall approval rate was 92.2% (419 of 454). The approval rates at the 2 sites were almost identical, with rates of 92% (332 of 361) and 93.5% (87 of 93) at Montefiore and Scripps, respectively (Fig 3, *A*). The approval rate was slightly higher for patients insured under MC Medicaid (197 of 208 = 0.95) and Medicare (57 of 61 = 0.93) than for those with commercial insurance (162 of 182 = 0.89) (data not shown). Among those who were approved, the overall administration rate was 89.7% (376 of 419). The administration rate was slightly lower at Montefiore (87.3% [290 of 332]) than at Scripps (99% [86 of 87]) (Fig 3, *B*). Notably, patients could still have received medication even if the prescriptions were denied by their insurance if they were approved through free drug programs offered by manufacturers of the biologics for asthma. However, because of the discrepancy in the availability of the free drug programs by income, most of the patients who benefited from these programs were insured through the government-sponsored insurance carriers. Commercially insured patients may receive copay assistance.

Even though the rates of approval were similar between the 2 sites, the time from prescription to approval was significantly shorter at Montefiore (median = 6 days [interquartile range (IQR) = 1-20 days]) than at Scripps (median = 22 days [IQR =10-36]) at $P < .001$ [Fig 4, *A*]). Within each site, we found that the approval time was similar among the insurance carriers (see Table E1 in the Online Repository at www.jaci-global.org) and for the types of prescribed biologics (data not shown). Furthermore, we found no association between approval time with the levels of biomarkers, IgE, or eosinophils (data not shown). The time from prescription to administration was similar at the 2 sites, with medians of 34 days (IQR = 18-63) at Montefiore and 34 days (IQR = 23-56) at Scripps ($P = .97$) (Fig 4, *B*). Even though the time of approval

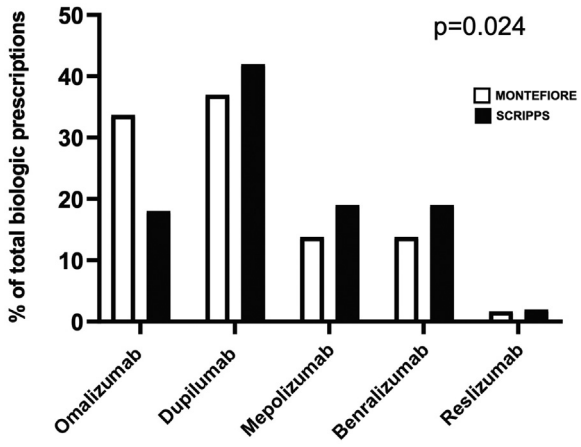

FIG 2. Distribution of biologic prescriptions at Montefiore and Scripps.

from the time of prescription was significantly shorter at Montefiore, the time of administration from the time of approval was significantly shorter at Scripps: 17 days (5.5-30.5 days) vs 22 days (8-43 days) ($P = .037$) (Fig 4, *C* and see Fig E1 in the Online Repository at www.jaci-global.org).

Time to approval after appeals to insurance. Insurance carriers initially denied 38.8% of the prescriptions (140 of 361) at Montefiore and 24.7% of the prescriptions (23 of 93) at Scripps. We compared the time to prescription approval on the first submission versus prescription approvals that were initially denied and then appealed. We observed that appeals necessitated significantly longer time for approval: 2.5 days (IQR = 1-7 days) for approvals on first submission of the prescription versus 23 days (IQR = 12-48 days) for prescriptions that needed appeals at Montefiore ($P < .001$), and 15.5 days (IQR = 7.2-28.8 days) versus 40.5 days (IQR = 29.3-48.7 days) at Scripps ($P < .001$) (Fig 5). Further comparison of the timing from prescription to approval on the first submission to insurance revealed that Montefiore patients under Medicare or MC Medicaid coverage had somewhat faster approval rates than did the patients with commercial coverage, although the difference was not significant (a median approval time of 1 day [IQR = 1.0-10.75 days] for Medicare, 2 days [IQR = 1.0-6.0 days] for MC Medicaid, and 4 days [IQR = 1.0-9.75 days] for commercial insurance [$P = .08$] [see Table E2 in the Online Repository at www.jaci-global.org]). However, site practices seemed to be of greater importance than insurance coverage.

There was no association of denials with either insurance carriers or type of biologic (data not shown).

Denials and discontinuation. The medical records of 108 patients were reviewed for additional details at Montefiore, for whom there were 131 prescriptions. All 70 patients with a total of 100 prescriptions from Scripps underwent detailed review. The prescription distribution by biologic was similar to the overall distribution of prescription by biologic at each site (data not shown).

The most common reasons for denials were similar at both sites: (1) no additional information was obtained from health care providers and (2) the biologic was excluded from the patient's benefits (Table II).

The rates of discontinuation were between 50% and 60% at both sites. Table III summarizes the most common reasons for discontinuation, namely, loss to follow-up or the COVID-19 pandemic (32.3%), followed by lack of response (30.7%).

ER and office visit and steroid prescriptions. Lastly, we evaluated the effect of biologics on asthma control in patients who completed at least 6 months of treatments. Overall, the rate of ER and office visits after the treatment decreased by 38% (95% CI = 29%-46%) compared with the rates during the 12 months preceding biologic treatment. The rates of corticosteroid prescriptions after the treatment decreased by 59% (95% CI = 51%-65%) compared with the rates preceding biologic treatment (see Table E3 in the Online Repository at www.jaci-global.org).

DISCUSSION

mAbs or biologics are often prescribed to patients with inadequately controlled moderate-to-severe asthma.[5-9] In this study we assessed the process from the biologic prescription to medication administration to patients from 2 medical centers that serve distinct populations in the states of New York and California. We found that the time from prescription to approval was shorter at Montefiore, where the population is mostly insured by federal insurance carriers (MC Medicaid). However, the time from biologic approval to its administration was faster at Scripps, leading to a nearly identical timing from prescription to administration at both Scripps and Montefiore. We found that at both sites, prescriptions needing an appeal required a longer time for approval. As expected, we observed a reduction in ER and office visits for asthma and corticosteroid prescriptions associated with asthma exacerbations when patients were undergoing biologic treatment, thus emphasizing the need for a faster process of biologic approvals.

At both sites, the approval time did not depend on the biomarker values such as IgE levels for the approval of omalizumab or eosinophil counts for approval of mepolizumab, benralizumab, or reslizumab, as was also observed by Dudiak et al.[18] The timing of approval on first submission to insurance indicated that federal insurance coverage provided comparable, and possibly faster, approvals than commercial insurance (see Table E2). The timing of approvals in this study was also related to the practices implemented by clinical teams that were developed on the basis of the specifics of insurance carriers. For example, at Scripps, the majority of the population was insured by commercial carriers, which frequently require a copayment for these costly medications. Additional investigation of the copayment affordability likely contributed to a major delay in biologic approvals. Only after patient acceptance of the copayment were prior authorization requests further processed by Scripps teams. At Montefiore, most patients were insured by MC Medicaid and had no copayment for a biologic therapy; therefore, the approval process was faster. The differences in insurance coverage could explain demographic differences in the 2 cohorts. MC Medicaid is a federal-state assistance program that serves individuals of every age in a low-income group.[20] The Bronx population is represented by racial and ethnic minorities, who are more likely to be publicly insured.[10,11] Although others found that public insurance poses disadvantages in access to biologics for asthma,[10,11] our study could not confirm this finding and indicated that federal insurance may offer a comparable, and possibly faster, approval timing of the biologics for asthma. Among all patients with asthma seen at both centers during the study period, slightly more patients (7.6%) were prescribed biologics at

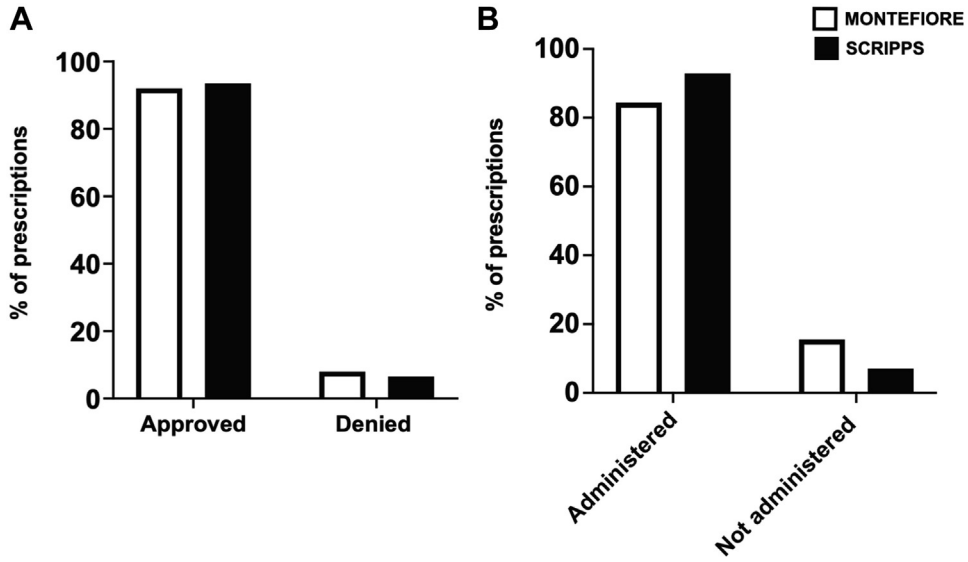

FIG 3. Rates of biologic approval (**A**) and administration (**B**) at Montefiore and Scripps.

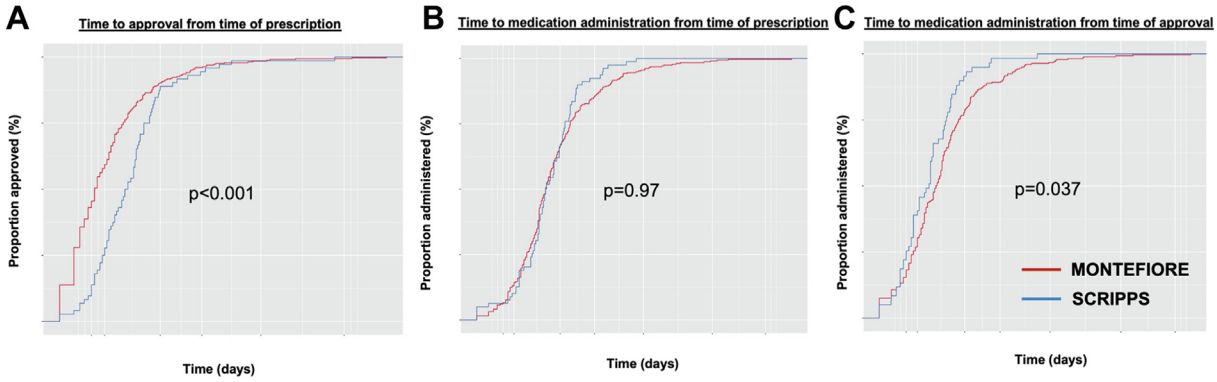

FIG 4. Duration from the time of prescription to time to approval (**A**) and to time of medication administration (**B**). **C,** Time to medication administration from the time of approval.

Montefiore than at Scripps (5.8%). The higher numbers of patients with asthma seen at Montefiore also correspond to the higher rates of asthma, and especially severe asthma, in Bronx, NY.[21-24]

The reasons for a longer time from approval to medication administration at Montefiore could likely be explained by several factors. Following the approval of the biologic, the prescription needed to be submitted to a specialty pharmacy for scheduling delivery, which is preceded by prescription verification, billing approvals, and contacting of patients. At Montefiore, patients were frequently unavailable for phone calls from the specialty pharmacy. Notably, the specialty pharmacies have also been identified as a reason for delay in filling prescriptions by Dudiak et al.[18]

We also found that a significantly longer time was needed for approvals if prescriptions were initially denied by the insurance. A quarter to a third of all patients required appeals. The most common reason for the denial was a lack of information provided to the insurance by clinical teams, which might be an area of potential improvement when submitting for biologic approvals. This finding is similar to the data from a recent study in which the most common reason for denial of biologics was the lack of the additional information.[18] A delay in the prior authorization process poses an increased risk of exacerbations for patients with severe asthma.[18]

A recent report showed higher out-of-pocket spending on inpatient and emergency health care among low-income patients with asthma.[25] We observed a significant decrease in ER and office visits and corticosteroid prescriptions for asthma exacerbations after patients started biologic treatment, emphasizing the importance of a quick and efficient approval process.

In a physician survey conducted by the American Medical Association in 2020, 94% of respondents reported care delays associated with prior authorizations and 79% reported that at least sometimes, this could lead to treatment abandonment by patients.[26] We recognize this same concern in our patients, and we also wonder whether denials and lengthy approval processes might lead to physician abandonment of pursuing approval. Given that the prior authorization might occasionally lead to abandonment of the biologic prescription owing to perceived or real issues with staff time commitment, this might be another way for the insurance to deny a biologic medication. Table IV lists the caveats

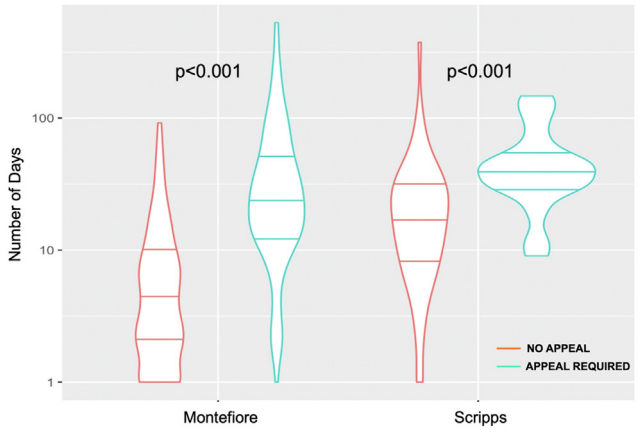

FIG 5. Violin plot comparing median time to approval between prescriptions that did not require appeals versus prescriptions that required appeals.

TABLE II. Reasons for denial of the biologics for patients as indicated by their insurance

Reason for denial	Prescriptions (n = 48)
No additional clinical information was provided, no. (%)	20 (41.7)
Excluded from patient benefit, no. (%)	11 (22.9)
Not medically necessary, no. (%)	10 (20.8)
Other reason, no. (%)	4 (8.3)
Patient advised to try an inhaled corticosteroid and long-acting β-agonist, no. (%)	3 (6.3)

TABLE III. Reasons for discontinuation of the biologic treatment

Reason for discontinuation	Prescriptions (n = 127)
Lost to follow-up or because of COVID-19 pandemic restrictions, no. (%)	41 (32.3)
Lack of response, no. (%)*	39 (30.7)
Side effects, no. (%)	14 (11)
Patient preference, no. (%)	14 (11)
Inadequate insurance coverage, no. (%)	11 (8.7)
Noncompliance, no. (%)	8 (6.3)

*Defined as the need for prednisone taper for treatment of asthma exacerbations while compliant with a biologic.

TABLE IV. Caveats associated with the process of approval and administration and possible areas of improvement

Delay and reasons	Possible remedy
Delay in approval and reasons	
Copayment	Determine copayment details during the time of prescription by a designated prior authorization team
Need for appeal because of inadequate information	Assign a designated prior authorization team that provides a prior authorization form along with the clinical notes up front
Delay in administration and reasons	
Involvement of specialty pharmacies	1. Streamline the process at specialty pharmacies 2. Consider a buy and bill option
Unavailability of the patients for phone calls from the specialty pharmacy	Ensure patient education about the biologic approval process, and encourage patient engagement and participation

associated with the process of approval and administration and possible areas of improvement. Streamlined prior authorization practices could be helpful in establishing an efficient process of biologic approval and administration.

This study has several limitations. We investigated the logistics of approval and administration of the biologics at only 2 sites. Other institutions may experience similar or different issues in biologic approvals. In addition, we were unable to compare MC Medicaid approval timing between the 2 sites, as Scripps had no patients who were insured under MC Medicaid. Another limitation was the high discontinuation rate of biologics. Unlike in other years, one of the main reasons for discontinuation was the COVID-19 pandemic. Finally, the fact that all of the initial biologic prescriptions were ordered using a procedure different from that used to order typical pharmaceuticals (whereas typical pharmaceuticals would be prescribed via an electronic prescription, the ordering of biologics occurred outside the EHR on paper forms) limited our ability to capture all data that were not scanned into the system.

This study also has several strengths. We evaluated the biologic prescription process at 2 study sites serving patient populations from diverse economic and cultural backgrounds. We carefully investigated the workflow at each site, identifying pitfalls and making it possible to suggest improvements. Our data set was reasonably complete, as we encountered missing information in less than 10% of patients at either site. Finally, we confirmed with "real-life" data that biologic treatment for moderate-to-severe asthma makes an important improvement in patient well-being by reducing the need for ER and office visits and for systemic corticosteroids.

In conclusion, there is a substantial delay between prescribing and administering a biologic medication in patients with moderate-to-severe uncontrolled asthma. This delay can be attributed to multiple factors, such as the initial requirement for prior authorization, requirement for appeals, and patient engagement. Prior authorization teams should work closely with insurance carriers and adjust the approval process to their requirements. A faster process by a dedicated prior authorization team, patient education, and greater affordability of biologics for patients with commercial insurance could help in reducing delays in approvals and administration of biologics.

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