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Treatment Delays Associated with Prior Authorization for Infusible Medications: A Cohort Study

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Abstract

Background: Prior authorizations (PA) are commonly used by health payers as cost-containment strategies for expensive medications, including infused biologics. There is scarce data about the effect of PA requirements on patient-oriented outcomes.

Methods: We included subjects for whom an infusible medication was prescribed for a rheumatologic condition. The exposures of interest were a PA requirement and whether or not the PA was denied. The primary outcome was the difference in days from medication request to infusion. Secondary outcomes included the proportion of denied PAs and differences in glucocorticoid exposure following PA request.

Results: Of the 225 subjects, 160 (71%) required a PA. PAs were associated with a greater median (IQR) number of days to infusion compared to cases in which no authorization was required (31 days [15, 60] vs 27 days [13, 41], p=0.045), especially among the 33 (21%) subjects whose PA was denied initially (50 days [31, 76] vs 27 days [13, 41], p<0.001). PA denials were associated with greater median (IQR) prednisone-equivalent glucocorticoid exposure in the 3 months following the request than when a PA was not required (605mg [0, 1575] vs 160mg [0, 675], p=0.01). Twenty-seven (82%) of the 33 PA requests initially denied were eventually approved. Thus, 96% of all PAs were ultimately approved.

Conclusion: PA requirements are associated with treatment delays and denials are associated with greater glucocorticoid exposure. Because the great majority of PA requests are ultimately approved, the value of PA requirements and their impact on patient safety should be re-evaluated.

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INTRODUCTION

Infused medications, many of which are biologics (e.g., rituximab, infliximab), have transformed the health and function of patients with multiple forms of disease, including rheumatoid arthritis, osteoporosis, systemic lupus erythematosus, vasculitis, multiple sclerosis, inflammatory bowel disease, pemphigus vulgaris, and many others (1–7). Infused medications are among the most expensive drugs. They are frequently used to treat rare conditions that can be organ- or life-threatening and for which few or no medications have received regulatory approval because of their relative scarcity (8). Infused medications often have neither generic substitutes nor oral or subcutaneous formulations and inevitably require advanced planning to administer (e.g., scheduling with an infusion center).

Infused medications typically require prior authorization (PA), a process commonly used by both public and private health payers to contain costs associated with drug coverage benefits, especially in recent years as drug costs have soared. However, the impact of PA requirements on individual patients remains poorly understood. Previous studies provided conflicting results regarding their impact on patients with neuro-psychiatric conditions, chronic infections, and other diagnoses (9). PA requirements may decrease drug use and associated costs but often carry unintended consequences, including increased healthcare utilization during delays as well as non-reimbursed provider time and administrative expenses. Such unintended consequences are estimated to cost the United States (US) healthcare system over $30 billion annually (9–12).

PA requirements for patients with rheumatic diseases may introduce additional lags in treatment for patients who already face diagnostic delays and poor outcomes when treatment is deferred (13–19). Moreover, PA denials for patients with certain rheumatologic diseases and the consequent delays in access to effective, glucocorticoid-sparing medications may put patients at higher risk of glucocorticoid-related toxicity, including infection, cardiovascular disease, and diabetes (20).

Little is known about the effect of PA requirements, especially for infused medications, on patient-oriented outcomes such as time to treatment. To address this knowledge gap, we leveraged the variability in PA requirements to assess the impact of PA requirements and denials on this important aspect of medical care.

MATERIALS AND METHODS

Source Population

We used the electronic medical record system to identify subjects for whom an infusible medication was ordered by a provider in the Rheumatology Unit of Massachusetts General Hospital between July 1st, 2016 and June 20th, 2018, when data were accessed. July 1st, 2016 was chosen because it was the date when a single administrative assistant assumed the responsibility for managing all infused medication authorization requests for the Rheumatology Unit. This study was approved by the Partners HealthCare Institutional Review Board.

We reviewed the electronic health record (EHR) of each identified subject and extracted relevant variables, including demographics, insurance provider at the time of authorization request, medication ordered, disease diagnosis, and date of order. We assessed whether or not there was an FDA-approved treatment for each condition as well as if the condition was designated as a rare disease (21). From our practice's routine EHR documentation, we extracted details regarding whether a PA was required and the date of that determination (i.e., index date), response from insurance provider, and any subsequent follow-up (i.e., peer-to-peer). We also extracted the cumulative prednisone-equivalent glucocorticoid exposure in the 90 days following the index date. We included consecutive subjects with complete data regarding the dates of therapy orders, determination of whether or not a PA was required (i.e., index date), health insurer response, and infusion (if approved either initially or upon appeal). We excluded subjects who had incomplete data regarding dates of PA statuses (N=241), approval but no documented infusion (N=20), those who received an infusion as an inpatient (N=6), and those who received treatment on an investigational basis (N=1). In a convenience sample analysis of 35% of the subjects with incomplete data, over half did not have a documented date of PA request which was used to measure the primary outcome. However, when we compared the difference in median number of days between physician order and infusion, our results were similar to those presented in Table 2, such that exclusion of these cases is unlikely to have significantly affected our results.

Primary and Secondary Outcomes

The primary outcome was the time between the index date and infusion among the cases requiring a PA compared with those who did not require a PA. For the analysis of secondary outcomes, we identified three key sub-groups: 1) those whose PA requests were denied; 2) those whose requests were approved; and 3) those who did not require a PA. Among those for whom a PA was required (sub-groups 1 and 2), we evaluated the proportion of PA requests denied and the proportion of denials successfully appealed. We then assessed the differences among the sub-groups in time between the index date and infusion as well as glucocorticoid exposure in the 90 days following the index date, using sub-group 3 as the reference.

Matching to Assess the Impact on Glucocorticoid Use

To account for differences in glucocorticoid usage across diagnoses, we also assessed differences in glucocorticoid exposure after matching patients on two factors: (1) the general condition for which the infusion was prescribed and (2) whether or not the PA request pertained to starting a new medication. Matching was done blinded to the glucocorticoid exposure for each subject. We matched each subject with a PA denial who eventually received the intended infusion to a subject who did not require authorization or received authorization on the same day as submission. Each control was used once.

Statistical Analyses

Continuous variables are reported as mean ± standard deviation (SD) or median and interquartile range (IQR), where appropriate. Categorical variables are reported as frequencies (%). Differences in time to infusion across sub-groups were compared using the Mann-Whitney U Test and quantile regression at the 75^{th} percentile adjusted for age, sex,

and insurance type (private vs public). After finding numerical differences in glucocorticoid exposure across sub-groups at the 75th percentile in the IQR, glucocorticoid exposure across the three sub-groups prior to matching was compared using quantile regression at the 75th percentile in both unadjusted and age-, sex-, and insurance-type-adjusted analyses. Differences in glucocorticoid in the matched analysis were compared using the Mann-Whitney U Test and using quantile regression at the 75th percentile adjusted for age and sex. Unadjusted and age- and sex-adjusted logistic regression was used to assess the association between a condition not having an FDA-approved medication for that indication and the odds of a PA being denied.

A two-sided P value of <0.05 was considered significant in all analyses. We used SAS, version 9.4 (SAS Institute, Cary, NC, USA) for all statistical analyses.

RESULTS

Demographics of Subjects

Among the 225 subjects with medications ordered for infusion, the majority were female (149, 66%), white (188, 84%), and non-Hispanic (213, 95%, Table 1). The average age at the time of the medication request was 53 (±15) years. Inflammatory arthritis (71, 32%), vasculitis (52, 23%), and IgG4-related disease (38, 17%) were the most common conditions for which an infused medication was ordered, and 119 (53%) of the orders were for diseases designated as rare. There was no FDA-approved medication for the condition being treated in 89 (40%) subjects. Rituximab was the most frequently requested medication (157, 70%), followed by infliximab (39, 17%).

Time to Infusion and Glucocorticoid Exposure According to PA Requirements

PA was required for 160 (71%) subjects. Compared to cases in which no PA was required, those requiring PA were associated with a significantly greater median number of days from the index date to insurance response (5 [1, 9] vs 0 [0, 0], p<0.001), insurance approval (6 [1, 15] vs 0 [0, 0], p<0.001), and infusion (31 [15, 60] vs 27 [13, 41], p=0.045) (Table 2). The statistical significance of these differences persisted in analyses adjusted for age, sex, and insurance type. The median time to infusion was 29 (15, 53) days from the index date for all subjects.

The median glucocorticoid exposure in the 90 days following the index date was 360mg (0, 900mg). The median glucocorticoid exposure among those who required a PA was 364mg (0, 1089mg) compared with 160mg [0, 675mg] for those who did not require a PA (p=0.1). This difference remained stable in analyses adjusted for age, sex, and insurance type (P=0.3).

Prior Authorization Denials

Of the subjects who required a PA (N=160), 127 (79%) were approved and 33 (21%) were denied after the first request. IgG4-related disease (10, 33%), connective tissue disease (9, 27%), and inflammatory arthritis (5, 15%) were the most common conditions for which PA requests were denied (Table 3, Appendix Table 1). The majority of the PA denials were for

the use of rituximab (23, 70%), followed by infliximab (4, 12%) and tocilizumab (4, 12%). Nearly half (16, 48%) of the subjects whose PA requests were denied had previously tried or were taking an oral disease-modifying anti-rheumatic drug (DMARD, e.g., methotrexate).

The most common reason for denial was off-label use of a medication (27, 82%), but in 21 (78%) of those cases, the condition had no FDA-approved treatment. Compared to those patients with a condition with an FDA-approved treatment, having a condition with no FDA-approved treatment was associated with a higher odds ratio (OR) of having a PA denied in unadjusted (OR 2.2 [95% CI: 1.03–4.86]) and age- and sex-adjusted analyses (aOR 2.9 [95% CI: 1.3–6.8]).

Twenty-seven (82%) of the 33 PAs originally denied were eventually approved after appeal. Of the denials, 26 (79%) were appealed successfully through a peer-to-peer discussion; one peer-to-peer was not initially successful, and the patient used the insurer's preferred drug. One additional denial was overturned after additional laboratory testing was performed to exclude infection. In five (16%) cases, the insurer's preferred drug (e.g., adalimumab) needed to be used rather than the requested infusion (e.g., infliximab). In total, 154 (96%) of required PAs were ultimately approved.

Time to Infusion and Glucocorticoid Exposure Among Subjects with PA Denial

PA denial was associated with a significantly greater median number of days from the index date to insurance response (8 [5, 13] vs 0 [0, 0], p<0.001), insurance approval (22 [15, 41] vs 0 [0, 0], p<0.001), and infusion (50 [31, 76] vs 27 [13, 41], p<0.001), compared to cases in which no PA was required (Table 2). The statistical significance of these differences persisted in analyses adjusted for age, sex, and insurance type. PA denials were also associated with significantly greater glucocorticoid exposure when compared to those in whom no authorization was required (605mg [0.0, 1575] vs 160mg [0.0, 675], p=0.01) and these differences persisted in age-, sex-, and insurance type-adjusted analyses (P=0.03).

Subjects whose PA requests were denied but later approved (n=27) were each matched to a subject who either did not require PA (n=25) or had same-day approval of a PA request if no other match was available (n=2). Diagnoses were similar for each matched pair (Appendix Table 2). Controls were older than cases (59 ±17 years vs 49 ±11 years, respectively; p=0.01); the sex distribution was identical (12 [44%] males in both groups). Compared to controls, subjects whose PAs were initially denied were more often prescribed glucocorticoids (18 [67%] vs 11 [41%], p=0.1) and had significantly greater prednisone-equivalent glucocorticoid exposure (740mg [0, 1,690] vs 0mg [0, 450], p=0.006) in the 90 days following the medication request. These differences persisted in age- and sex-adjusted analyses (P=0.01).

DISCUSSION

PA requirements for infusible medications introduce delays in treatment for rheumatology patients, especially for the approximately 20% of patients whose PAs are initially denied. US physicians reported this phenomenon in a recent American Medical Association survey (11), but, to our knowledge, this is the first study to assess this clinically-relevant endpoint.

The delays are particularly relevant for this patient population, many of whom have rare or uncommon diseases with no FDA-approved medications or few options which may be ineffective in some. In addition to delays in infusion initiation, denied PAs are associated with excess glucocorticoid exposure. Thus, PAs constitute a barrier to the introduction of effective treatment in an expeditious manner and facilitate unnecessary glucocorticoid exposure and the attendant adverse effects of glucocorticoid medications which can occur at low doses and with short-term use (13–19, 22, 23).

More than 25 million Americans suffer from rare or uncommon diseases such as lupus nephritis, vasculitis, and IgG4-related disease (21). These conditions are associated with diagnostic delays, can be organ- or life-threatening, and often have no FDA-approved therapies (21). Off-label medication use was the most common reason for PA denial in our study even though the FDA has acknowledged the need for off-label use in certain instances (8). Indeed, we found that the condition being treated had no FDA-approved medication in 78% of denials. Moreover, nearly half of the denied patients had already tried an oral DMARD – often less expensive than an infused medication – before their PA was denied. These findings demonstrate that the downstream detrimental effects of PA denials are often imposed on patients with rare diseases and other conditions for which the treatment options are limited.

Our results have implications for policies regarding the management of infusible medications under Medicare, which covers many patients with immune-mediated conditions (24–26). For many Medicare patients, infusible medications are covered under medical benefits (i.e., Part B) and have not traditionally required PA; our results demonstrate this policy as older patients were less likely to require a PA. However, recent Federal policies meant to control rising expenditures on medications allow Medicare plans to use PAs for medications administered under Part B (27). Our data suggest that patients covered by Medicare, especially those with rare conditions who may face PA denials, are likely to face treatment delays and greater glucocorticoid exposure under such a policy change.

Our findings highlight opportunities to improve access to treatment for patients who might benefit from infusible medications. First, if 96% of PA request are ultimately approved, the value of such gatekeeping should be reconsidered. Second, if PAs are required, then the turn-around time for requests, appeals, and peer-to-peer discussions must be shortened and a standardized, streamlined process for conducting such appeals should be provided. These adjustments would require commitments from both insurers as well as providers. Third, the median delay in the institution of treatment was 29 days, regardless of PA requirements. Similar challenges have been reported across other specialties employing biologic medications (28–31). Improving the operational efficiency of infusion centers may help them accommodate additional infusions each day, which could shorten the delay in treatment experienced by most patients, even those not requiring a PA, and may minimize the difference in delays in infusion between those whose PA is initially approved and those who did not require one.

Strengths of our study include its assessment of two complementary patient-oriented outcomes (time-to-treatment and glucocorticoid exposure) and its novel approach to

addressing issues important to both patients and providers in a data-driven way. The study also has certain limitations, however. Because this is a single-center study, the generalizability of our findings is limited by the referral patterns, practice approaches, and demographics of our tertiary referral center. As a referral center, we may be more likely to see a case mix enriched for increased complexity or rare conditions not typically managed in other settings; therefore, the frequency of PA requirements or delays in treatment may not be generalizable to other centers. However, our study allowed us to evaluate details of each case (e.g., disease manifestations, treatment history and response) typically unavailable in claims databases. Moreover, our PA approval rate is similar to that described at other tertiary care centers investigating PAs for different medications (32, 33) and our findings are consistent with sentiments expressed in a recent national survey of providers (11). Second, we were unable to assess some potential confounders (e.g., socioeconomic status, prior glucocorticoid toxicity) and relevant outcomes (e.g., healthcare utilization, infection, cardiovascular events) that may differ depending on PA requirements because of the relatively small size of our cohort, the retrospective design, and inability to account for events that occur outside of our healthcare system. However, we were still able to account for certain relevant confounders in adjusted analyses and to detect significant differences with regard to time-to-treatment and glucocorticoid exposure (34–36). It is important to note that our intention was not to demonstrate the efficacy of treatments used off-label or after PA appeal but to assess the impact that PA requirements have on patient access to treatment deemed appropriate by their providers.

Although the vast majority of PAs are eventually approved, their requirement is associated with delays in treatment and may contribute to excess glucocorticoid exposure, especially when denied. In addition to previously described administrative and physician burdens associated with PA requirements, our observations suggest that PA requirements interfere with the delivery of timely and appropriate care for rheumatology patients. In light of these findings, the value of PA requirements in healthcare is unclear and future studies should prospectively evaluate their impact on other patient-oriented outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE AND INNOVATION

- Prior authorizations (PA) are commonly used by health payers to contain costs but their impact on patient-oriented outcomes in rheumatology is poorly understood.
- We found that PAs are required in 71% of cases in which an infused medication is ordered and 21% of these are initially denied.
- Following appeals, 96% of all PA requests are ultimately approved.
- PA requirements are associated with delays in time to infusion and greater glucocorticoid exposure, especially when the initial PA request is denied.

Table 1:

Baseline Demographics of Cohort

	Overall N (%)	No PA Required N (%)	PA Required N (%)
N	225 (100)	65 (29)	160 (71)
Female	149 (66)	41 (63)	108 (68)
Race			
White	188 (84)	54 (83)	134 (84)
Black	11 (5)	3 (5)	8 (5)
Asian	10 (4)	3 (5)	7 (4)
Other	13 (6)	3 (5)	10 (6)
Unknown	3 (1)	2 (3)	1 (1)
Ethnicity			
Non-Hispanic	213 (95)	62 (95)	151 (94)
Hispanic	12 (5)	3 (5)	9 (6)
Age [Mean, SD]	53 [15]	62 [16]	50 [13]
Disease or Disease Category			
Inflammatory Arthritis	71 (32)	27 (42)	44 (28)
Vasculitis	52 (23)	16 (25)	37 (23)
IgG4-Related Disease	38 (17)	9 (14)	29 (18)
Connective Tissue Disorder	23 (10)	3 (5)	20 (13)
Myositis/Interstitial Lung Disease	20 (9)	5 (8)	15 (9)
Other*	21 (9)	5 (8)	15 (9)
Designated Rare Disease†	119 (53)	33 (51)	86 (54)
Condition with no FDA-Approved Medication	89 (40)	22 (34)	67 (42)
Private Insurance	160 (71)	28 (43)	132 (83)
Medication			
Rituximab	157 (70)	49 (75)	108 (68)
Infliximab	39 (17)	10 (15)	29 (18)
Tocilizumab	21 (9)	6 (9)	15 (9)
Zoledronic Acid	7 (3)	0 (0)	7 (4)
Intravenous Immunoglobulin	1 (<1)	0 (0)	1 (1)
New Request	131 (51)	30 (46)	101 (63)
Outcomes Following Infusion Order			
PA – Approval	127 (56)	0 (0)	127 (79)
PA – Denial	33 (15)	0 (0)	33 (21)
No Authorization Required	65 (29)	65 (100)	0 (0)

*Other refers to: Psoriasis, Sarcoidosis, Osteoporosis, SAPHO Syndrome, Neuromyelitis optica, Idiopathic Uveitis, and Orbital Pseudotumor

†Examples include systemic vasculitis, interstitial lung disease related to connective tissue disease, IgG4-related disease, inflammatory myopathy, and autoinflammatory disorders

Table 2:

Patient-Oriented Outcomes Following Prior Authorization (PA) Request Submission Among Patients Requiring Prior Authorization Compared with Patients not Requiring Prior Authorization

	Overall	No PA Required	PA Required		
			All	Approved	Denied
N	225 (100%)	65 (29%)	160 (71%)	127 (79%)	33 (21%)
Days between PA request [*] and insurance response (Median, IQR) [†]	1 (0, 7)	0 (0, 0)	**5 (1, 9)**	**4 (0, 9)**	**8 (5, 13)**
Days between PA request and insurance approval	1 (0, 9)	0 (0, 0)	**6 (1, 15)**	**4 (0, 9)**	**22 (15, 41)**
Days between PA request and infusion	29 (15, 53)	27 (13, 41)	**31 (15, 60)**	27 (13, 56)	**50 (31, 76)**
90 Day Glucocorticoid (mg) Exposure [‡]	360 (0, 900)	160 (0, 675)	364 (0, 1089)	280 (0, 1035)	**605 (0, 1575)**

Bold font indicates P<0.05 when comparing category vs. no PA required. These results remained unchanged in quantile regression models adjusted for age and sex as well as age, sex, and insurance type.

[*] PA request refers to either date of PA request or, for patients who did not require a PA, the date that that determination was made;

[†] Across all subgroups, the median (IQR) time between physician order and PA request processing was 1 (0, 3) days;

[‡] Prednisone-equivalent glucocorticoid exposure

Table 3:

Characteristics of Denied Prior Authorizations

	PA Denied N (%)
Number of Denials	33 (100)
Disease or Disease Category	
IgG4-Related Disease	10 (33)
Connective Tissue Disease	9 (27)
Inflammatory Arthritis	5 (15)
Vasculitis	3 (9)
Myositis/Interstitial Lung Disease	2 (6)
Other[^]	4 (12)
Designated Rare Disease	20 (61)
Medication Requested	
Rituximab	23 (70)
Infliximab	4 (12)
Tocilizumab	4 (12)
Intravenous Immunoglobulin	1 (3)
Zoledronic acid[#]	1 (3)
Reason for Request[*]	
Prednisone-sparing	13 (39)
Currently on or had tried oral DMARD[**]	16 (48)
Organ-threatening disease	10 (30)
Subcutaneous formulation not ideal for patient	3 (9)
Prior response to requested treatment	6 (18)
Reason for Denial	
Off-Label Use	27 (82)
Condition has no FDA-approved medication	21 (78)
Systemic Lupus Erythematosus	5 (19)
Diagnostic uncertainty	1 (4)
Preferred drug not tried[†]	5 (16)
Safety concern	1 (3)
Response to Denial[‡]	
Physician peer-to-peer	27 (82)
Additional laboratory testing	1 (3)
Treatment postponed	1 (3)
Use preferred drug	5 (15)
Ultimately approved	27 (82)

[*] Multiple reasons possible for one patient, totals greater than 100%;

[†] Psoriatic Arthritis, Rheumatoid Arthritis, Uveitis;

** Disease-Modifying Anti-Rheumatic Drug (DMARD);

‡ One subject had a failed peer-to-peer and tried preferred drug;

^ Other refers to: SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome, CVID-associated granulomatous disease, SAMHD1 mutation-associated arteriopathy, and idiopathic uveitis;

Zoledronic acid prescribed for SAPHO Syndrome