Adherence to self-administered biologic disease-modifying antirheumatic drugs across health-system specialty pharmacies

Autumn D. Zuckerman, PharmD, BCPS, AAHIVP, CSP, Vanderbilt University Medical Center, Nashville, TN, USA

Josh DeClercq, MS, Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA

Leena Choi, PhD, Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA

Nicole Cowgill, PharmD, CSP, CHS Specialty Pharmacy Service at Atrium Health, Charlotte, NC, USA

Kate McCarthy, PharmD, BCACP, Specialty Pharmacy, University of Rochester Medical Center, Rochester, NY, USA

Brian Lounsbery, RPh, CSP, Avera Specialty Pharmacy, Sioux Falls, SD, USA

Rushabh Shah, PharmD, MBA, AAHIVP, CSP, UK Specialty Pharmacy and Infusion Services, University of Kentucky, Lexington, KY, USA

Amanuel Kehasse, PharmD, PhD, Boston Medical Center Health System, Boston, MA, USA

Karen Thomas, PharmD, PhD, Pharmacy Ambulatory Clinical Care Center, University of Utah Health, Salt Lake City, UT, USA

Louis Sokos, BS Pharm, MBA, West Virginia University Health System, Morgantown, WV, USA

Martha Stutsky, PharmD, BCPS, Specialty and Retail Pharmacy Services, Yale New Haven Health System, New Haven, CT, USA

Jennifer Young, PharmD, BCPS, CSP, Specialty Pharmacy Services, Wake Forest Baptist Health, Winston-Salem, NC, USA

Jennifer Carter, PharmD, BCPS, Medical University of South Carolina, Charleston, SC, USA

Monika Lach, PharmD, BCPS, University of Chicago Medicine, Chicago, IL, USA

Kelly Wise, PharmD, BCACP, Nationwide Children's Hospital, Columbus, OH, USA

Toby T. Thomas, PharmD, BCPS, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

Melissa Ortega PharmD, MS, Tufts Medical Center, Boston, MA, USA

Jinkyu Lee, PharmD, CSP, Beth Israel Deaconess Medical Center, Boston, MA, USA

Kate Lewis, PharmD, BCPS, Froedtert & the Medical College of Wisconsin, Milwaukee, WI, USA

Jillian Dura, PharmD, Cleveland Clinic, Cleveland, OH, USA

Nicholas P. Gazda, PharmD, MS, BCPS, CSP, Cone Health, Greensboro, NC, USA

Lana Gerzenshtein, PharmD, BCPS, CSP, ExceleraRx Corp., Minneapolis, MN, USA

Scott Canfield, PharmD, CSP, Johns Hopkins Home Care Group, Baltimore, MD, USA

Address correspondence to Dr. Zuckerman (Autumn.Zuckerman@vumc.org).

Abstract

Purpose. Adherence to self-administered biologic disease-modifying antirheumatic drugs (bDMARDs) is necessary for therapeutic benefit. Health-system specialty pharmacies (HSSPs) have reported high adherence rates across several disease states; however, adherence outcomes in rheumatoid arthritis (RA) populations have not yet been established.

Methods. We performed a multisite retrospective cohort study including patients with RA and 3 or more documented dispenses of bDMARDs from January through December 2018. Pharmacy claims were used to calculate proportion of days covered (PDC). Electronic health records of patients with a PDC of <0.8 were reviewed to identify reasons for gaps in pharmacy claims (true nonadherence or appropriate treatment holds). Outcomes included median PDC across sites, reasons for treatment gaps in patients with a PDC of <0.8, and the impact of adjusting PDC when accounting for appropriate therapy gaps.

Results. There were 29,994 prescriptions for 3,530 patients across 20 sites. The patient cohort was mostly female (75%), with a median age of 55 years (interquartile range [IQR], 42-63 years). The original(ie, prereview) median PDC was 0.94 (IQR, 0.83-0.99). Upon review, 327 patients had no appropriate treatment gaps identified, 6 patients were excluded due to multiple unquantifiable appropriate gaps, and 420 patients had an adjustment in the PDC denominator due to appropriate treatment gaps (43 instances of days' supply adjusted based on discordant days' supply information between prescriptions and physician administration instructions, 11 instances of missing fills added, and 421 instances of clinically appropriate treatment gaps). The final median PDC after accounting for appropriate gaps in therapy was 0.95 (IQR, 0.87-0.99).

Conclusion. This large, multisite retrospective cohort study was the first to demonstrate adherence rates across several HSSPs and provided novel insights into rates and reasons for appropriate gaps in therapy.

Keywords: antirheumatic agents; arthritis, rheumatoid; medication adherence; pharmaceutical services; pharmacy

Am J Health-Syst Pharm. 2021;78(x):xxx-xxx

Many patients with rheumatoid arthritis (RA) receive treatment with self-administered biologic disease-modifying antirheumatic drugs (bDMARDs), including injectable products (eg, tumor necrosis factor α inhibitors, interleukin antagonists) as well as a growing number of newer oral agents (eg, Janus kinase inhibitors). Biologic DMARDs are often selected for patients with ongoing moderate or high disease activity after treatment with conventional DMARDs (eg, methotrexate), given their demonstrated ability to slow disease progression, induce remission, and improve radiologic outcomes.[1] Despite the benefits of bDMARDs, previous research has found that medication adherence within the RA population ranges from 44% to 83%.[2-5] The optimal level of medication adherence and preferred method for evaluating adherence in RA are not established; however, nonadherence to antirheumatic treatments is associated with poor 28-joint Disease Activity Scores, indicating worse disease activity.[6,7] Though a specific threshold for adherence correlated to clinical outcomes has not been reported, the Pharmacy Quality Alliance, a public-private cooperative founded to promote appropriate medication use, recommends an adherence threshold of 0.8, calculated as proportion of days covered (PDC), for patients with RA taking noninfused biologic medications.[8] PDC is determined using pharmacy claims data to calculate the amount of medication a patient has in hand (covered days) divided by the number of days in a timeframe.[9] As with all adherence calculations using pharmacy claims data, PDC is a surrogate endpoint of actual patient administration and is used to estimate adherence.[9] Alongside adherence challenges, drug spend on biologic products used in the treatment of RA and other inflammatory conditions is significant and was identified as the highest per-

member-per-month contributor to annual drug expenditures for top commercial pharmacy benefit managers throughout a recent 5-year period (2015-2019).[10]

Specialty pharmacies play a key role in assisting patients and prescribers who utilize bDMARDs by providing insurance navigation, care coordination, medication dispensing, and longitudinal patient monitoring services. Health-system specialty pharmacy (HSSP) programs have grown rapidly in recent years. As of 2019, over 26% of all hospitals and 89% of larger hospitals (over 600 staffed beds) reported operating a specialty pharmacy.[11] Within the HSSP care model, pharmacists and pharmacy technicians provide integrated care for patients alongside physicians and other clinical care team members. These integrated programs have demonstrated their ability to optimize patient adherence as measured by PDC and medication possession ratio (MPR) in a variety of specialty disease categories, including oncology, multiple sclerosis, and pulmonary arterial hypertension.[12-14] A recent study demonstrated high rates of bDMARD adherence in 675 patients served by one HSSP.[15] However, more data is needed to assess if the growing number of HSSPs have similar rates of high adherence.

Health-system specialty pharmacists have several touch points with patients on specialty medications due to their integration within clinics. This entails frequent communication with patients, often in person and via audio and/or video communications. The HSSP care model includes shared documentation systems within the electronic health record (EHR), whereby the entire multidisciplinary care team documents treatment decision making, disease progression, and treatment outcomes. This integration also allows for comprehensive tracking of patient adherence patterns, including documentation of instances of clinically appropriate medication holds. Although interruption in treatment is common in RA due to active infections or surgical interventions, these holds would not be

accounted for in traditional PDC calculations because the clinical details of the treatment timeline are not incorporated. The PDC method and other claims-based adherence calculations suffer from a lack of industry standardization and transparency and from reliance on pharmacy claims data alone to approximate adherence.[9] The lack of clinical details in the traditional PDC calculation can cause appropriate gaps in therapy to be labeled as periods of nonadherence. The impact of the HSSP model on adherence in RA across multiple HSSP programs has not been previously explored. Additionally, given HSSP access to clinical data, there is a previously unreported opportunity to understand the frequency of appropriate medication holds and their impact on traditionally calculated PDC compared to an adjusted PDC accounting for appropriate gaps in claims.

The objectives of the multisite study described here were to evaluate adherence to specialty medications in patients with RA receiving care within integrated HSSP models and to investigate the frequency at which retrospectively reviewing integrated care team documentation of a suboptimal PDC (ie, <0.8) revealed an opportunity to correct PDC calculation to more accurately reflect true medication adherence.

Methods

Design. A multisite retrospective cohort study was performed. The Health-System Specialty Pharmacy Outcomes Research Consortium was created in June 2019 to foster collaboration among HSSPs in research and best practices sharing. The consortium is open to any HSSP in the United States, with no membership or fee requirements. A call for sites interested in participating on the multisite study was sent in June 2019, and respondents collaborated on study design, execution, and authorship. Patients who had 3 or more prescription fills for eligible bDMARDs written by a provider at one of the 20 participating

health systems and whose health records contained International Classification of Diseases code M05, M06, or M08 documented between January 2018 and December 2018 were included. Eligible bDMARDs included abatacept, adalimumab, certolizumab, etanercept, tocilizumab, and tofacitinib. Deidentified fill data were collected by each site using pharmacy records generated during normal clinical practice and imported into a centralized, password-protected, Health Insurance Portability and Accountability Act–compliant data entry system. EHRs of patients with a PDC of <0.8 were reviewed by the individual sites to identify whether gaps in refill history were attributable to either true nonadherence or documented appropriate treatment holds, which were then recorded in the data entry system at each study site. Institutional review board approval was obtained at all participating institutions.

Settings. All sites had HSSPs in which specialty pharmacists were integrated within health-system specialty clinics either in a centralized (offsite specialty pharmacy and/or centralized pharmacy services location within the health-system), decentralized (pharmacy staff within the clinic) model or mixed centralized and decentralized model. HSSPs varied in their level of pharmacy integration within clinics, number of clinics and disease states represented, referral process (how and when specialty prescriptions were received), and patient management practices, including frequency of pharmacist assessments and methods of patient communication. Roles and involvement of HSSP personnel, including pharmacists, pharmacy technician, nurses, and support staff, may also have differed amongst sites. Specifically for RA clinic coverage, on average (median, IQR), participating sites employed 1 (1-2) clinic-based pharmacist, 0.75 (0-1) clinic-based pharmacy technician; 1 (0.4-1.6) centralized pharmacist, and 2 (0.9-2.6) centralized pharmacy technicians. Two sites employed nurses within the HSSP; one site had 2 clinic-based nurses and the other had

1 centralized nurse. Figure 1 illustrates the shared and unique roles of clinic staff as reported by participating HSSPs and the number and type of clinic staff within participating HSSPs. Similarities in the HSSP practice model existed, allowing for the ability to combine and report adherence data. HSSPs had access to their respective health-system EHRs, enabling comprehensive patient clinical review and communication with prescribing providers. When HSSPs received a referral for a new specialty medication, pharmacy staff performed a benefits investigation and assessed the patient's ability (based on payer and manufacturer restrictions) and willingness to fill the prescription at the HSSP. Depending on this determination and the HSSP's practice model, the HSSP then assisted with insurance approval and obtaining financial assistance for the patient as needed. If the HSSP was unable to fill the prescription or the patient preferred an alternate pharmacy, the prescription was triaged to the patient-preferred or insurance- or manufacturer-mandated pharmacy. Due to their integration, HSSPs serve as a resource for specialty patients regardless of whether they receive drugs dispensed from the HSSP, often answering drug information questions and helping address and mitigate adverse effects resulting from specialty therapy.

PDC calculation and appropriate reasons for therapy gaps. *Initial PDC calculation.* PDC was calculated by generating a supply diary for each patient from the time of the index prescription (the date of first fill of an included medication within the study period) to the date of the last fill, omitting the days' supply in the patient's last fill. A fill was defined as the "sold date" within the pharmacy dispensing software. Excess supply due to overlapping refills was shifted forward, never backward, and oversupply at the end of the time period was truncated from the total supply. Among patients who switched therapy, it was assumed that patients stopped the first drug before starting the next drug, and thus excess supply

from the first drug was not carried forward when a new drug was filled. A single PDC value was calculated for each patient, with all fills for any included medication for a single patient analyzed in aggregate.

Identification of appropriate reasons for therapy gaps and adjustment of PDC. After an initial PDC calculation, sites were provided a list of study IDs and gap dates for patients with a PDC of <0.8. Sites then reviewed EHR and pharmacy dispensing data for patients with a PDC of <0.8 to assess for a reason for gaps in fill data. Patients could have had more than one appropriate gap and thus more than one reason. Reasons for appropriate gaps in therapy (as documented in claims data) were discussed and agreed upon by all sites a priori. Sites were responsible for reviewing individual patient data and determining whether an appropriate gap existed and into which category the reason for the gap was assigned. Unique instances were discussed among all sites and final categorization was agreed upon. Patients were excluded from the final PDC analysis if there were multiple appropriate extended gaps for which dates of gaps could not be quantified. If the reason for gaps in fill data was discordance between physician directions and the prescription-specified days' supply, the days' supply (PDC denominator) was adjusted to mirror physician administration instructions and the PDC recalculated based on the new days' supply data. If sites found fills that were not present upon the first data extraction, the missing fill was added to the dataset and the PDC recalculated with the new fill's days' supply in the numerator and denominator. Sites recorded the number of days that accounted for appropriate therapy gaps due to the following reasons: infections, physician-directed drug holiday, external fills, patient utilized samples and/or patient assistance program enrollment, transition to intravenous therapy, transition to an oral or infused medication that was not included in the study list of medications, allergic reaction, held for pregnancy. For these instances, the

number of days of the appropriate gap were removed from the PDC denominator. Therefore, each patient's adjusted PDC resulted from accounting for adjusting days' supply based on physician instructions, adding missing fills, and removing appropriate gap days from the PDC denominator. Patients were grouped into 3 PDC categories (>0.5, 0.5-0.8, and <0.5) before and after PDC adjustment.

Statistical analysis. Descriptive statistics were used to describe data. Proportions were calculated for categorical variables, while the mean, median, standard deviation (SD), and IQR were used to describe continuous variables. The primary outcome was PDC across all sites. Secondary outcomes included reasons for apparent nonadherence or treatment gaps in patients with a PDC of <0.8 and the impact of adjusting PDC when accounting for appropriate gaps in therapy.

With the summary data for PDC from 20 sites, such as mean (SD) values as well as sample size for each site, we performed a meta-analysis using a random-effects model. The metafor package for R (R Foundation for Statistical Computing, Vienna, Austria) was utilized to perform the meta-analysis and make a forest plot to present the results.

Results

There were 29,994 prescriptions from 3,530 patients across the 20 sites included. The patients were mostly female (75%; *n* = 2,649) and had a median age of 55 years (IQR, 42-63 years). Indications for treatment included rheumatoid factor (RF)–negative RA (66%; *n* = 2,346), RF-positive RA (37%; *n* = 1,306), and juvenile idiopathic arthritis (9.7%; *n* = 343). The most common bDMARD fills were for adalimumab (33.3%; *n* = 9,976), etanercept (31.3%; *n* = 9,362), and abatacept (10.3%; *n* = 3,085). The mean (SD) number of fills per patient was 8.5 (3.4). Over half of prescriptions fills were through commercial insurance

(53.4%; *n* = 16,001), followed by Medicare (27.1%; *n* = 8,114) and Medicaid (18.8%; *n* = 5,628). Over the 12-month study period, 86.6% of patients (*n* = 3,056) did not change therapy, 11.6% (*n* = 408) had 1 therapy change, and 1.9% (*n* = 66) had 2 or more therapy changes.

The original median PDC (ie, the PDC prior to review) of patients with a PDC of <0.8 was 0.94 (IQR, 0.83-0.99). Outcomes of review of patients with a PDC of <0.8 (*n* = 753) are shown in Table 1, and Figure 2 illustrates patient flow after review. Six patients were excluded due to multiple unquantifiable gaps, and 327 patients had no appropriate reason for treatment gaps. An adjusted PDC was calculated due to the identification of clinically appropriate treatment gaps for 420 patients for the following reasons: 43 instances of days' supply adjusted based on discordant days' supply and physician administration instructions, 11 instances of missing fills added, and 421 instances of clinically appropriate treatment gaps (Table 1). A median of 134 days (IQR, 102-175 days) were removed from the PDC denominators for patients with an original PDC of <0.5, and 36 days (IQR, 24-63 days) were removed from the PDC denominators for patients with an original PDC of 0.5 to 0.8. The final median PDC for the cohort after excluding 6 patients with multiple unquantifiable gaps and accounting for appropriate gaps in therapy was 0.95 (IQR, 0.87-0.99), with 87.9% of patients having a PDC of >0.8 (Figure 3). PDC rate categories changed slightly upon review for appropriate gaps: the percentage of patients with a PDC of <0.5 decreased from 2.8% to 1.2%, the percentage with a PDC between 0.5 and 0.8 decreased from 17.5% to 11%, the percentage with a PDC between 0.8 and 1 increased from 59.2% to 65.1%, and the percentage with a PDC of 1 increased from 20.6% to 22.8%.

Mean PDC ranged from 0.89 to 0.97 across sites; these data are presented along with the corresponding 95% confidence intervals (CIs) for individual sites in Figure 4. The

overall mean across all sites, as calculated via random-effects modeling, was 0.91 (95% CI, 0.90-0.92), as shown at the bottom of Figure 4.

Discussion

High rates of adherence to bDMARDs were seen across 20 HSSPs, demonstrating the benefits of HSSPs in helping patients with RA remain on effective therapies. Adherence to and appropriate utilization of bDMARDs are crucial in achieving remission, slowing disease progression, and avoiding significant healthcare costs from uncontrolled disease.[1,6] The median PDC of 0.95 across all sites exceeded figures reported in previous research,[2-5] and 87.9% of patients within our cohort had a PDC above the Pharmacy Quality Alliance–suggested adherence threshold of >0.8.[8] In our meta-analysis from all sites, the overall mean PDC was 0.91 and all of the lower bounds of the 95% CIs for all sites were well above the suggested PDC threshold of 0.8. These findings align with the findings of Berger and colleagues,[15] who found a median PDC of 0.95 (IQR, 0.84-1.00), with 80% of patients having a PDC of >0.8 among those serviced at an HSSP, and further substantiate the growing body of evidence that the HSSP model of care benefits providers, patients, and health systems.[15,16] Patients prescribed bDMARDs may face several logistical and financial barriers to maintaining on appropriate therapy due to complex insurance coverage pathways, cost of treatment, cost and coordination of required monitoring, defined distribution and payor network restrictions, and unique shipping requirements.[17-19] Integrated into outpatient specialty clinics, HSSPs are ideally positioned to address these potential barriers to enable uninterrupted therapy for as long as it remains appropriate for the patient.[20,21] HSSP pharmacists and technicians proactively contact patients for refills, identify and address treatment or adherence concerns, monitor for ongoing safety and effectiveness of therapy,

and seamlessly communicate with the patient and the provider through the shared EHR. This model of care has been demonstrated to result in high adherence rates within individual institutions among patients with RA (median PDC, 0.95[15]), multiple sclerosis (median PDC, 0.94[12]; mean MPR, 0.86[22]), pulmonary arterial hypertension (mean PDC, 0.96[14]), human immunodeficiency virus infection (median MPR, 1.0[23]), and inflammatory bowel disease (mean MPR, 0.89[24]). The effectiveness of this model in enabling patient adherence is likely due to frequent and proactive patient outreach, rapid and efficient provider communication within the EHR, and pharmacist and technician expertise in navigating insurance requirements and monitoring therapy. Our study is the first to demonstrate high adherence rates across several HSSPs within the same disease state.

Limitations of using pharmacy claims to evaluate patient adherence have previously been described.[9,25,26] A small study of specialty pharmacy patients serviced by an HSSP found that up to 40% of patients with a PDC of <0.8 had appropriate reasons for gaps in therapy, primarily due to provider-directed medication holds (69%).[25] However, our study is among the first to quantify rates and reasons for low PDC rates that may inaccurately describe true medication adherence in a rheumatology population. Accounting for treatment gaps is important when evaluating bDMARD adherence, as patients are often directed to hold therapy due to infections, surgery, or other illnesses. EHR review revealed that over half of patients with a PDC of <0.8 had an appropriate reason for gaps in pharmacy claims, most commonly due to clinically appropriate holds. Due to the large sample size and its inclusion of few patients with an original PDC of <0.8, the overall impact of adjusting PDC based on appropriate gaps was minimal, with the median increasing from 0.94 to 0.95. However, after adjusting for appropriate gaps, fewer patients remained in the lower-PDC categories (<0.5 and 0.5-0.8, with decreases from 2.8% to 1.2% and from 17.5% to 11%,

respectively), while more patients entered the higher-PDC categories (0.8-1 and 1, with increases from 59.2% to 65.1% and from 20.6% to 22.8%, respectively). Based on these findings, we believe additional clinical data, not just pharmacy claims alone, is likely needed to accurately assess adherence in an RA population. The clinical information to accurately identify these scenarios is available within the HSSP model due the integrated care model and shared documentation, but such information is unlikely to be accessible to or accurately depicted by nonintegrated specialty pharmacies.[26] These results also demonstrate the limitations of assessing adherence using pharmacy claims generated at the pharmacy level, as 79 patients appeared nonadherent due to filling medications external to the HSSP during the study period. As adherence is often a quality measure for accreditation and contracting standards to which pharmacies are accountable, it is important to note that this limitation of data availability may falsely lower calculated adherence rates at the pharmacy level.[9]

The study was not without limitations. Patients with a PDC of >0.8 were not reviewed for potential appropriate reasons for nonadherence. Additionally, other potential reasons for appropriate nonadherence, such as a patient having a sufficient supply on hand or waiting to start treatment, were identified upon chart review; however, these were not accounted for as they were not agreed-upon valid reasons a priori. These limitations could have led to bias such that reported PDC rates were lower than the true adherence rates. For patients with PDC of <0.8, site reviewers assessed the EHR for evidence of reasons for interruption in therapy, and the number of days removed from the PDC denominator to account for an appropriate gap was dependent on the reviewer's interpretation of the clinical information. Therefore, review bias may have occurred during evaluation of the patient's EHR.

Conclusion

The large, multisite retrospective cohort study was the first to demonstrate bDMARD adherence rates across several HSSPs and demonstrate the benefit of the HSSP model in supporting high adherence rates. Additionally, the results provide novel insights into rates and reasons for appropriate gaps in bDMARD therapy that are otherwise unaccounted for by common methods of approximating medication adherence. Accounting for appropriate gaps in pharmacy claims is an important element of evaluating true nonadherence in specialty disease states in which clinically appropriate therapy holds are common. However, accessibility to this data is often limited beyond the HSSP model, which represents a unique opportunity for HSSP practices to further investigate the optimal methods for quantifying medication adherence.

Acknowledgments

We acknowledge Bridget Lynch, PharmD, for her assistance with data collection and assimilation. Additionally, we acknowledge the integrated health-system specialty pharmacists and pharmacy technicians who provide optimal patient care at each of our institutions.

Disclosures

Dr. Zuckerman, Dr. DeClercq, and Dr. Choi report research support from Sanofi, Inc., unrelated to the work described here within the last 36 months.

References

1. Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheum.* 2016;68(1):1-26.
2. Barlow JF, Faris RJ, Wang W, et al. Impact of specialty pharmacy on treatment costs for rheumatoid arthritis. *Am J Pharm Benefits.* 2012;4(special issue):SP49-SP57.
3. Curkendall S, Patel V, Gleeson M, et al. Compliance with biologic therapies for rheumatoid arthritis: do patient out-of-pocket payments matter? *Arthritis Rheum.* 2008;59(10):1519-1526.
4. Khilfeh I, Guyette E, Watkins J, et al. Adherence, persistence, and expenditures for high-cost anti-inflammatory drugs in rheumatoid arthritis: an exploratory study. *J Manag Care Spec Pharm.* 2019;25(4):461-467.
5. Tkacz J, Ellis L, Bolge SC, et al. Utilization and adherence patterns of subcutaneously administered anti-tumor necrosis factor treatment among rheumatoid arthritis patients. *Clin Ther.* 2014;36(5):737-747.
6. Bluett J, Morgan C, Thurston L, et al. Impact of inadequate adherence on response to subcutaneously administered anti-tumour necrosis factor drugs: results from the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate cohort. *Rheumatology (Oxford).* 2015;54(3):494-499.
7. Kuipers JG, Koller M, Zeman F, et al. Adherence and health literacy as related to outcome of patients treated for rheumatoid arthritis: analyses of a large-scale observational study. *Z Rheumatol.* 2019;78(1):74-81.

8. Pharmacy Quality Alliance Adherence: PQA measure overview. Accessed November 6, 2020. https://www.pqaalliance.org/adherence-measures

9. Canfield SL, Zuckerman A, Anguiano RH, et al. Navigating the Wild West of medication adherence reporting in specialty pharmacy. *J Manag Care Spec Pharm.* 2019;25(10):1073-1077.

10. Express Scripts. Express Scripts drug trend report (2015-2019). Accessed November 6, 2020. https://www.express-scripts.com/corporate/drug-trend-report

11. Pedersen CA, Schneider PJ, Ganio MC, et al. ASHP national survey of pharmacy practice in hospital settings: prescribing and transcribing—2019. *Am J Health-Syst Pharm.* 2020;77(13):1026-1050.

12. Banks AM, Peter ME, Holder GM, et al. Adherence to disease-modifying therapies at a multiple sclerosis clinic: the role of the specialty pharmacist. *J Pharm Pract.* 2019:0897190018824821.

13. Hanson RL. Integrated clinical and specialty pharmacy practice model for management of patients with multiple sclerosis. *Am J Health-Syst Pharm.* 2014;71(6):463-469.

14. Shah NB, Mitchell RE, Proctor ST, et al. High rates of medication adherence in patients with pulmonary arterial hypertension: an integrated specialty pharmacy approach. *PLOS One.* 2019;14(6):e0217798.

15. Berger N, Peter M, DeClercq J, et al. Rheumatoid arthritis medication adherence in a health system specialty pharmacy. *Am J Manag Care.* 2020;26(12):e380-e387.

16. Rim MH, Thomas KC, Barrus SA, et al. Analyzing the costs of developing and operating an integrated health-system specialty pharmacy: the case of a centralized

insurance navigation process for specialty clinic patients. *Am J Health-Syst Pharm.* 2021;78(11):982-988.

17. Kibbons AM, Peter M, DeClercq J, et al. Pharmacist interventions to improve specialty medication adherence: study protocol for a randomized controlled trial. *Drugs Real World Outcomes.* 2020;7(4):295-305.

18. Cocohoba J, Pohlman B, Tran JS, et al. Modeling specialty medicine access: understanding key health system processes and players. *J Am Pharm Assoc (2003).* 2019;59(1):43-50.e3.

19. Hanson RL. Specialty pharmacy and the medication access dilemma. Editorial. *Am J Health-Syst Pharm.* 2015;72(9):695.

20. Pulvermacher A, Nelson C. Benefits of developing a collaborative, outcomes-based specialty pharmacy program. *Am J Health-Syst Pharm.* 2016;73(11):839-843.

21. Bagwell A, Kelley T, Carver A, et al. Advancing patient care through specialty pharmacy services in an academic health system. *J Manag Care Spec Pharm.* 2017;23(8):815-820.

22. Tan H, Yu J, Tabby D, et al. Clinical and economic impact of a specialty care management program among patients with multiple sclerosis: a cohort study. *Mult Scler.* 2010;16(8):956-963.

23. Barnes E, Zhao J, Giumenta A, et al. The effect of an integrated health system specialty pharmacy on HIV antiretroviral therapy adherence, viral suppression, and CD4 count in an outpatient infectious disease clinic. *J Manag Care Spec Pharm.* 2020;26(2):95-102.

24. Shah NB, Haydek J, Slaughter J, et al. Risk factors for medication nonadherence to self-injectable biologic therapy in adult patients with inflammatory bowel disease. *Inflamm Bowel Dis.* 2019;26(2):314-320.

25. Paolella D, Cherry E, Jolly JA, et al. Closing the gap: identifying rates and reasons for nonadherence in a specialty population. *J Manag Care Spec Pharm.* 2019;25(11):1282-1288.

26. Carroll NM, Ellis JL, Luckett CF, et al. Improving the validity of determining medication adherence from electronic health record medications orders. *J Am Med Inform Assoc.* 2011;18(5):717-720.

Figure 1. Health-system specialty pharmacy (HSSP) rheumatoid arthritis practice description. The 20 HSSPS in the study shared some standard practice elements but also offered unique services based on the needs of their respective institutions and clinics. This figure demonstrates those standard and unique elements and the HSSP staff member(s) responsible for completing a task. Ancillary clinic services that did not fall within a specific staff member role are illustrated at the bottom of the figure. CPhT indicates pharmacy technician; PAP, patient assistance program; PharmD, pharmacist; RN; nurse.

[a]Two sites use nurses to complete treatment monitoring assessments.

Figure 2. Patient review and adherence calculation process. This figure describes the process of proportion of days covered (PDC) calculation, patient review, and final PDC adjustment. PDC was calculated for all patients (*n* = 3,530) meeting inclusion criteria. For patients with a PDC of <0.8, a list of patients and gap dates were provided to sites, which reviewed patient electronic health records (EHRs) for reasons for pharmacy claims gaps. Patients with multiple unquantifiable appropriate gaps (*n* = 6) were excluded from the final PDC calculation. Patients with no identifiable reason for an appropriate gap (*n* = 327) had no changes made to their data or PDC calculation. PDC was adjusted if EHR review demonstrated discordant physician and prescription directions on days' supply, if there were missing fills added to the dataset that were not in the initial dataset, or if there were clinically appropriate treatment gaps. Adjustment was indicated for 420 patients, and adjustment methods are noted. Of note, patients may have had more than 1 reason for therapy gaps and therefore may have had their PDC adjusted in multiple ways. A final PDC was calculated for the cohort, excluding those with multiple unquantifiable appropriate gaps (*n* = 3,524).

[a]Patients may have had more than 1 reason for therapy gaps.

Figure 3. Proportion of days covered (PDC) outcomes before and after patient review. The left-hand bar graph shows the distribution of PDC categories before and after review of appropriate reasons for gaps in therapy (the corresponding percentage values are as follows: PDC of <0.5, 2.8%-1.2%; PDC of 0.5-0.8, 17.5%-11%; PDC of 0.8-1, 59.2%-65.1%; and PDC of 1, 20.6%-22.8%). The bar graph at right illustrates the distribution of final PDC values after adjusting for appropriate gaps in therapy (802 patients with a PDC of 1 were omitted to illustrate more granular detail for patients with a PDC of <1).

Figure 4. Proportion of days covered (PDC) values by institution. Forest plot showing the results of meta-analysis for PDC from 20 sites. Solid squares and lines represent the means with the corresponding 95% confidence intervals (CIs) for individual sites. The overall mean across all sites along with the 95% CI based on a random-effects (RE) model are presented at the bottom. The sample size for each site is also shown.

Key Points

- This large, multisite retrospective cohort study is the first to demonstrate adherence rates to biologic disease-modifying antirheumatic drugs across several health-system specialty pharmacies, demonstrating the benefit of this increasingly common model.
- This study is among the first to utilize the review of health-system integrated clinical documentation to investigate gaps and reasons for inappropriate and appropriate gaps in pharmacy claims data.

- The study results demonstrate the impact on proportion of days covered when the calculation is modified to correct for clinically appropriate gaps in refill history.

Table 1. Outcomes of Review of Patients with PDC of <0.8

	No. (%)		
	Original PDC <0.5 (*n* = 116 reasons for 107 patients)	**Original PDC of 0.5-0.8 (*n* = 692 reasons for 646 patients)**	**Total (All Patients with PDC <0.8) (*n* = 808 reasons for 753 patients)**
No appropriate therapy gap reason	39 (33.6)	288 (41.6)	327 (40.5)
Excluded due to multiple unquantifiable appropriate gaps	2 (1.7)	4 (0.6)	6 (0.7)
Appropriate reason for therapy gap			
Infections[a]	23 (19.8)	154 (22.3)	177 (21.9)
Physician-directed drug holiday[a]	24 (20.7)	112 (16.2)	136 (16.8)
External fills[a]	12 (10.3)	39 (5.6)	51 (6.3)
Discordant physician directions and prescription-specified days' supply[b]	6 (5.2)	37 (5.3)	43 (5.3)
Patient utilized samples/patient assistance program[a]	1 (<1)	27 (3.9)	28 (3.5)
Missing fill added[c]	1 (<1)	10 (1.4)	11 (1.4)
Transition to intravenous therapy[a]	3 (2.6)	6 (<1)	9 (1.1)
Transition to nonincluded medication[a]	3 (2.6)	5 (<1)	8 (1)

Allergic reaction[a]	1 (<1)	7 (1)	8 (1)
Held for pregnancy[a]	1 (<1)	2 (<1)	3 (<1)
Surgery[a]	0 (0)	1 (<1)	1 (<1)

Abbreviation: PDC, proportion of days covered.

[a]Number of days of appropriate gap removed from PDC denominator.

[b]Days' supply was adjusted to mirror physician administration instructions and PDC recalculated based on new days' supply.

[c]Previously missing fill was added to data and PDC recalculated with new fill.

Figure 1

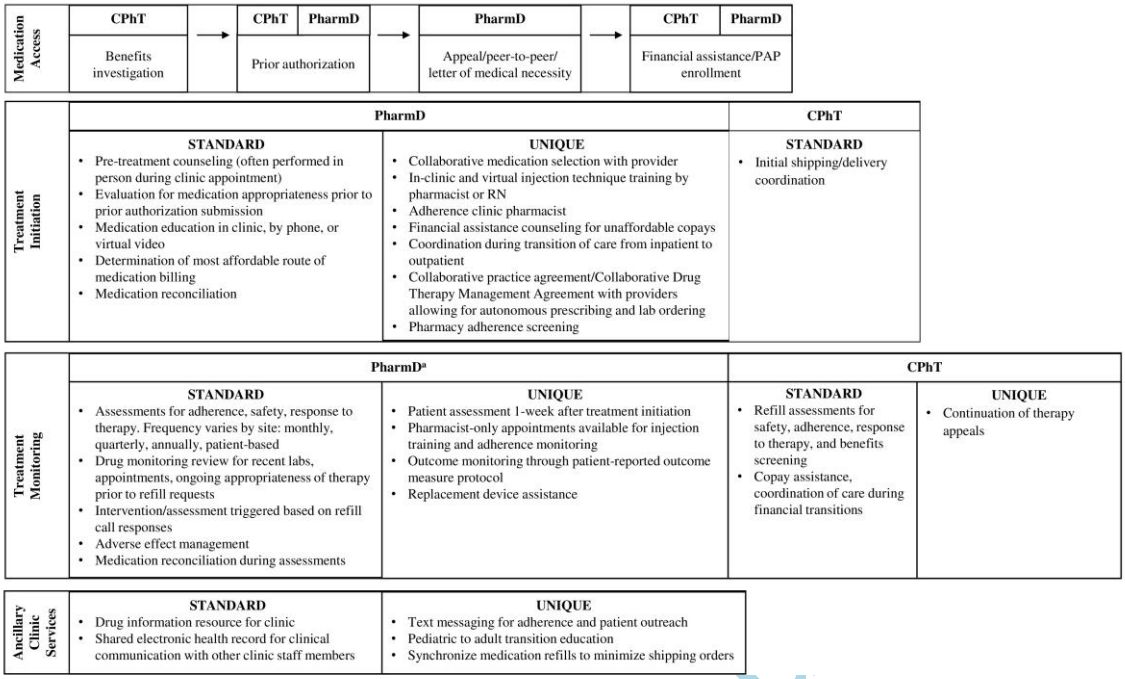

Figure 2

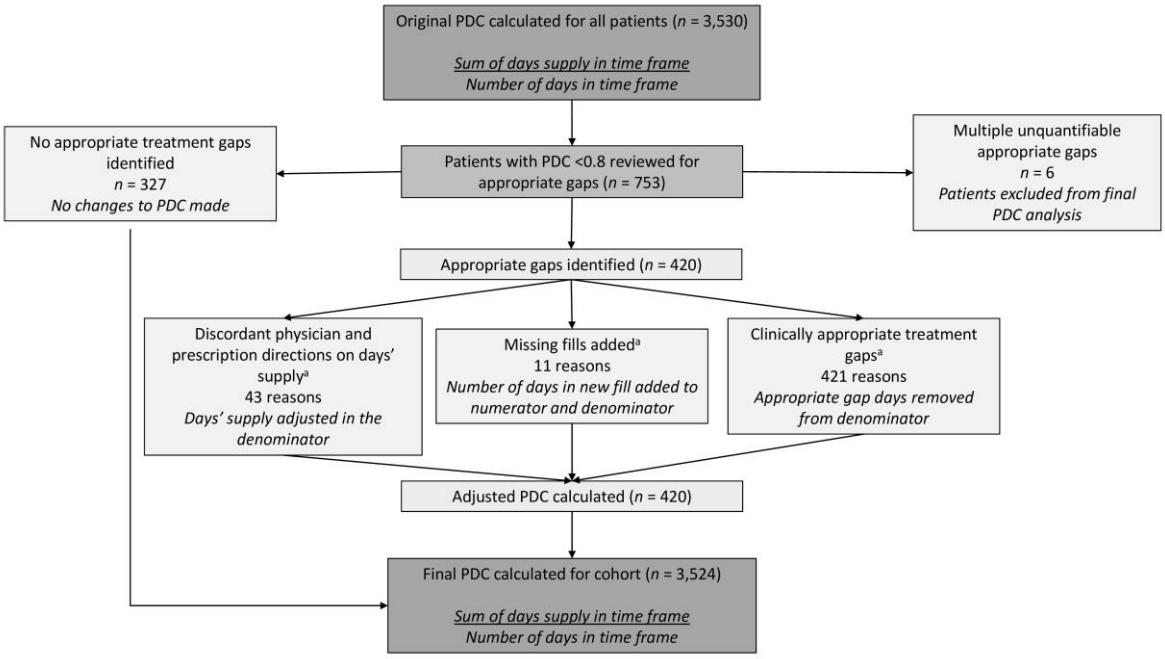

Figure 3

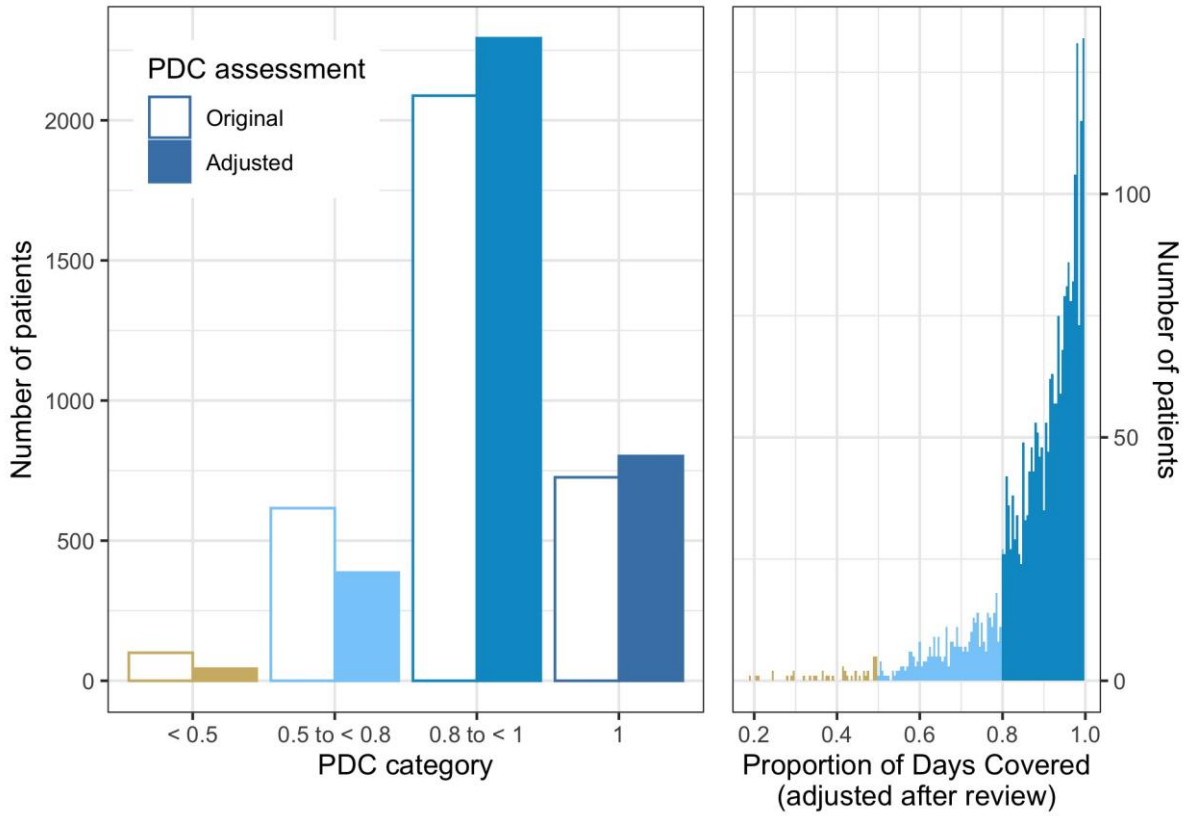

Figure 4