RESEARCH

Outcomes of a Rheumatoid Arthritis Disease Therapy Management Program Focusing on Medication Adherence

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ABSTRACT

BACKGROUND: A national pharmacy benefits management company implemented a rheumatoid arthritis (RA) disease therapy management (DTM) program as an enhanced offering to patients receiving specialty pharmacy services. The program was designed to improve medication adherence, maximize therapeutic outcomes, and enhance physical functioning and health-related quality of life (HRQOL) by empowering patients and improving their knowledge of RA.

OBJECTIVES: To evaluate (a) adherence to injectable RA medications for patients participating in an RA DTM program compared with nonparticipating patients receiving injectable RA medications at specialty or community pharmacies and (b) HRQOL, work productivity, and physical functioning before versus after completing the RA DTM program.

METHODS: Patients who had an RA diagnosis and a pharmacy claim for an injectable RA medication during the identification period (August 2007 through September 2008) and were continuously enrolled with the plan from 4 months before through 8 months after the identification date were stratified into 3 patient cohorts: DTM, specialty pharmacy, and community pharmacy. DTM patients were further categorized into a DTM intent-to-treat (ITT) cohort (all 340 DTM-enrolled patients) and a DTM completer cohort (subset of 266 ITT patients who completed the month 6 consultation). DTM completer, specialty, and community pharmacy cohorts were matched 1:1:1 (n = 244 in each cohort after matching) using a propensity score that represented the likelihood of completing the DTM program. The primary outcome was adherence to injectable RA medications, measured as the proportion of days covered (PDC) over an 8-month post-identification period. Patient-reported outcomes (short form [SF]-12, Work Productivity Activity Impairment [WPAI], and Health Assessment Questionnaire-Disability Index [HAQ-DI]) were evaluated among all 371 DTM patients who completed the month 0 and month 6 consultations regardless of whether they met continuous enrollment requirements (patient-reported sample).

RESULTS: Of specialty pharmacy patients, approximately 14% chose DTM participation. During the post-identification period, mean PDC was 0.83 for DTM ITT, 0.89 for DTM completer, 0.81 for specialty pharmacy, and 0.60 for community pharmacy patients. Differences were statistically significant for both DTM cohorts compared with the community pharmacy cohort ($P < 0.001$) and for the DTM completer cohort compared with the specialty pharmacy cohort ($P < 0.001$), but not for the DTM ITT cohort compared with the specialty pharmacy cohort ($P = 0.291$). In the patient-reported sample, mean SF-12 physical component scores significantly increased by 1.1 points ($P = 0.048$); mean SF-12 mental component scores were not significantly changed ($P = 0.679$); mean WPAI work productivity decreased by 10.8 percentage points ($P = 0.045$); and mean HAQ-DI scores significantly improved by 0.08 points ($P < 0.001$).

CONCLUSIONS: Patients participating in the RA DTM program had significantly higher injectable RA medication adherence compared with community pharmacy patients. Adherence to injectable RA medications was significantly higher for patients completing the RA DTM program, but not for the DTM ITT group, compared with patients receiving specialty pharmacy services alone. Patients completing the RA DTM program experienced improvements in SF-12 physical component and HAQ-DI scores but did not demonstrate improvements to SF-12 mental scores or work productivity.

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What is already known about this subject

- Research conducted by Lorig et al. (1993) and Barlow et al. (1998) suggests that self-management programs for rheumatoid arthritis (RA) that focus on patient empowerment have positive effects and are additive to the benefits of RA medication therapy.
- Esselens et al. (2009) found that patients who participated in an outpatient RA care program that provided multidisciplinary care with immediate access to different health professionals had higher remission rates and were able to better preserve functionality and general health status compared with patients who received standard care provided by a rheumatologist.
- Although medication education was included as part of these programs, medication management was not the main focus. Limited research is available evaluating RA disease management programs that incorporate comprehensive medication therapy management as a core program component.

What this study adds

- In 2007, a national pharmacy benefits management (PBM) company implemented an RA disease therapy management (DTM) program as an enhanced offering to patients receiving specialty pharmacy services. The program was designed to improve medication adherence, maximize therapeutic outcomes, and enhance physical functioning and health-related quality of life (HRQOL) by empowering patients and improving their knowledge of RA.
- A study was conducted to evaluate adherence to injectable RA medications for patients participating in the RA DTM program compared with groups of patients receiving injectable RA medications from specialty or community pharmacies. We also examined changes in HRQOL, work productivity, and physical functioning before versus after completing the RA DTM program.
- Mean medication adherence, measured as percent of days covered (PDC), was significantly higher for the DTM intent-to-treat (ITT) cohort (PDC = 0.83) and for the DTM completer cohort (PDC = 0.89) compared with the community pharmacy cohort (PDC = 0.60, $P < 0.001$ for both comparisons). Compared with patients receiving specialty pharmacy services without DTM (PDC = 0.81), the DTM completer cohort had significantly higher adherence ($P < 0.001$), but the DTM ITT cohort was not significantly different ($P = 0.291$).

What this study adds *(continued)*

- From month 0 to month 6, short-form (SF)-12 physical component scores significantly increased by 1.1 points ($P = 0.048$); SF-12 mental component scores were not significantly changed ($P = 0.679$); and Health Assessment Questionnaire-Disability Index (HAQ-DI) scores significantly improved by 0.08 points ($P < 0.001$). Despite these positive changes in physical functioning, mean work productivity significantly decreased by 10.8 percentage points ($P = 0.045$) for reasons that could not be determined from this study.

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease that affects an estimated 1.3 million adults in the United States.[1] It primarily affects joints, causing joint pain, swelling, and stiffness, but can also affect other organs in the body. As the disease progresses and joint damage occurs, patients experience greater disability and decreasing quality of life. RA is associated with significant levels of morbidity and mortality and has a significant impact on total health care costs.[2,3]

Patients with moderate to severe RA have benefited from the availability of injectable biological disease-modifying antirheumatic drugs (DMARDs), which include the tumor necrosis factor (TNF) antagonists (etanercept [Enbrel], infliximab [Remicade], and adalimumab [Humira], certolizumab [Cimzia], and golimumab [Simponi]), T cell modulators (abatacept [Orencia]), interleukin-1 antagonists (anti-IL-1, anakinra [Kineret]), and C20 directed cytolytic antibodies (rituximab [Rituxan]). These medications have been shown effective in lowering disease activity, while improving physical function, quality of life, and retarding disease progression.[4] However, the full benefit of biological DMARDs can be achieved only if patients adhere to and continue with the prescribed medication regimen.[5] Factors influencing medication adherence and persistence include injection site issues, serious side effects, initial expectations, efficacy results, patient's perception of the burden of treatment, and out-of-pocket costs.[6,7] Physicians and health care providers also play an important role in influencing both adherence and persistence.[6]

Evidence suggests that self-management programs that focus on patient empowerment have positive effects and are additive to the benefits of RA medication.[8,9] In addition, an outpatient RA program that provided multidisciplinary care with immediate access to different health professionals demonstrated higher remission rates and better preservation of functionality and general health status compared with standard care provided by a rheumatologist.[10] Although medication education was included as part of these programs, medication management was not the main focus. Limited research is available evaluating RA disease management programs that incorporate comprehensive medication therapy management as a core program component and whether these efforts translate into improved adherence outcomes.

In 2007, a national pharmacy benefits management (PBM) company implemented an RA disease therapy management (DTM) program as an enhanced offering to patients who were receiving specialty pharmacy services through the PBM. The program was designed to improve medication adherence, maximize therapeutic outcomes, and enhance physical functioning and health-related quality of life (HRQOL) by empowering patients and improving their knowledge of RA. This study evaluates the RA DTM program. The objectives of this study were (a) to evaluate adherence to injectable RA medications for patients participating in an RA DTM program added to specialty pharmacy services compared with cohorts of nonparticipating patients receiving their medications at specialty or community pharmacies and (b) to examine changes in HRQOL, work productivity, and physical functioning before versus after completing the RA DTM program.

Methods

Program Description and Implementation

Patients with RA who were using injectable medications were eligible to receive routine specialty pharmacy management services offered by the PBM. These services were provided through the PBM's mail service pharmacy and included a patient welcome brochure (detailing medication ordering, storing and monitoring, and proper disposal of ancillary supplies), mail service medication delivery, refill reminders by patient care coordinators, and access to a pharmacist 24 hours a day, 7 days a week.

In addition, the PBM implemented an RA DTM program as an enhanced service for patients already receiving routine specialty pharmacy management services. The DTM program used a patient-centric model to provide coordinated health care interventions and communications to patients with conditions that require significant self-care efforts. While supporting the physician/patient relationship, the program provided patients with education and support to successfully attain skills in the self-management of their symptoms and their medication therapy.

Patients were eligible for the DTM program if they had a pharmacy claim for an injectable RA medication through the PBM's specialty pharmacy and a diagnosis of RA (obtained through prior authorization request data). Eligible patients were identified on a weekly basis and were sent a DTM welcome packet. An outbound call was made to patients who returned a patient availability form indicating their preferred day and time for a phone consultation.

Patients received telephone consultations with a clinician (licensed pharmacist or registered nurse). Each patient was assigned an individual clinician for the entirety of the program. During each telephone consultation, the clinician educated the patient on his or her medical condition and treatment options

and helped to maximize therapeutic outcomes by promoting medication adherence and persistence. To maintain consistency across clinicians, each consultation contained standardized required assessment questions and educational topics. However, the clinician could also provide additional consultation on other subjects that were not included in the standard assessment.

During the initial consultation (month 0), clinicians used the INTERMED, a validated observer-rated instrument for assessing case complexity and health care needs using a biopsychosocial model,[11-18] to stratify patients into either the regular-intensity (score of 0 through 20) or high-intensity (score of 21 or more) program. For the regular-intensity program, consultations were conducted intermittently at enrollment (month 0) and months 1, 4, and 6. For the high-intensity program, consultations were conducted monthly from month 0 to month 6. The initial consultation typically lasted 40-60 minutes, and follow-up consultations lasted 20-30 minutes. During each consultation, the clinician assessed patient knowledge and health concerns and provided education on core topics (Table 1).

To help improve medication adherence, the program was designed to address all 5 of the dimensions of adherence identified by the World Health Organization: (1) health-system/health care team factors, (2) therapy-related factors, (3) condition-related factors, (4) patient-related factors, and (5) social and economic factors.[19] Health-system factors, such as poor quality of provider/patient relationship and communication, were addressed by encouraging patients to find a provider they were content with and could speak openly with about their issues. Patients were also advised to keep a journal or write down questions that may have arisen between appointments. Therapy-related adherence barriers were addressed by providing education on adverse drug reactions (including injection site reactions and how to manage them) and the consequences of missed doses. To overcome condition-related adherence issues, patients were educated on the damaging effects of RA and the potential damage that may occur due to medication nonadherence. Because the injectable RA medications are not always taken daily, patients may forget to take their medications. To overcome this patient-related barrier, a medication chart or calendar was provided to improve adherence and prevent double dosing. Finally, socioeconomic barriers to adherence were improved by including resources to national foundations and medication manufacturers with medication financial assistance programs.

The clinician developed a personalized care plan for the patient that summarized the phone consultation. The care plan contained information tailored to the patient's needs, such as information about RA and RA symptoms, medications and adverse drug reactions, healthy living, provider/patient communication, home safety, and resources. The care plan was sent to the patient as well as to the prescriber of the injectable RA medication. Patients also received monthly educational mailings specific to RA from month 1 through month 6. Monthly educational materials were not individualized, were sent both to regular- and high-intensity patients, and included general information on RA topics, such as life with RA, RA medications, exercises, nutrition, preventive medicine, psychological issues, and pain management.

TABLE 1 Rheumatoid Arthritis Disease Therapy Management Program Core Consultation Topics

- Pathophysiology of rheumatoid arthritis
- Laboratory values pertaining to rheumatoid arthritis or medication therapy
- Optimization of medication therapy including medication adherence
- Symptom management
- Pain management
- Stress management
- Importance of a balanced diet
- Importance of exercise
- Importance of patient-provider communication
- Appropriate use of assistive devices
- Home safety
- Additional resources (including financial)

Program Evaluation Design and Sample

The RA DTM program was evaluated using an observational cohort study design. Patients participating in Medicare Advantage Prescription Drug plan (MAPD), Prescription Drug Plan (PDP), or commercial health plans that use the PBM's specialty pharmacy were eligible for the analysis. Patient data were obtained from the DTM program database, the PBM's prior authorization database, and the PBM's electronic pharmacy claims database. Institutional review board (IRB) exemption certification was obtained from an external IRB.

Patients were eligible for the analysis if they had a prior authorization request for an injectable RA medication, a diagnosis of RA in the prior authorization system, and a pharmacy claim for an injectable RA medication during the identification period (August 2007 through September 2008). Table 2 lists the injectable RA medications and Generic Product Identifier (GPI, Medi-Span, Indianapolis, IN) codes used in the analysis.

Identified patients were categorized into 1 of 3 mutually exclusive study groups (Figure 1): (a) DTM (patients who filled a prescription for an injectable RA medication through the PBM's specialty pharmacy and enrolled in the DTM program); (b) specialty pharmacy (patients who filled a prescription for an injectable RA medication through the PBM's specialty pharmacy but did not enroll in the DTM program); or (c) community pharmacy (patients who filled a prescription for an injectable RA medication at a community pharmacy and

TABLE 2 *Injectable Rheumatoid Arthritis Medications and GPI Codes*

Generic (Brand) Name	GPI Code Beginning with:
Etanercept (Enbrel)	66290030
Infliximab (Remicade)	52505040
Adalimumab (Humira)	66270015
Anakinra (Kineret)	66260010
Abatacept (Orencia)	66400010
Rituximab (Rituxan)	21353060
Certolizumab (Cimzia)	52505020
Golimumab (Simponi)	66270040

GPI = generic product identifier.

did not have any injectable RA medications filled through the PBM's specialty pharmacy). Because the specialty pharmacy group received refill reminder calls, patient educational materials, mail service delivery, and 24-hour access to a pharmacist, the community pharmacy group was included to provide a comparison group of patients who had no contact with the specialty pharmacy or DTM program. Although it was possible that some DTM and specialty pharmacy patients could have also filled some prescriptions for RA injectables at a community pharmacy, patients were classified according to their highest level of service during the study period.

There were 2 analysis samples—a claims data sample used in the primary analysis and a patient-reported data sample (Figure 1). To be eligible for the claims data sample, patients had to be continuously enrolled in the health plan from 4 months before (pre-identification period) through 8 months after (post-identification period) the identification date. For the DTM cohort, the identification date was defined as the date of the last prescription fill for an injectable RA medication prior to the month 0 consultation. For the specialty pharmacy cohort, the identification date was defined as the date of the last prescription fill for injectable RA medication prior to the date the patient was identified as being eligible for the DTM program during the weekly DTM program eligibility identifications. For the community pharmacy cohort, the identification date was the date of the last prescription fill for an injectable RA medication prior to a randomly selected date within the identification period (August 2007 through September 2008). DTM patients were further categorized into a DTM intent-to-treat (ITT) cohort (all patients eligible for the pharmacy claims cohort who enrolled in the DTM program) and a DTM completer cohort (subset of ITT patients who completed the month 6 consultation).

Patients in the specialty pharmacy and community pharmacy cohorts were matched 1:1:1 with a patient in the DTM completer cohort. Matching was performed using the propensity score method.[20] Logistic regression was used to calculate a propensity score that represented each patient's likelihood of completing the DTM program. Variables included in the propensity scoring model were age, gender, health plan type (MAPD, PDP, commercial), geographic state, pre-identification period chronic disease score (a measure of comorbidity developed for use with pharmacy claims data with possible scores ranging from 0, no comorbidity, to 36),[21] index injectable RA medication, and pharmacy costs for injectable RA medications during the pre-identification period. Patients in the community pharmacy cohort were first matched to patients in the DTM completer cohort; then patients meeting the criteria for the specialty pharmacy cohort were matched to each patient in this DTM-community matched cohort.

The patient-reported sample consisted of those patients who were enrolled in the DTM program and completed the month 0 and month 6 consultations. To include the maximum number of patients with patient-reported data, continuous enrollment in the plan was not an eligibility requirement for the patient-reported sample.

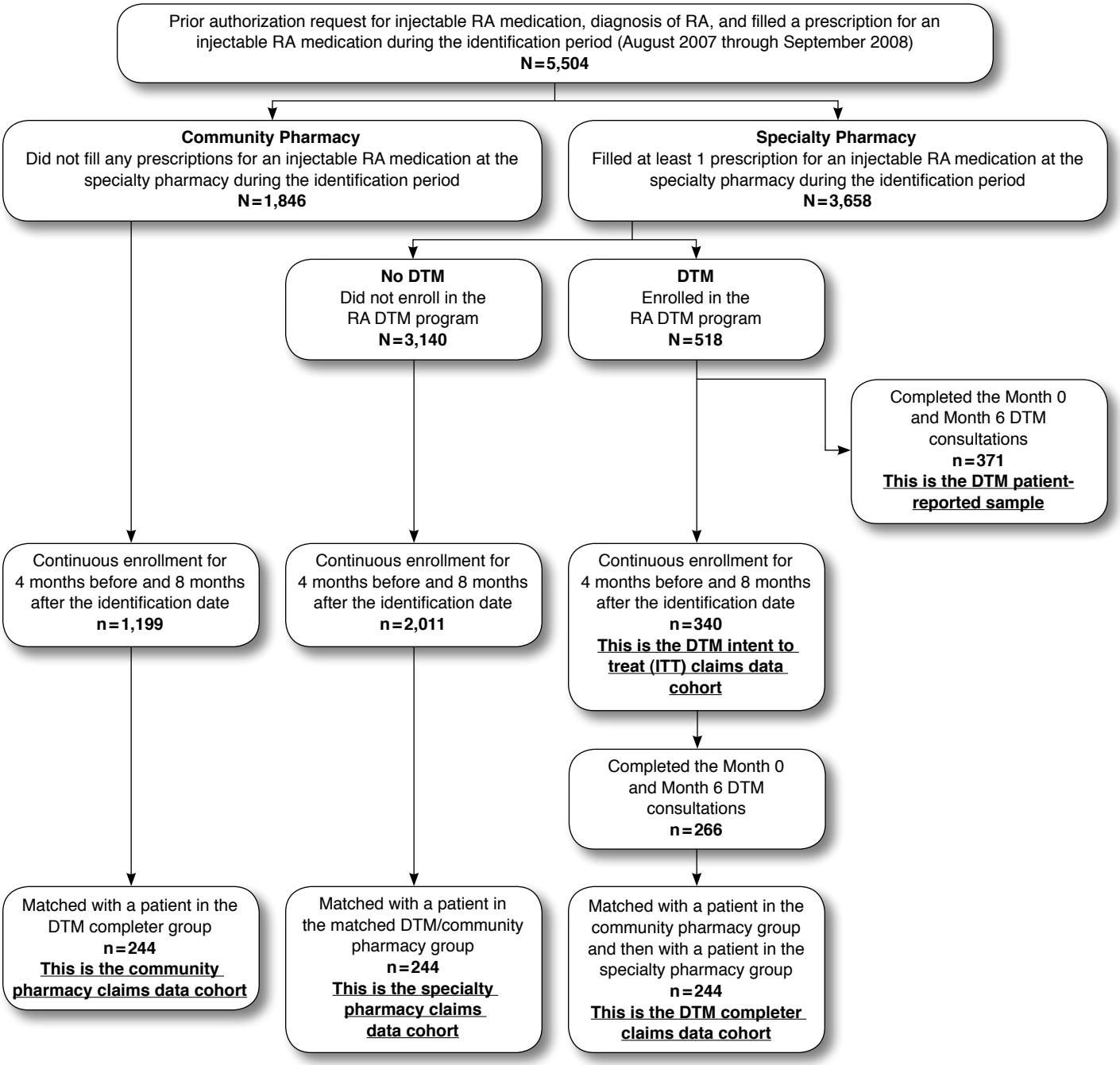
Outcome Variables

The primary outcome was adherence to injectable RA medications, which was evaluated among the claims data sample. Adherence to the injectable RA medications was measured using the proportion of days covered (PDC), which was defined as the sum of days supply for all fills during the post-identification period divided by 240 days. Days covered by more than 1 prescription fill of an injectable RA medication were counted only once. Adherence was reported for the index injectable RA medication as well as for the entire therapeutic class of injectable RA medications.

To further characterize the use patterns of the injectable RA medications, we evaluated rates of discontinuation and switching of the injectable RA medications during the period extending from the identification date until the end of the post-identification period. Discontinuation was defined as a gap of at least 30 days between the depletion date (fill date plus days supply) for the last filled prescription and the end of the post-identification period. Switching was defined as having a prescription fill for an injectable RA medication other than the index medication during the post-identification period. Pharmacy ingredient costs for any injectable RA medication and total pharmacy ingredient costs (for all medications, including both RA medications and other medications) were measured for each patient over the post-identification period.

Among the patient-reported sample, changes in HRQOL, work productivity, and physical functioning were evaluated from month 0 to month 6. To assess these outcomes, a series of validated questionnaires were administered by the clinician during the month 0 and month 6 telephone consultations. Clinicians were instructed to ask the patient to answer each question. If patients were unwilling or unable to answer all the questions, clinicians would try to obtain as much information as possible but moved forward with the other program assessments and patient education.

FIGURE 1 Patient Identification



DTM = disease therapy management; RA = rheumatoid arthritis.

HRQOL was measured using the short-form (SF)-12, version 2 (Quality Metric, Lincoln, RI), which has previously been used in evaluations of patients with RA.[22,23] The SF-12 consists of 12 questions asking patients to rate their quality of life during the past 4 weeks. The questionnaire produces 2 scores, a physical component score and a mental component score. Scoring is on a scale of 0 to 100 with a score of 0 representing the lowest level of health and a score of 100 representing the highest level of health.

Work productivity was measured using the Work

Productivity and Activity Impairment (WPAI) Questionnaire: General Health version 2.0 (Reilly Associates, New York, NY).[24] The WPAI consists of 6 questions regarding the ability to work and perform regular activities during the past 7 days. The results produce 4 scores: (1) absenteeism (work time missed), (2) presenteeism (impairment at work), (3) work productivity loss (overall work impairment), and (4) activity impairment. The first 3 scores are evaluated only among patients who are employed, whereas the fourth score (activity impairment) is evaluated among all patients regardless of employment. Scores are expressed as percentages, with a higher percentage indicating greater impairment and less productivity.

Physical functioning was assessed using the Health Assessment Questionnaire (HAQ) Alternative Disability Index (DI).[25] The HAQ-DI consists of 20 questions evaluating functional status during the past week. Scoring yields a DI ranging from 0 to 3, with a higher score representing more functional limitation. Scores are also calculated for each of 8 subcategories (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities).

Statistical Methods

Data extraction and statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc., Cary, NC). For nonmatched cohorts, means were compared using t-tests for normal distributions or Wilcoxon rank-sum (also called Mann-Whitney U) test for non-normal distributions, and percentages were compared using Pearson chi-square tests. For matched cohorts in the pharmacy claims sample and the analysis of changes in month 0 and month 6 responses for the patient-reported sample, means were compared using the paired t-test for normal distributions or the Wilcoxon signed-rank test for non-normal distributions, and percentages were compared using McNemar's test. All comparisons were 2-sided and performed at a 0.05 level of significance.

Results

Of the 5,504 patients with a prior authorization request for an RA medication, a diagnosis of RA, and a prescription fill of an RA medication, 3,658 patients filled at least 1 prescription for their injectable RA medication at the specialty pharmacy, whereas 1,846 patients filled no prescriptions for an injectable RA medication at the specialty pharmacy and were categorized as community pharmacy patients (Figure 1). A total of 518 patients with a prescription fill of an injectable RA medication at the specialty pharmacy (14.2% of 3,658 specialty pharmacy users) were enrolled in the RA DTM program. Of these, 371 completed the month 6 consultation, which qualified them for the patient-reported sample. In addition, 340 of these 518 patients were continuously enrolled for the pre-identification and post-identification periods, which qualified them for the DTM ITT cohort for the claims data sample. After excluding DTM patients who did not have a month 6 consultation, 266 patients remained eligible for the DTM completer cohort.

Of the 74 DTM patients who were excluded for not having a month 6 consultation (and hence were in the DTM ITT group but not the DTM completer group), 25 (33.8%) had only the initial (month 0) consultation, 23 (31.1%) had 2 consultations (month 0 plus 1 additional consultation), 20 (27.0%) had 3 consultations (month 0 plus 2 additional consultations), 5 (6.8%) had 4 consultations (month 0 plus 3 additional consultations), and 1 (1.4%) had 5 consultations (month 0 plus 4 additional consultations). During the matching process, 22 DTM completer patients were eliminated from the analysis due to failure to find a match.

The final claims data sample consisted of 244 DTM completer patients who were able to be matched with 244 patients in each of the specialty and community pharmacy cohorts. For the propensity scoring models, the c-statistic was 0.71 for the first model containing DTM completer and community pharmacy patients and 0.70 for the second model containing the specialty patients and the matched DTM completer patients.

For the claims data sample, baseline demographics and clinical characteristics were similar for the DTM ITT, DTM completer, specialty, and community pharmacy cohorts (Table 3). Mean pharmacy ingredient costs for the injectable RA medications during the pre-identification period were similar for the cohorts, reflecting the fact that this variable was included in the propensity scoring models used for matching. Mean total days supply for injectable RA medications also did not significantly differ among the cohorts. However, total pharmacy ingredient costs (which included costs for all medications filled by the patient) were not included in the propensity scoring model. Thus, it was not surprising to note a difference in pre-identification period total pharmacy costs, which were higher in the DTM completer patients than specialty pharmacy patients (mean [SD] $4,714 [$2,729] vs. $4,271 [$2,662], respectively, $P = 0.038$).

Medication utilization and cost outcomes for the claims data sample during the post-identification period are shown in Table 4. Adherence to any injectable RA medication (including the index drug and other RA injectables) was significantly higher for the DTM ITT cohort (mean PDC = 0.83) and for the DTM completer cohort (mean PDC = 0.89) than for the community pharmacy cohort (mean PDC = 0.60, $P < 0.001$). When compared with patients receiving specialty pharmacy services without DTM (mean PDC = 0.81), the DTM completer cohort had significantly higher adherence ($P < 0.001$), but the DTM ITT cohort was not significantly different ($P = 0.291$). Rates of discontinuation and switching of injectable RA medications were significantly lower for the DTM ITT cohort compared with the community pharmacy cohort, but similar when compared with the specialty pharmacy cohort.

The improved medication adherence by DTM patients resulted in higher pharmacy costs during the post-identification period for DTM patients versus specialty or

TABLE 3 Baseline Characteristics of the Claims Data Sample[a]

	DTM ITT (n = 340)		DTM Completer (n = 244)		Specialty Pharmacy (n = 244)		Community Pharmacy (n = 244)		*P* Value for Comparison of DTM ITT with Other Cohorts[b]		*P* Value for Comparison of DTM Completer with Other Cohorts[b]	
									DTM ITT Versus Specialty	DTM ITT Versus Community	DTM Completer Versus Specialty	DTM Completer Versus Community
Age in years, mean [SD]	61.4	[10.9]	62.2	[10.1]	62.8	[11.6]	61.2	[13.0]	0.157	0.838	0.389	0.343
Chronic disease score, mean [SD]	4.69	[3.18]	4.75	[3.06]	4.38	[3.14]	4.95	[3.13]	0.243	0.320	0.118	0.334
	n	(%)	n	(%)	n	(%)	n	(%)				
Female gender	285	(83.8)	205	(84.0)	205	(84.0)	200	(82.0)	0.950	0.555	>0.999	0.535
Health plan type									0.041	0.086	0.797	0.971
MAPD	103	(30.3)	77	(31.6)	71	(29.1)	76	(31.1)				
PDP	174	(51.2)	138	(56.6)	145	(59.4)	139	(57.0)				
Commercial	63	(18.5)	29	(11.9)	28	(11.5)	29	(11.9)				
Geographic state									0.090	0.673	0.997	>0.999
Arizona	35	(10.3)	24	(9.8)	17	(7.0)	26	(10.7)				
California	71	(20.9)	40	(16.4)	50	(20.5)	33	(13.5)				
Colorado	15	(4.4)	8	(3.3)	5	(2.0)	6	(2.5)				
Florida	38	(11.2)	32	(13.1)	14	(5.7)	35	(14.3)				
Indiana	5	(1.5)	3	(1.2)	5	(2.0)	4	(1.6)				
Missouri	8	(2.4)	7	(2.9)	3	(1.2)	10	(4.1)				
North Carolina	10	(2.9)	7	(2.9)	7	(2.9)	7	(2.9)				
Nevada	3	(0.9)	2	(0.8)	2	(0.8)	3	(1.2)				
Ohio	4	(1.2)	4	(1.6)	8	(3.3)	2	(0.8)				
Pennsylvania	9	(2.7)	7	(2.9)	7	(2.9)	6	(2.5)				
Texas	22	(6.5)	14	(5.7)	18	(7.4)	17	(7.0)				
Washington	4	(1.2)	4	(1.6)	9	(3.7)	3	(1.2)				
Other states	116	(34.1)	92	(37.7)	99	(40.6)	92	(37.7)				
Index medication									0.267	0.687	0.196	0.784
Etanercept	170	(50.0)	121	(49.6)	141	(57.8)	131	(53.7)				
Adalimumab	161	(47.4)	117	(48.0)	98	(40.2)	110	(45.1)				
Anakinra	2	(0.6)	2	(0.8)	0		1	(0.4)				
Abatacept	2	(0.6)	1	(0.4)	0		0					
Infliximab	4	(1.2)	3	(1.2)	4	(1.6)	1	(0.4)				
Rituximab	1	(0.3)	0		1	(0.4)	1	(0.4)				
Pre-identification period medication use, per patient mean [SD]												
Total days supply for all injectable RA medications	68.8	[40.8]	68.8	[40.5]	65.5	[42.8]	66.1	[42.0]	0.338	0.431	0.158	0.488
Pharmacy ingredient costs for all injectable RA medications	$3,501	[$2,088]	$3,508	[$2,108]	$3,470	[$2,396]	$3,555	[$2,385]	0.867	0.774	0.616	0.684
Total pharmacy ingredient costs for all medications	$4,641	[$2,664]	$4,714	[$2,729]	$4,271	[$2,662]	$4,961	[$3,270]	0.098	0.193	0.038	0.354

[a]*The DTM ITT cohort consisted of all patients enrolled in the DTM ITT program who were continuously enrolled in the plan for the 4-month pre-identification period and 8-month post-identification period. The DTM completer cohort consists of the subset of DTM ITT patients who completed the month 6 DTM consultation and who could be matched to patients in the community pharmacy and specialty pharmacy cohorts. The community pharmacy and specialty pharmacy cohorts consist of continuously enrolled patients who could be matched to the DTM completer patients. Values are n (%) unless noted otherwise.*

[b]*For the comparison of the DTM ITT patients with the specialty or community cohorts, means were compared using t-tests for data with normal distributions or Wilcoxon rank-sum tests for data with non-normal distributions. Percentages were compared using Pearson chi-square tests. For the comparison of DTM completer patients with the matched specialty or community cohorts, means were compared using paired t-tests for data with normal distributions or Wilcoxon signed-rank tests for data with non-normal distributions. Percentages were compared using McNemar's tests.*

DTM = disease therapy management; ITT = intent-to-treat; MAPD = Medicare Advantage Prescription Drug plan; PDP = Prescription Drug Plan; RA = rheumatoid arthritis; SD = standard deviation.

community pharmacy patients. Mean (SD) pharmacy ingredient costs per patient for the injectable RA medications were $11,697 ($4,102) for the DTM ITT cohort, $12,679 ($3,745) for the DTM completer cohort, $11,518 ($4,613) for the specialty pharmacy cohort, and $8,470 ($5,355) for the community pharmacy cohort. Total pharmacy ingredient costs per patient averaged $14,485, $15,556, $14,073, and $11,478 for the respective cohorts. Differences were statistically significant ($P < 0.001$) for the comparisons of DTM ITT or DTM completers versus community pharmacy patients and the comparison of

TABLE 4 Medication Utilization and Costs During Post-Identification Period (Claims Data Sample)[a]

	DTM ITT (n = 340)	DTM Completer (n = 244)	Specialty Pharmacy (n = 244)	Community Pharmacy (n = 244)	*P* Value for Comparison of DTM ITT with Other Cohorts[b]		*P* Value for Comparison of DTM Completer with Other Cohorts[b]	
					DTM ITT Versus Specialty	DTM ITT Versus Community	DTM Completer Versus Specialty	DTM Completer Versus Community
Adherence to injectable RA medications								
PDC for index injectable RA medication, mean [SD][c]	0.82 [0.24]	0.88 [0.19]	0.79 [0.26]	0.57 [0.34]	0.186	<0.001	<0.001	<0.001
PDC for any injectable RA medication, mean [SD][c]	0.83 [0.23]	0.89 [0.18]	0.81 [0.24]	0.60 [0.34]	0.291	<0.001	<0.001	<0.001
Discontinuation and switching of injectable RA medications								
Discontinuation of index injectable RA medication, n (%)	76 (22.4)	31 (12.7)	61 (25.0)	109 (44.7)	0.457	<0.001	<0.001	<0.001
Discontinuation of any injectable RA medications, n (%)	69 (20.3)	26 (10.7)	54 (22.1)	99 (40.6)	0.591	<0.001	<0.001	<0.001
Switch from index injectable RA medication to another injectable RA medication, n (%)	9 (2.6)	6 (2.5)	12 (4.9)	18 (7.4)	0.146	0.007	0.157	0.014
Medication costs								
Pharmacy ingredient costs per patient for any injectable RA medication, mean [SD]	$11,697 [$4,102]	$12,679 [$3,745]	$11,518 [$4,613]	$8,470 [$5,355]	0.623	<0.001	0.001	<0.001
Total pharmacy ingredient for all medications, mean [SD]	$14,485 [$5,330]	$15,556 [$5,035]	$14,073 [$5,665]	$11,478 [$7,506]	0.371	<0.001	<0.001	<0.001

[a]The DTM ITT cohort consists of all patients enrolled in the DTM program who were continuously enrolled in the plan for the 4-month pre-identification period and 8-month post-identification period. The DTM completer cohort consists of the subset of DTM ITT patients who completed the month 6 DTM consultation and who could be matched to patients in the community pharmacy and specialty pharmacy cohorts. The community pharmacy and specialty pharmacy cohorts consist of continuously enrolled patients who could be matched to the DTM completer patients.

[b]For the comparison of the DTM ITT patients with the specialty or community cohorts, means were compared using t-tests for data with normal distributions and Wilcoxon rank-sum tests for data with non-normal distributions. Percentages were compared using Pearson chi-square tests. For the comparison of DTM completer patients with the matched specialty or community cohorts, means were compared using paired t-tests for data with normal distributions and Wilcoxon signed-rank tests for data with non-normal distributions. Percentages were compared using McNemar's tests.

[c]PDC was calculated as the sum of the days supply for all claims during the post-identification period divided by 240 days. Days covered by more than 1 claim were counted only once.

DTM = disease therapy management; ITT = intent-to-treat; PDC = proportion of days covered; RA = rheumatoid arthritis; SD = standard deviation.

DTM completers with specialty pharmacy patients.

Of the patient-reported sample, 336 (90.6%) patients were assigned to the regular-intensity program, and 35 (9.4%) patients were assigned to the high-intensity program. Mean (SD) duration of disease was 12.7 (11.5) years, and 69 patients (18.6%) were employed. Table 5 compares the SF-12, WPAI, and HAQ-DI scores for the patient-reported sample at month 0 and month 6. Mean SF-12 physical component scores were 34.9 at month 0 and 36.0 at month 6 ($P = 0.048$), while mean SF-12 mental component scores remained similar from month 0 to month 6 (51.8 vs. 51.7, $P = 0.679$). Mean work productivity loss on the WPAI for employed patients was 12.9% at month 0 and was significantly higher at month 6 (28.3%), indicating greater impairment ($P = 0.045$). HAQ-DI scores improved by 0.08 points, decreasing from 1.18 at month 0 to 1.09 at month 6 ($P < 0.001$). Statistically significant improvements were also noted in the individual subscales of dressing and grooming, arising, grip, and reach.

At month 6, patients were asked "Overall, how helpful was the program in better managing your health?" Of the 371 patients in the patient-reported sample, 268 (72.2%) reported "very helpful"; 96 (25.9%) reported "somewhat helpful"; 5 (1.4%) reported "not very helpful"; and 2 (0.5%) did not respond. When these patients were asked how they would rate the program, 217 (58.5%) rated it as "excellent"; 121 (32.6%) rated it as "very good"; 29 (7.8%) rated it as "good"; and 4 (1.1%) rated it as "fair" (data not shown).

Discussion

Patients participating in an RA DTM program focusing on medication management had significantly higher injectable RA medication adherence compared with patients receiving their medication from a community pharmacy. In addition, adherence to injectable RA medications was significantly

TABLE 5 SF-12, WPAI, and HAQ-DI Scores at Month 0 and Month 6 Consultations for the Patient-Reported Sample (N = 371)

	All Patients Completing Questionnaire		Patients Completing Both the Month 0 and Month 6 Questionnaires			
	Month 0	Month 6	Month 0	Month 6	Change from Month 0 to Month 6	*P* Value[a]
SF-12						
Number of patients with complete data	296	352	283	283	283	
Physical component score, mean [SD]	34.9 [10.8]	36.0 [11.1]	34.9 [10.9]	36.1 [11.0]	1.1 [9.7]	0.048
Mental component score, mean [SD]	51.8 [9.8]	51.7 [9.9]	51.8 [9.7]	51.9 [9.9]	0.1 [10.0]	0.679
WPAI						
Work time missed (absenteeism)						
Number of patients with complete data	52	48	39	39	39	
% absenteeism, mean [SD]	1.2 [6.3]	7.2 [19.8]	1.28 [6.5]	5.9 [15.2]	3.7 [16.6]	0.164
Impairment at work (presenteeism)						
Number of patients with complete data	55	53	45	45	45	
% presenteeism, mean [SD]	11.6 [18.8]	23.0 [27.4]	12.2 [19.5]	19.3 [24.4]	7.1 [27.1]	0.083
Overall work impairment (work productivity loss)						
Number of patients with complete data	51	48	38	38	38	
% work productivity loss, mean [SD]	12.9 [20.2]	28.3 [29.0]	14.4 [21.7]	25.1 [25.9]	10.8 [31.4]	0.045
Activity impairment due to health						
Number of patients with complete data	289	299	275	275	275	
% activity impairment, mean [SD]	37.8 [28.7]	36.8 [27.4]	38.2 [28.9]	36.6 [27.8]	1.6 [27.4]	0.409
HAQ-DI						
Number of patients with complete data	367	370	366	366	366	
Overall score, mean [SD]	1.18 [0.66]	1.09 [0.70]	1.18 [0.66]	1.09 [0.70]	-0.08 [0.49]	<0.001
Subscale scores, mean [SD]						
Dressing and grooming	0.78 [0.86]	0.68 [0.87]	0.78 [0.87]	0.68 [0.87]	-0.09 [0.82]	0.034
Arising	1.01 [0.91]	0.82 [0.86]	1.01 [0.91]	0.83 [0.85]	-0.18 [0.91]	<0.001
Eating	1.17 [1.02]	1.08 [1.00]	1.17 [1.01]	1.09 [1.00]	-0.08 [1.02]	0.119
Walking	0.96 [0.93]	0.95 [0.90]	0.96 [0.93]	0.95 [0.90]	0 [0.84]	0.965
Hygiene	1.71 [1.23]	1.73 [1.23]	1.71 [1.23]	1.74 [1.23]	0.04 [1.17]	0.515
Reach	1.49 [1.08]	1.30 [1.08]	1.49 [1.08]	1.30 [1.07]	-0.19 [0.98]	<0.001
Grip	0.91 [0.93]	0.78 [0.89]	0.90 [0.92]	0.79 [0.89]	-0.12 [0.95]	0.012
Activities	1.40 [1.01]	1.36 [1.09]	1.40 [1.01]	1.37 [1.09]	-0.03 [0.98]	0.599

[a]*P values calculated using a paired t-test or Wilcoxon signed-rank test for the patients with complete data at the month 0 and month 6 consultations.*

HAQ-DI = Health Assessment Questionnaire, Alternative Disability Index; SD = standard deviation; SF = short-form; WPAI = Work Productivity Activity Index.

higher for patients completing the RA DTM program, but not for all patients initiating the program (DTM ITT), compared with patients receiving specialty pharmacy services alone. After completing the RA DTM program, patients experienced improvements in SF-12 physical component and HAQ-DI scores but did not have improved SF-12 mental scores or work productivity.

Although these findings are consistent with those of other studies that have shown that patient education programs for arthritis can be a useful method of enhancing self-care management techniques and improving physical outcomes,[8,9,26,27] limited research is available evaluating RA disease management programs that incorporate comprehensive medication therapy management. The present study provides new insight into the benefits of a combined telephone and mail intervention designed to increase patient adherence to injectable RA medications and to empower patients by improving their knowledge of RA. While prior studies have not specifically examined injectable RA medication adherence for patients with RA receiving pharmacist-delivered telephone medication management, one prospective randomized controlled study evaluated medication adherence following a pharmacist-delivered telephone intervention to elderly patients in England who were newly prescribed medication for a chronic condition including stroke, cardiovascular disease, asthma, diabetes, or RA.[28] After 4 weeks of follow-up, patients who had the telephone intervention compared with patients who did not receive the intervention had a significantly lower rate of nonadherence to their medication (9% vs. 16%, respectively, $P = 0.032$) and a significantly lower rate of medication-related problems (23% vs. 34%, respectively, $P = 0.021$). With the expanding role of pharmacists in the provision of medication therapy management services, our study adds to the growing literature that is necessary to demonstrate the benefits of telephone pharmacist- (or nurse) delivered interventions in improving patient adherence to chronic medications.

The rates of adherence to injectable RA medications observed in our analysis are consistent with those observed in other retrospective analyses of administrative claims data.[5,29] Although patients were not necessarily new users of injectable RA medications, the mean PDC for any injectable RA medication for the DTM ITT cohort (0.83) was similar to medication possession ratios (MPRs) previously reported in the literature for new users of etanercept (MPR 0.83), adalimumab (MPR 0.85), etanercept plus methotrexate (MPR 0.64), and adalimumab plus methotrexate (MPR 0.72) within a Medicaid population.[5] Another analysis of medication adherence conducted by Borah et al. (2009) within a large U.S. managed health care plan in 2005 reported mean adherence rates of 0.63 to 0.65 for naïve users of adalimumab or etanercept,[29] which is similar to the mean PDC observed in our community pharmacy cohort (0.60). Patients already receiving adalimumab or etanercept had slightly higher mean adherence rates (0.70 to 0.73),[29] but rates were still lower than those observed for the DTM ITT, DTM completer, or specialty pharmacy cohorts (0.83, 0.89, and 0.81, respectively). A recent Cochrane review that evaluated 9 randomized control trials of interventions for enhancing medication adherence concluded that even the most effective interventions did not lead to large improvements in adherence and treatment outcomes.[30] Considering limited information about the effectiveness of interventions for improving medication adherence, our study results suggest that the combination of pharmacist- or nurse-delivered telephone consultations and educational mailings may be an effective method for improving adherence to injectable RA medications.

Patients completing the DTM program had improvements in physical functioning manifested by significant improvements in the SF-12 physical component and HAQ-DI scores. With a mean age of 61 years and an average duration of disease of 12.7 years, patients in this population would not be expected to have large improvements in HAQ-DI because HAQ-DI is generally considered to increase with age and disease duration.[9] Nonetheless, the HAQ-DI score significantly improved by a mean reduction of 0.08 points from month 0 to month 6. To better understand the clinical importance of this change in HAQ-DI, it is necessary to interpret these findings in the context of the minimally clinically important difference (MCID), which is defined as the threshold of improvement that is perceptible and considered clinically meaningful to an individual patient. Although prior research on the use of the HAQ-DI in patients with RA has suggested that the MCID is a decrease in score of at least 0.22 points,[31] additional research in patients with RA in the clinical practice setting has found clinical improvements in physical status with a reduction in HAQ-DI score as small as 0.09 points.[32] In the present study, the mean reduction of 0.08 points in the HAQ-DI approached the levels of MCID of 0.09 that were observed in clinical practice.

While the physical component scores on the SF-12 are consistent with and follow the same trend of physical improvements as HAQ-DI scores, the lack of a change in SF-12 mental component score is not surprising. Previous research has shown that scales assessing pain and physical health status tend to be more responsive to treatment than scales assessing mental health status when measuring quality of life in a disease with physical implications, such as RA.[33]

Work productivity results were available for only a small number of patients because only 18.6% of respondents to the month 0 questionnaire were employed. Research on the use of WPAI in patients with RA is limited. One study reported in a poster abstract found that patients with RA had a work impairment of 9.0% when in remission, 28.1% with low disease activity, and 47.9% with moderate to high disease activity.[34] In the present study, even though patients did not demonstrate an improvement in WPAI after completing the program, work impairment for the DTM patients who completed the program was 28.3%, which is consistent with responses for patients with RA with low disease activity. However, the small sample size of employed patients makes it difficult to interpret these results.

The DTM cohorts incurred increased pharmacy costs, which would be expected due to improved adherence and persistence to injectable RA medication therapy. To gain a better understanding of the impact of the DTM program on overall medical costs, a post-hoc analysis of total health care costs among the subset of patients with medical claims data (67 DTM ITT patients, 46 DTM completer patients, 55 specialty pharmacy patients, and 32 community pharmacy patients) was conducted. Although preliminary results suggested that increased pharmacy costs were partially offset by smaller medical costs for the DTM cohorts than the specialty or community pharmacy cohorts, total health care costs were evaluable only for the subgroup of patients with medical claims data and may not accurately reflect those of the entire population. In addition, sample sizes of patients with medical claims data were too small to detect differences among the cohorts. Further research is necessary to evaluate short- and long-term total health care costs for patients participating versus not participating in RA DTM programs.

Limitations

The study had several limitations that are consistent with its observational design. First, because the DTM completer cohort consisted of patients who participated in and completed the DTM program, there was potential selection bias favoring the more compliant patients being included in this cohort. The results observed for the DTM ITT cohort may be less subject to this bias because the DTM ITT cohort includes patients who did not complete the DTM program. Second, although we matched patients in the DTM, specialty, and community pharmacy cohorts based on models that accurately predicted the

likelihood of DTM completion 70% of the time using variables available in the pharmacy claims database, we were unable to match on additional clinical variables not found in pharmacy claims such as duration and severity of RA.

Third, because certain injectable RA medications can be administered in the physician's office, it is possible that some patients received injectable RA medications directly from their physicians, resulting in exclusion of some utilization of injectable RA medications from the study database. We do not have data on the proportion of enrollees who obtain RA injectable medications through medical versus pharmacy benefits. However, many health plans require that the medication supply for physician-administered injectables be filled through contracted pharmacies. Although patients were matched according to the specific injectable RA medication they filled on the identification date, physician office administration of the injectable RA medications may not be equally distributed across the DTM, specialty, and community pharmacy cohorts. In addition, community pharmacy patients may be less likely than specialty pharmacy patients to have a standing order to continue receiving their medications and therefore more likely to switch to physician office administration of these medications, which may bias the adherence results.

Fourth, the DTM program and the study sample were not limited to new users of injectable RA therapy. In addition, because patient medication utilization data were not available for time periods prior to plan enrollment, we were unable to control for duration of injectable RA medication therapy in the analyses.

Fifth, because patient-reported responses were collected only for DTM program participants, patient-reported outcomes had to be evaluated with a pre- versus post-intervention design among DTM completers and could not be evaluated among the specialty pharmacy, community pharmacy, or DTM ITT cohorts.

Sixth, the present study findings may not be generalizable to patients with characteristics different than those of our study sample. Participants in DTM may represent a group of patients that are more proactive in the care of their health, which may influence the success of the program. In addition, the majority of DTM enrollees had RA for many years (average duration of RA was 12.7 years among DTM patients), which could affect response to therapy, quality of life, physical functioning, and work productivity.

Seventh, because the patients studied were not all part of the same plan, changes in plan benefits could have influenced patient willingness to participate in the DTM program. For example, changes in copayments may affect patient adherence to medications. It is also possible that patients could have participated in other disease management programs offered outside the study PBM.

Finally, study outcomes such as medication adherence were evaluated over the 8-month period following the index date, and results may not necessarily be representative of what would happen over a longer follow-up period. Although the 8-month duration of follow-up was selected to evaluate medication adherence outcomes during the time that patients were enrolled in the 7-month DTM program, a longer duration of follow-up would be needed to evaluate whether medication adherence outcomes change after patients complete the program.

Conclusions

Despite these limitations, this study provides valuable information on the potential benefits of an RA DTM program focusing on pharmacological self-management. Patients participating in the RA DTM program demonstrated significantly higher injectable RA medication adherence compared with patients receiving their medication from a community pharmacy. In addition, adherence to injectable RA medications was significantly higher for patients completing the RA DTM program, but not for all patients entering the DTM program, compared with patients receiving specialty pharmacy services alone. Patients completing the RA DTM program experienced improvements in SF-12 physical component and HAQ-DI scores although they did not have improved SF-12 mental scores or work productivity.

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