Characteristics and Medication Use of Psoriasis Patients Who May or May Not Qualify for Randomized Controlled Trials

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ABSTRACT

BACKGROUND: Clinical trials impose exclusion criteria that may limit the generalizability of results.

OBJECTIVES: To (a) determine the percentage of real-world patients who would qualify for psoriasis randomized controlled trials; (b) ascertain differences between moderate-to-severe psoriasis patients who would be eligible, ineligible, or potentially eligible for clinical trials; and (c) compare their biologic treatment patterns.

METHODS: Moderate-to-severe psoriasis patients were identified from the U.S. Department of Defense health care database from January 1, 2008, to October 31, 2013. Eligibility classification for psoriasis trials was based on common trial exclusion criteria involving medical conditions and recent treatment history. Patient characteristics and treatment patterns of 4 biologics (adalimumab, etanercept, infliximab, and ustekinumab) were compared between groups. Adherence was measured by medication possession ratio and persistence as continuous time on drug with ≤90-day gap between supply times.

RESULTS: Among 16,284 qualifying psoriasis patients, 4,677 (28.7%) were medically ineligible, and 8,466 (52.0%) had ineligibility-related treatments that could be stopped prior to trial entry; the latter patients were considered potentially eligible for psoriasis trials. Common reasons for medical ineligibility included malignancies and hematologic disorders; treatment ineligibilities included use of topical corticosteroids and phototherapy. Medically ineligible patients were older and had more comorbidities, while potentially eligible patients were younger and healthier than trial-eligible patients. Most treatment patterns were similar across groups, except that, compared with the trial-eligible group, medically ineligible patients had greater adherence to infliximab and potentially trial-eligible patients had greater adherence and persistence to adalimumab.

CONCLUSIONS: This large real-world study found that patients who may be ineligible for psoriasis trials differ in important respects (e.g., comorbidities, prior treatments) from their trial-eligible counterparts. Regardless of their differences at baseline, adherence, persistence, and switching of biologic medications are largely similar, with few differences noted among groups.

What is already known about this subject

- Clinical trials impose many restrictions on eligibility that may result in trial populations not being representative of those receiving the studied drug in the real-world setting.
- Real-world treatment adherence and persistence are generally lower than with treatment given under the more tightly controlled conditions of a randomized controlled trial.

What this study adds

- Results from this study corroborate what has been observed across other disease domains: that patients who may be ineligible for psoriasis trials differ in important respects (e.g., comorbidities, prior treatments) from their trial-eligible counterparts. Regardless of their differences, adherence, persistence, and switching of biologic medications are largely similar.
- In clinical practice, patients with moderate-to-severe psoriasis would be expected to have more comorbidities but similar biologic medication use patterns (e.g., adherence, persistence) to those seen in clinical trial patients.

Psoriasis is a chronic, inflammatory, and proliferative dermatologic disorder that follows a repeated course of remission and relapse. It is characterized by scaly erythematous plaques that are often painful and/or pruritic.[1] In addition to skin and joint diseases, psoriasis is also linked to other comorbidities (e.g., autoimmune diseases, cardiovascular disease, metabolic syndrome, skin cancer) and psychological stress (e.g., depression, suicidality) and has a significant impact on patients' quality of life.[2]

Several classes of therapy are available to manage psoriasis, including topical agents, phototherapy, nonbiologic oral systemic agents, and biologic agents; clinical guidelines[3] and emerging evidence from randomized controlled trials (RCTs) should guide their use. Although RCTs are the "gold standard" for assessing a medicine's efficacy, they still have limitations.[4] The hallmark strength of an RCT is that randomization generally distributes potential confounders similarly across treatment groups; thus, an observed difference between treatment groups is presumed to be causally related to the intervention. A limitation of RCTs is that the very elements that contribute to an unbiased, precise effect estimate (e.g., optimized drug administration and adherence, homogeneous study population) may have a negative effect on the generalizability of results.[5] To maximize internal validity and reduce the risk of adverse events, RCTs may include restrictive eligibility criteria,[6-10] which may be increasing over time in psoriasis[11] and other disease states.[12,13] In addition, RCTs have formal study procedures that may not apply to clinical practice; the Psoriasis

Area and Severity Index (PASI) is commonly used to assess disease severity in psoriasis clinical trials but has limited use in clinical practice.[2] As a result, the real-world applicability of RCT results may be debated.[6,8,11,13-20]

The objectives of this retrospective cohort study were to (a) determine the percentage of real-world patients who would qualify for psoriasis RCTs; (b) compare differences in baseline characteristics between groups eligible and ineligible for psoriasis RCTs; and (c) assess whether biologic treatment patterns differ based on trial eligibility.

■ Methods

Data Source
The U.S. Department of Defense (DoD) health care database served as the sole data source for this study and included data from January 1, 2008, to October 31, 2014. The DoD database represents one of the largest health care databases in the United States and includes integrated inpatient, outpatient, and medication data for nearly 10 million active beneficiaries, composed of military personnel, retirees, and their families.[21] The database includes administrative claims-level information (e.g., diagnosis and procedure codes, pharmacy drug fills) for care delivered in civilian facilities and claims plus electronic health record-level information (e.g., laboratory results) for care in military facilities. Research data were derived from an approved Naval Medical Center, Portsmouth, Virginia, institutional review board protocol "NMCP.2015.0030."

Patient Selection
A claims-based psoriasis diagnosis by a dermatologist with evidence of prior receipt of systemic therapy or phototherapy was used as a proxy for moderate-to-severe psoriasis. Qualifying patients met all of the following inclusion criteria: had an outpatient psoriasis diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 696.1) from a dermatologist during the cohort selection period (January 1, 2008, to October 31, 2013), received phototherapy and/or systemic therapy before the index date, had continuous enrollment with medical and pharmacy benefits 12 months pre-index, and were ≥18 years as of the index date; the index date was defined as the earliest claim with a psoriasis diagnosis after meeting all inclusion criteria. Exclusion criteria were active-duty military during the study period (restrictions exist for biologic use during active duty) and a psoriasis diagnosis code appearing only on claims with a phototherapy procedure code and not on other dermatologist visit claims (the diagnosis code was frequently observed during chart review to be erroneously entered as justification for treatment; Figure 1).

The algorithm for defining psoriasis (claims showing a dermatologist diagnosis plus systemic or phototherapy) was tested via chart review of a random sample of 250 patients treated in military facilities. Results of the chart review indicated that the algorithm had a positive predictive value of 83%.

Patients with moderate-to-severe psoriasis were categorized into a trial-eligible cohort if they had none of a list of RCT exclusion criteria commonly used in trials of medications for moderate-to-severe psoriasis (Table 1); patients with treatment-related exclusion criteria (i.e., received systemic nonbiologic psoriasis therapy within 4 weeks prior to index, biologic agents [etanercept <28 days; infliximab, adalimumab, or alefacept <60 days; ustekinumab <8 months; rituximab or efalizumab <12 months prior to index], or a live vaccine 12 weeks prior to index) were categorized as potentially trial-eligible, since these patients theoretically could be eligible if the excluded treatment was stopped or if trial enrollment was delayed in the case of vaccine exposure. Patients with the remaining nonmodifiable ineligibility criteria listed in Table 1 were categorized into a medically trial-ineligible cohort.

Baseline Variables
Baseline comorbidities were identified using diagnosis and procedure codes from the baseline period, defined as 12 months prior to the index date (i.e., the first claim with an outpatient psoriasis diagnosis by a dermatologist following a claim for systemic therapy or phototherapy) through the index date (inclusive). Baseline variables included demographics, Charlson Comorbidity Index (CCI), psoriasis disease duration (derived from all available claims data before index), other autoimmune conditions, cardiovascular conditions/other comorbidities, and use of medications for psoriasis, including the number of biologics received during the baseline period.

Biologic Usage Measures
Each patient's index therapy was defined as the first biologic received on or after the index date; eligible biologics included etanercept, adalimumab, infliximab, and ustekinumab. Analyses were conducted for each biologic separately. The following measures were estimated for each biologic initiated from the index date through end of follow-up:
1. Adherence was estimated using the medication possession ratio (MPR) for up to 12 months following initiation. MPR was calculated by dividing total days' supply of filled biologic over the number of days following initiation, censoring data for patients who unenrolled from the health plan prior to 12 months after the index date. MPR values were capped at 100% for patients with overlapping prescriptions. MPR ≥80% was considered highly adherent.
2. Persistence with the index biologic was examined as the continuous time, assessed up to 12 months following initiation, on drug with a ≤90-day gap between supply times; each biologic was assigned a supply time of the indicated days between sequential administrations during the maintenance phase of use. The following supply-time calculations pertained only to clinic-administered drugs; for pharmacy-dispensed drugs, days supply data were used.

TABLE 1 Frequencies of Psoriasis Biologic Trial Ineligibility Criteria Among Moderate-to-Severe Psoriasis Patients

Baseline Patient Characteristics	Patients with Moderate-to-Severe Psoriasis (n=16,284)		Medically Trial-Ineligible Cohort (n=4,677)		Potentially Trial-Eligible Cohort (n=8,466)	
Received systemic nonbiologic psoriasis therapy within 4 weeks prior to index date or topical psoriasis treatment (classes 1-5) within 2 weeks prior to index date, n (%)						
Systemic nonbiologic therapy						
Cyclosporine	150	(0.9)	33	(0.7)	117	(1.4)
Oral/IV corticosteroids	1,204	(7.4)	362	(7.7)	842	(9.9)
Methotrexate	1,827	(11.2)	474	(10.1)	1,353	(16.0)
Oral retinoids (acitretin)	813	(5.0)	216	(4.6)	597	(7.1)
Mycophenolate mofetil	49	(0.3)	14	(0.3)	35	(0.4)
Thioguanine	4	(0.02)	1	(0.02)	3	(0.04)
Hydroxyurea	25	(0.2)	21	(0.4)	4	(0.05)
Sirolimus	4	(0.02)	3	(0.06)	1	(0.01)
Azathioprine	66	(0.4)	32	(0.7)	34	(0.4)
Phototherapy/PUVA, UVB	2,541	(15.6)	730	(15.6)	1,811	(21.4)
Topical medications						
Topical corticosteroids (classes 1-5)	4,233	(26.0)	1,320	(28.2)	2,913	(34.4)
Anthralin (dithranol)	1	(0.006)	1	(0.02)	0	(0.0)
Calcipotriene	1,424	(8.7)	380	(8.1)	1,044	(12.3)
Tazarotene	80	(0.5)	21	(0.4)	59	(0.7)
Concurrent or recent use of any biologic agent within the specified washout periods, n (%)						
Etanercept <28 days	1,504	(9.2)	333	(7.1)	1,171	(13.8)
Infliximab <60 days	313	(1.9)	95	(2.0)	218	(2.6)
Adalimumab <60 days	1,832	(11.3)	434	(9.3)	1,398	(16.5)
Alefacept <60 days	23	(0.1)	4	(0.09)	19	(0.2)
Ustekinumab <8 months	82	(0.5)	20	(0.4)	62	(0.7)
Rituximab <12 months	110	(0.7)	96	(2.1)	14	(0.2)
Efalizumab <12 months	283	(1.7)	73	(1.6)	210	(2.5)
Lymphoproliferative disease or malignant disease <12 months, n (%)						
Lymphoproliferative disease	31	(0.2)	31	(0.7)	0	(0.0)
Malignant disease	2,248	(13.8)	2,248	(48.1)	0	(0.0)
Cerebro-cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic, or neuropsychiatric disorders within 12 weeks before index date, n (%)						
Cerebro-cardiovascular						
Myocardial infarction	39	(0.2)	39	(0.8)	0	(0.0)
Unstable angina	47	(0.3)	47	(1.0)	0	(0.0)
Hypertension diagnosis or at least 1 high BP reading (systolic BP >160 mm Hg or diastolic BP >100 mm Hg)	316	(1.9)	316	(6.8)	0	(0.0)
Moderate-to-severe heart failure	360	(2.2)	360	(7.7)	0	(0.0)
Cerebrovascular accident	146	(0.9)	146	(3.1)	0	(0.0)
Respiratory	9	(0.06)	9	(0.2)	0	(0.0)
Hepatic	311	(1.9)	311	(6.6)	0	(0.0)
Renal	519	(3.2)	519	(11.1)	0	(0.0)
Gastrointestinal disorder	205	(1.3)	205	(4.4)	0	(0.0)
Endocrine disorder	26	(0.2)	26	(0.6)	0	(0.0)
Hematologic disorder	998	(6.1)	998	(21.3)	0	(0.0)
Neurologic or neuropsychiatric disorders	4	(0.02)	4	(0.09)	0	(0.0)
Infection either during an inpatient stay or on a claim for IV antibiotics within 12 weeks prior to index, n (%)						
Pneumonia	45	(0.3)	45	(1.0)	0	(0.0)
Cellulitis	62	(0.4)	62	(1.3)	0	(0.0)
Sepsis	21	(0.1)	21	(0.4)	0	(0.0)
Herpes zoster infection or any other clinically apparent varicella-zoster virus infection within 12 weeks prior to index, n (%)						
Herpes zoster	91	(0.6)	91	(1.9)	0	(0.0)
Human immunodeficiency virus	8	(0.05)	8	(0.2)	0	(0.0)

Baseline Patient Characteristics	Patients with Moderate-to-Severe Psoriasis (n=16,284)		Medically Trial-Ineligible Cohort (n=4,677)		Potentially Trial-Eligible Cohort (n=8,466)	
TABLE 1 Frequencies of Psoriasis Biologic Trial Ineligibility Criteria Among Moderate-to-Severe Psoriasis Patients *(continued)*						
Herpes zoster infection or any other clinically apparent varicella-zoster virus infection within 12 weeks prior to index, n (%)						
Hepatitis B	46	(0.3)	46	(1.0)	0	(0.0)
Abnormal labs within 30 days prior to or on index, n/N (%)						
Neutrophil count <1,500 cells/μL	10/647	(1.5)	10/228	(4.4)	0/352	(0.0)
Lymphocyte count <800 cells/μL	14/654	(2.1)	14/227	(6.2)	0/357	(0.0)
Platelet count <100,000 cells/μL	5/811	(0.6)	5/287	(1.7)	0/443	(0.0)
AST level >2.5 times the ULN	11/873	(1.3)	11/295	(3.7)	0/492	(0.0)
ALT level >2.5 times the ULN	20/868	(2.3)	20/293	(6.8)	0/490	(0.0)
Total WBC count <3,000 cells/μL	9/839	(1.1)	9/295	(3.1)	0/460	(0.0)
Hemoglobin level <8.5 g/dL for males; <8.0 g/dL for females	3/837	(0.4)	3/295	(1.0)	0/459	(0.0)
Serum creatinine level >2.0 mg/dL	8/757	(1.1)	8/291	(2.7)	0/397	(0.0)
Pregnancy	294	(1.8)	294	(6.3)	0	(0.0)
Active or latent tuberculosis	52	(0.3)	52	(1.1)	0	(0.0)
Hepatitis C	99	(0.6)	99	(2.1)	0	(0.0)
Natalizumab or vedolizumab during cohort selection period	4	(0.02)	4	(0.09)	0	(0.0)
Live vaccination within 12 weeks prior to index date	86	(0.5)	24	(0.5)	62	(0.7)
Inpatient hospitalization within 12 weeks before index date	502	(3.1)	502	(10.7)	0	(0.0)
Demyelinating disorder	51	(0.3)	51	(1.1)	0	(0.0)
Body temperature ≥38°C (100.5°F) at index date	0	(0.0)	0	(0.0)	0	(0.0)
Presence of at least one of the above (i.e., qualifies as trial-ineligible)	13,143	(80.7)	4,677	(100.0)	8,466	(100.0)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; IV = intravenous; PUVA = psoralen/ultraviolet A; SD = standard deviation; ULN = upper limit of normal; UVB = ultraviolet B; WBC = white blood cell.

a. The indicated intervals between administrations of etanercept, adalimumab, infliximab, and ustekinumab are 7, 14, 56, and 84 days, respectively, so each administration was assumed to last the corresponding number of days depending on the biologic. A subsequent administration during the indicated period or within the next 90 days continued the treatment episode, counting as continuous use. A gap of 90 or more days after finishing the indicated supply days was considered a discontinuation, as was switching to a different biologic without a continuation of the initial biologic.

3. Switching was defined as discontinuing the index biologic and starting a different biologic within 90 days. Time to first switch was calculated as the number of days from the index biologic start date to the initiation of the second biologic.

4. Medication restart was defined as a claim for the same medication following a discontinuation (i.e., a >90-day gap in treatment), regardless of other biologics that may have been used following the discontinuation. Time to restart was calculated as the number of days from the index biologic stop date to the reinitiation of the same biologic.

5. Discontinuation of the index biologic prior to end of follow-up was examined for each patient.

6. Time to start of the first biologic received on or after the index date was also examined.
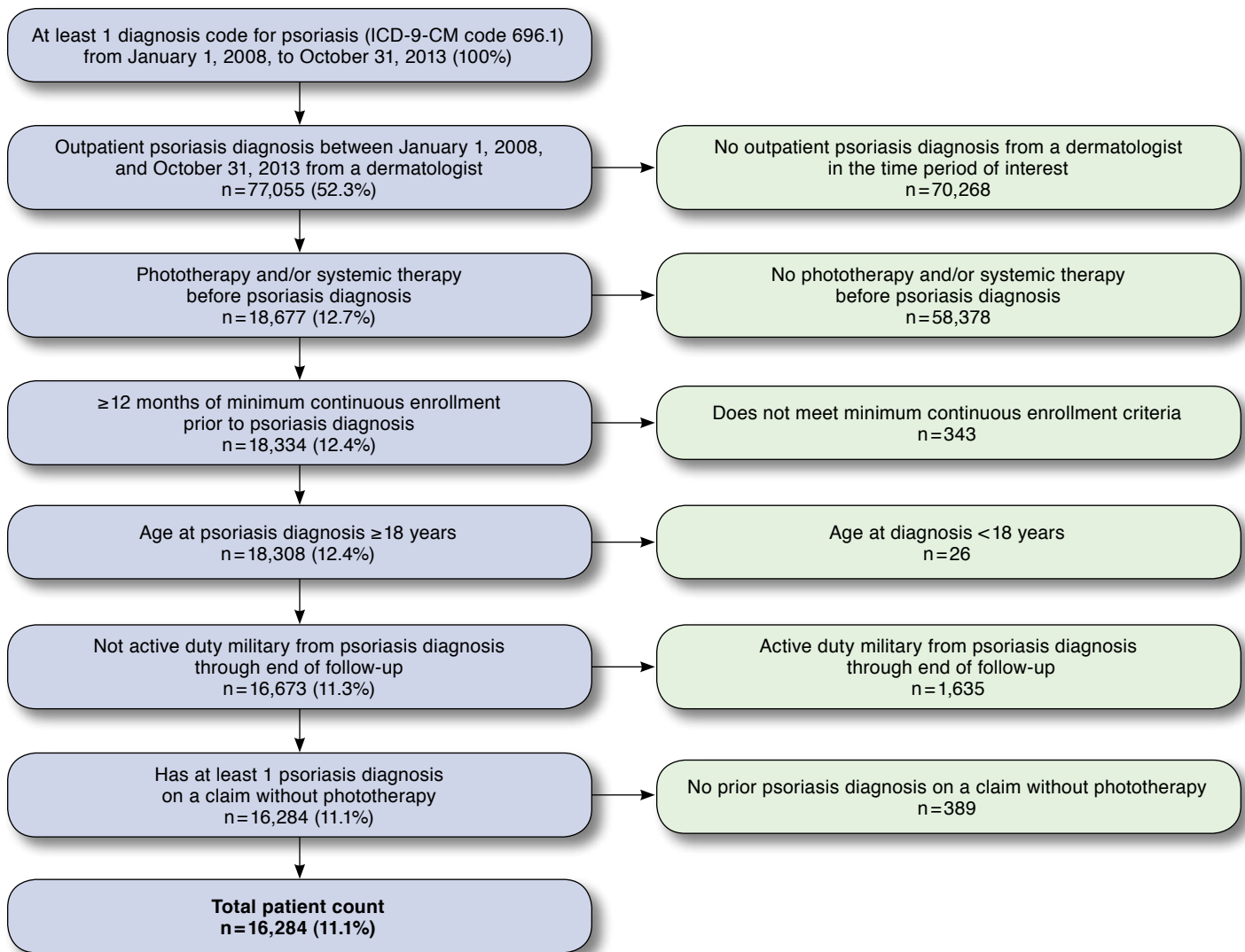
Statistical Analyses

SAS software version 9.3 (SAS Institute, Cary, NC) was used to conduct the analyses. The number and percentage of patients meeting each trial-ineligibility criteria were tabulated for the full cohort and separately among the 2 subgroups of trial-ineligible patients.

Demographic, clinical, and other baseline variables were summarized for each subgroup and the overall cohort as the counts and percentages for categorical variables and means, medians, standard deviations (SDs), and ranges for continuous variables. Differences between cohorts were assessed using chi-square or Fisher's exact tests for categorical variables and t-tests or analysis of variance for continuous variables. Nonparametric tests (e.g., Wilcoxon rank-sum test for ordinal variables) were used as appropriate.

Biologic utilization was compared separately for initiators of etanercept, adalimumab, infliximab, and ustekinumab as the index therapy. Adherence, persistence, and switching were examined within each of these 4 groups. Adherence was summarized as continuous values of MPR (mean, SD, median, range) and categorically in intervals of 20%. Adherence was also dichotomized as high (≥80%) versus low (<80%), as is commonly used in medication adherence research.[22] The number and percentage of patients who discontinued the index biologic at any time during follow-up, who discontinued and

FIGURE 1 Patient Attrition

At least 1 diagnosis code for psoriasis (ICD-9-CM code 696.1)
from January 1, 2008, to October 31, 2013 (100%)

Outpatient psoriasis diagnosis between January 1, 2008,
and October 31, 2013 from a dermatologist
n=77,055 (52.3%)

No outpatient psoriasis diagnosis from a dermatologist
in the time period of interest
n=70,268

Phototherapy and/or systemic therapy
before psoriasis diagnosis
n=18,677 (12.7%)

No phototherapy and/or systemic therapy
before psoriasis diagnosis
n=58,378

≥12 months of minimum continuous enrollment
prior to psoriasis diagnosis
n=18,334 (12.4%)

Does not meet minimum continuous enrollment criteria
n=343

Age at psoriasis diagnosis ≥18 years
n=18,308 (12.4%)

Age at diagnosis <18 years
n=26

Not active duty military from psoriasis diagnosis
through end of follow-up
n=16,673 (11.3%)

Active duty military from psoriasis diagnosis
through end of follow-up
n=1,635

Has at least 1 psoriasis diagnosis
on a claim without phototherapy
n=16,284 (11.1%)

No prior psoriasis diagnosis on a claim without phototherapy
n=389

Total patient count
n=16,284 (11.1%)

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

then restarted, and who switched to a different biologic were presented. Chi-square tests were used for the above metrics, with MPR categorized as ≥80% versus <80%. Kaplan-Meier (KM) curves and log-rank tests were used to evaluate time to discontinuation (persistence) of the index biologic, with a separate plot for each drug and separate curves for trial-eligible, medically trial-ineligible, and potentially eligible patients. Median time to each of these events was obtained from the KM plots. For each outcome, pairwise comparisons were made between (1) medically ineligible versus trial-eligible and (2) potentially eligible versus trial-eligible patients.

MPR ≥ 80% was compared between groups using logistic regression modeling, examining all baseline characteristics not used as ineligibility criteria. Univariate models estimated the odds ratio (OR) and 95% confidence intervals (CIs) for each variable. A final, fully adjusted model was constructed using backward selection with $P < 0.05$ to identify all simultaneously significant predictors of high adherence. Time to treatment discontinuation was similarly modeled, with univariate and multivariable Cox models providing hazard ratios (HRs) and 95% CIs.

■ Results

Cohort Selection and Trial Eligibility

In total, 147,323 patients in the DoD database had a diagnosis code for psoriasis during the study period (Figure 1). Of these, 77,055 (52.3%) had at least 1 psoriasis diagnosis from a dermatologist, and 18,677 (12.7%) had claims for systemic therapy or phototherapy. Applying additional inclusion and exclusion criteria resulted in a final cohort size of 16,284 patients.

In the claims data, 4,677 (28.7%) patients met 1 or more medical ineligibility criteria for psoriasis biologic trials, while 8,466 (52.0%) had ongoing treatment that made them ineligible for trials as of their index date but who could be potentially eligible if they discontinued that treatment (Table 1). The most common reasons for medical ineligibility were malignant disease during the past year (2,248 patients; 13.8% of all patients and 48.1% of medically ineligible patients) and hematologic disorders during the past year (998 patients; 6.1% of all patients and 21.3% of medically ineligible patients). The most common trial ineligibility criteria in the potentially eligible cohort were topical corticosteroid use within 2 weeks prior to the index date (26.0% [4,233] of all patients; 34.3% [2,913] of potentially eligible patients), phototherapy use (15.6% [2,541] of all patients; 21.4% [1,811] of potentially eligible patients) or methotrexate use (11.2% [1,827] of all patients; 16.0% [1,353] of potentially eligible patients) within the same time frame, and adalimumab use within 60 days prior to the index date (11.3% [1,832] of all patients; 16.5% [1,398] of potentially eligible patients).

Numerous baseline characteristics differed between trial-eligible, medically trial-ineligible, and potentially eligible groups (Table 2). The medically ineligible patients were, on average, 7 years older than the trial-eligible patients ($P < 0.0001$) but had a similar gender distribution. Compared with the patients who would have been eligible for trials, the medically ineligible group had a higher mean CCI ($P < 0.001$) and a shorter mean duration of psoriasis (difference of 4.6 months, $P < 0.001$). All examined comorbidities, except ankylosing spondylitis and psoriatic arthritis, were significantly ($P < 0.05$) more common among the medically ineligible patients. History of coronary artery bypass graft during the baseline period was not significantly different between groups. The medically ineligible patients were more likely than their trial-eligible counterparts to have received oral/intravenous (IV) or topical corticosteroids ($P < 0.001$), mycophenolate mofetil ($P < 0.001$), hydroxyurea ($P < 0.001$), azathioprine ($P = 0.0055$), topical corticosteroids (class 1-5; $P < 0.001$), and phototherapy ($P < 0.001$) during baseline but less likely to have received oral retinoids ($P < 0.001$) and methotrexate ($P = 0.034$). Prior biologic use was more common among the medically ineligible patients, although the specific biologics used showed differential patterns between groups: the medically ineligible patients were more often treated with adalimumab or infliximab than the trial-eligible patients but less likely to be treated with etanercept.

In contrast to the first comparison, the potentially eligible group was about 2 years younger than the trial-eligible patients ($P < 0.001$), with a slightly lower mean CCI ($P = 0.0078$). Different results were also seen for comorbidities: while almost all of the considered comorbidities were more prevalent in the medically ineligible group versus the trial-eligible group, only one comorbidity (obesity) was more common in the potentially eligible group versus trial-eligible patients ($P = 0.026$); peripheral vascular disease (PVD) was less frequent in the potentially eligible group ($P < 0.001$). Similar to the medically ineligible group, potentially eligible patients were more likely than their trial-eligible counterparts to have received oral/IV or topical corticosteroids ($P = 0.0064$) and phototherapy ($P < 0.001$) during baseline and less likely to have received oral retinoids ($P < 0.001$) and methotrexate ($P < 0.001$). The potentially eligible patients were also more likely to have used calcipotriene ($P < 0.001$) and tazarotene ($P = 0.012$) than the trial-eligible group. Potentially eligible patients had more baseline treatment with adalimumab or infliximab than the trial-eligible group but were less likely to be treated with etanercept.

Biologic Utilization Patterns

Of the 16,284 patients in the full study cohort, 4,343 (26.7%) initiated a biologic on or after the index date. Adalimumab was most commonly the first biologic started on or after the index date, followed by etanercept, in all 3 cohorts.

Adherence was similar between the trial-eligible and medically ineligible etanercept initiators and between the trial-eligible and potentially eligible etanercept initiators (Figure 2), with 27.9% of the trial-eligible and 26.9% and 30.5% of medically ineligible and potentially eligible groups, respectively, attaining an MPR ≥ 80%, calculated for up to 12 months following initiation. Frequencies of discontinuing and switching from etanercept were also similar between the trial-eligible (discontinued during the study follow-up period: 80.6%; switched: 16.2%), medically ineligible (discontinued: 75.2%; switched: 16.5%), and potentially eligible (discontinued: 76.2%; switched: 18.3%) groups. Overall, in all eligibility groups, the majority of patients who switched from etanercept moved to adalimumab. Trial-eligible patients had a median treatment duration of 279 days, which was not significantly different from the medically ineligible group (262 days; $P = 0.66$; Figure 3) or the potentially eligible group (263 days; $P = 0.59$; Figure 3).

In the multivariable logistic regression model examining predictors of adherence for etanercept (tabular results not shown), patients 55-64 years old (OR = 1.84; 95% CI = 1.24-2.71; $P = 0.0022$) and 65-74 years old (OR = 2.29; 95% CI = 1.51-3.48; $P < 0.001$) had significantly greater odds of high adherence compared with those 18-44 years old; phototherapy within the past year was associated with decreased

TABLE 2 Baseline Characteristics of Patients with Moderate-to-Severe Psoriasis Who Would Be Eligible, Potentially Eligible, or Medically Ineligible for Clinical Trials

Baseline[a] Patient Characteristics	Trial-Eligible Cohort (n = 3,141)		Medically Trial-Ineligible Cohort (n = 4,677)		P Value[b] vs. Trial-Eligible	Potentially Trial-Eligible Cohort (n = 8,466)		P Value[b] vs. Trial-Eligible
Age (years)								
Mean (SD)	56.3	(16.1)	62.9	(15.6)	< 0.0001	54.6	(15.9)	< 0.0001
Median (range)	59 (18-85)		66 (18-85)			56 (18-85)		
Age, categorized, n (%)								
18 to < 45	692	(22.0)	655	(14.0)	< 0.0001	2,054	(24.3)	< 0.0001
45 to < 55	587	(18.7)	477	(10.2)		1,736	(20.5)	
55 to < 65	778	(24.8)	1,025	(21.9)		2,192	(25.9)	
65 to < 75	725	(23.1)	1,369	(29.3)		1,751	(20.7)	
75+	359	(11.4)	1,151	(24.6)		733	(8.7)	
Gender, n (%)								
Male	1,264	(40.2)	1,957	(41.8)	0.16	3,386	(40.0)	0.81
Female	1,877	(59.8)	2,720	(58.2)		5,080	(60.0)	
CCI								
Mean (SD)	0.9	(1.4)	2.6	(2.5)	< 0.0001	0.8	(1.3)	0.0078
Median (range)	0	(0-10)	2	(0-17)		0	(0-11)	
CCI, categorized, n (%)								
0-1	2,489	(79.2)	1,811	(38.7)	< 0.0001	6,864	(81.1)	0.013
2	267	(8.5)	789	(16.9)		749	(8.8)	
3	190	(6.0)	672	(14.4)		421	(5.0)	
4+	195	(6.2)	1,405	(30.0)		432	(5.1)	
Disease duration of psoriasis, months								
Mean (SD)	33.5	(22.0)	28.9	(23.3)	< 0.0001	28.3	(22.5)	< 0.0001
Median (range)	39	(0-60)	30	(0-60)		27	(0-60)	
Disease duration of psoriasis, categorized, n (%)								
< 6 months	621	(19.8)	1,395	(29.8)	< 0.0001	2,334	(27.6)	< 0.0001
6 to < 12 months	188	(6.0)	294	(6.3)		664	(7.8)	
12 to < 24 months	323	(10.3)	452	(9.7)		1,017	(12.0)	
24 to < 36 months	335	(10.7)	434	(9.3)		833	(9.8)	
36+ months	1,674	(53.3)	2,102	(44.9)		3,618	(42.7)	
Conditions during baseline,[a] n (%)								
Depression	374	(11.9)	752	(16.1)	< 0.0001	1,060	(12.5)	0.37
Ankylosing spondylitis	13	(0.4)	26	(0.6)	0.38	52	(0.6)	0.2
Rheumatoid arthritis	274	(8.7)	620	(13.3)	< 0.0001	801	(9.5)	0.22
Ulcerative colitis	35	(1.1)	83	(1.8)	0.019	79	(0.9)	0.38
Psoriatic arthritis	502	(16.0)	817	(17.5)	0.085	1,521	(18.0)	0.012
Diabetes, uncomplicated	619	(19.7)	1,404	(30.0)	< 0.0001	1,561	(18.4)	0.12
Diabetes, complicated	187	(6.0)	569	(12.2)	< 0.0001	437	(5.2)	0.093
Dyslipidemia	1,566	(49.9)	2,880	(61.6)	< 0.0001	4,066	(48.0)	0.08
Obesity	277	(8.8)	623	(13.3)	< 0.0001	864	(10.2)	0.026
Chronic obstructive pulmonary disease	61	(1.9)	269	(5.8)	< 0.0001	156	(1.8)	0.73
Cardiac arrhythmias	218	(6.9)	859	(18.4)	< 0.0001	536	(6.3)	0.24
Peripheral vascular disorders	184	(5.9)	614	(13.1)	< 0.0001	371	(4.4)	0.0009
Percutaneous transluminal coronary angioplasty	18	(0.6)	78	(1.7)	< 0.0001	36	(0.4)	0.3
Coronary artery bypass graft	8	(0.3)	21	(0.4)	0.17	13	(0.2)	0.25
Systemic nonbiologic therapy from baseline[a] up to 4 weeks prior to index date, n (%)								
Cyclosporine	48	(1.5)	58	(1.2)	0.28	115	(1.4)	0.49
Oral/IV corticosteroids	779	(24.8)	1,565	(33.5)	< 0.0001	2,313	(27.3)	0.0064
Methotrexate	650	(20.7)	877	(18.8)	0.034	1,481	(17.5)	< 0.0001
Oral retinoids (acitretin)	357	(11.4)	308	(6.6)	< 0.0001	552	(6.5)	< 0.0001
Mycophenolate mofetil	12	(0.4)	55	(1.2)	0.0002	41	(0.5)	0.47
Thioguanine	0	(0.0)	4	(0.09)	0.15	3	(0.04)	0.57
Hydroxyurea	2	(0.06)	52	(1.1)	< 0.0001	5	(0.06)	1

continued on next page

TABLE 2	Baseline Characteristics of Patients with Moderate-to-Severe Psoriasis Who Would Be Eligible, Potentially Eligible, or Medically Ineligible for Clinical Trials *(continued)*					
Baseline[a] Patient Characteristics	**Trial-Eligible Cohort (n = 3,141)**		**Medically Trial-Ineligible Cohort (n = 4,677)**		***P* Value[b] vs. Trial-Eligible**	**Potentially Trial-Eligible Cohort (n = 8,466)**		***P* Value[b] vs. Trial-Eligible**

Baseline[a] Patient Characteristics	Trial-Eligible n	(%)	Medically n	(%)	*P* Value	Potentially n	(%)	*P* Value
Systemic nonbiologic therapy from baseline[a] up to 4 weeks prior to index date, n (%)								
Sirolimus	1	(0.03)	6	(0.1)	0.25	1	(0.01)	0.47
Azathioprine	27	(0.9)	74	(1.6)	0.0055	52	(0.6)	0.15
Phototherapy/PUVA, UVB	165	(5.3)	366	(7.8)	< 0.0001	671	(7.9)	< 0.0001
Topical medications from baseline[a] up to 2 weeks prior to index date, n (%)								
Topical corticosteroids (classes 1-5)	1,634	(52.0)	2,918	(62.4)	< 0.0001	5,598	(66.1)	< 0.0001
Anthralin (dithranol)	5	(0.2)	6	(0.1)	0.72	20	(0.2)	0.43
Calcipotriene	725	(23.1)	1,108	(23.7)	0.53	2,336	(27.6)	< 0.0001
Tazarotene	48	(1.5)	90	(1.9)	0.19	193	(2.3)	0.012
Biologic therapy, n (%)								
Etanercept from baseline to 28 days before index date	607	(19.3)	593	(12.7)	< 0.0001	1,422	(16.8)	0.0014
Infliximab from baseline to 60 days before index date	33	(1.1)	135	(2.9)	< 0.0001	248	(2.9)	< 0.0001
Adalimumab from baseline to 60 days before index date	238	(7.6)	416	(8.9)	0.039	1,058	(12.5)	< 0.0001
Alefacept from baseline to 60 days before index date	6	(0.2)	10	(0.2)	0.83	13	(0.2)	0.66
Ustekinumab from baseline to 8 months before index date	7	(0.2)	5	(0.1)	0.2	23	(0.3)	0.65
Number of previous biologics prescribed during baseline[a] excluding index date, n (%)								
0	2,277	(72.5)	3,208	(68.6)	< 0.0001	5,001	(59.1)	< 0.0001
1	837	(26.6)	1,379	(29.5)		3,218	(38.0)	
2 or more	27	(0.9)	90	(1.9)		247	(2.9)	

[a]Baseline period covers 12 months before index date through the index date (inclusive).
[b]P values were calculated between trial-eligible and trial-ineligible from t-tests for continuous variables and chi-square tests for categorical variables.
CCI = Charlson Comorbidity Index; IV = intravenous; PUVA = psoralen/ultraviolet A; SD = standard deviation; UVB = ultraviolet B.

odds of high adherence (OR = 0.40; 95% CI = 0.19-0.83; *P* = 0.014). In the Cox model, older age (45-54 years, HR = 0.81, *P* = 0.041; 55-64 years, HR = 0.82, *P* = 0.047; 65-74 years, HR = 0.67, *P* < 0.001; each vs. patients 18-44) was associated with a decreased risk of discontinuation, while male sex (HR = 1.29; *P* < 0.001) and PVD within the past year (HR = 1.60; *P* = 0.015) were associated with increased risk of etanercept discontinuation.

Only 234 infliximab initiators were available for analysis, leading to few useful results for this subgroup (Figure 2). The percentage of patients with high adherence (MPR ≥ 80%) was greater for infliximab (57.7% overall vs. 29.0% for etanercept). Medically ineligible patients had greater adherence (71.4%) compared with trial-eligible patients (51.2%; *P* = 0.032). Median duration of treatment was 651 days for trial-eligible patients, 816 days for medically ineligible patients, and 433 days for potentially eligible patients (*P* > 0.05; Figure 3). The multivariable model showed that the medically ineligible patients had increased odds of high adherence to infliximab compared with trial-eligible patients (OR = 2.47; 95% CI = 1.09-5.62; *P* = 0.031). Use of oral/IV corticosteroids within the past year was associated with poorer infliximab adherence (OR = 0.42; 95% CI = 0.24-0.73; *P* = 0.0019). Only use of oral/IV corticosteroids within the past year was associated with a significant risk of infliximab discontinuation (HR = 1.75; 95% CI = 1.26-2.43; *P* < 0.001).

Adalimumab initiators comprised the largest treatment cohort (2,443 patients). Trial-eligible and potentially eligible patients had differences in adherence and persistence outcomes (Figure 2). High adherence (MPR ≥ 80%) was seen in 32.7% of trial-eligible patients versus 41.8% of potentially eligible patients (*P* < 0.001); medically ineligible patients showed no difference (36.3%; *P* = 0.23) versus the trial-eligible group. Overall discontinuation was more common among the trial-eligible than potentially eligible patients (73.3% vs. 67.7% [*P* = 0.017], respectively). Switching was not significantly different across groups (trial-eligible: 6.8%; medically ineligible: 9.7%; potentially eligible: 9.4%). Among switchers, the next drug started was most often etanercept or ustekinumab. Trial-eligible patients had a median treatment duration of 331 days; this was not significantly different (*P* = 0.62) from the medically ineligible patients (307 days) but was significantly shorter than the potentially eligible patients (407 days, *P* = 0.009; Figure 3). In contrast to the findings for infliximab, the potentially eligible patients had increased odds of high adherence to adalimumab compared with trial-eligible patients (OR = 1.49; 95% CI = 1.21-1.84; *P* < 0.001). Older age was also associated with greater adherence. Potentially eligible patients also had a significantly decreased risk of adalimumab discontinuation (HR = 0.85; 95% CI = 0.75-0.95; *P* = 0.006), as did older patients, males, those with a lower CCI, or those with methotrexate use within the past year.

FIGURE 2 *Medication Adherence Among Psoriasis Trial-Eligible and Trial-Ineligible Biologic Treatment Initiators*

Percentage with MPR≥80%

Legend: ■ Eligible ■ Potentially trial-eligible ■ Medically trial-ineligible
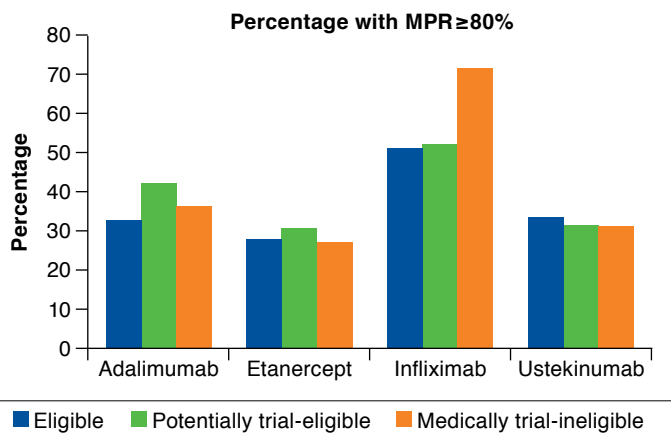
Note: MPR was calculated for up to 12 months following initiation of biologic. MPR = medication possession ratio.

Among the 495 ustekinumab initiators, adherence, discontinuation, and persistence were similar between the trial-eligible and medically ineligible patients. A lower percentage of potentially eligible patients compared with trial-eligible patients switched to a different drug (1.7% and 6.1%, respectively; $P = 0.022$). Median treatment duration was 309, 298, and 324 days for the trial-eligible, medically ineligible, and trial-ineligible groups, respectively ($P > 0.05$; Figure 3). In the multivariable logistic regression model for ustekinumab, the only significant predictors of high adherence were age 65-74 compared with age 18-44 (OR = 1.94; $P = 0.041$), disease duration 18 to < 24 months compared with ≥ 24 months (OR = 0.46; $P = 0.044$), and tazarotene use within the past year (OR = 16.54; $P = 0.01$). Significant independent predictors of ustekinumab discontinuation were age 65-74 compared with age 18-44 (OR = 0.61; $P = 0.038$), psoriatic arthritis in the past year (OR = 1.66; $P < 0.001$), and uncomplicated diabetes in the past year (OR = 1.46; $P = 0.016$).

■ Discussion

This study provides answers to often-posed but seldom-answered questions regarding the differences between RCT and "real-world" psoriasis patients. On the one hand, this study shows that patients who may be ineligible for psoriasis trials differ in important respects (e.g., comorbidities, prior treatments) from their trial-eligible counterparts. On the other hand, regardless of their differences at baseline, adherence, persistence, and switching of biologic medications were largely similar across groups.

The observed higher comorbidity burden, medication burden, and older age in ineligible patients is expected. One surprising finding was the shorter duration of psoriasis among the trial-ineligible patients. Given the slightly older age of trial-ineligible patients, we would expect disease duration to be longer and cannot think of a compelling reason for this difference.

Almost by design, real-world adherence and persistence will be lower than with treatment given under the more tightly controlled conditions of an RCT.[23,24] The key question is whether there is something about the patients who do not qualify for RCTs that would make them have higher or lower adherence/persistence to a medicine. To our knowledge, this has not been studied. These results suggest that treatment utilization may vary slightly between psoriasis patients who are/are not eligible for clinical trials of biologics. Infliximab initiators who were trial-ineligible due to medical reasons demonstrated greater adherence to treatment than their trial-eligible counterparts. No such patterns were found for other biologics, however, which suggests that the difference in the relatively small infliximab subgroup may have been simply due to chance. Adalimumab initiators who would have been ineligible due to recent/ongoing treatment but who would be potentially eligible if they stopped treatment had greater adherence and longer time on treatment than trial-eligible patients. Again, this finding was seen only in the adalimumab subgroup and may therefore have been by chance. However, the adalimumab users comprised the largest biologic treatment group, making the findings more robust than for the other biologics. A limitation of medication usage analyses is the small number of patients available for analyses of infliximab and ustekinumab. It is possible that the trial ineligibility criteria involving recent use of psoriasis treatment selected for patients with greater adherence to treatment in the past, who therefore were more likely to continue demonstrating high adherence upon starting a new psoriasis treatment. Older patients also tended to have greater adherence and persistence; this finding is consistent with prior studies of psoriasis patients' adherence to biologics.[25] The degree of biologic initiation among moderate-to-severe psoriasis patients seen in this study is similar to that reported from a medical record review of moderate-to-severe psoriasis patients treated with systemic therapy in which 28.6% were currently receiving or had previously received treatment with a biologic agent at the time of the study.[26] A survey of actively practicing U.S. general dermatologists treating 10 or more psoriasis patients per month found that 56%-63% received systemic therapy, including biologics.[27] The low proportion of patients considered adherent (i.e., MPR≥80%) in this study was consistent with other studies, which generally show low adherence to psoriasis medications,[28,29] although adherence to biologic therapy appears to be greater compared with topical therapies, oral therapies, and phototherapy.[28]

FIGURE 3 Kaplan-Meier Plots of Persistence to Biologic Therapy Among Trial-Eligible, Medically Ineligible, and Potentially Eligible Initiators
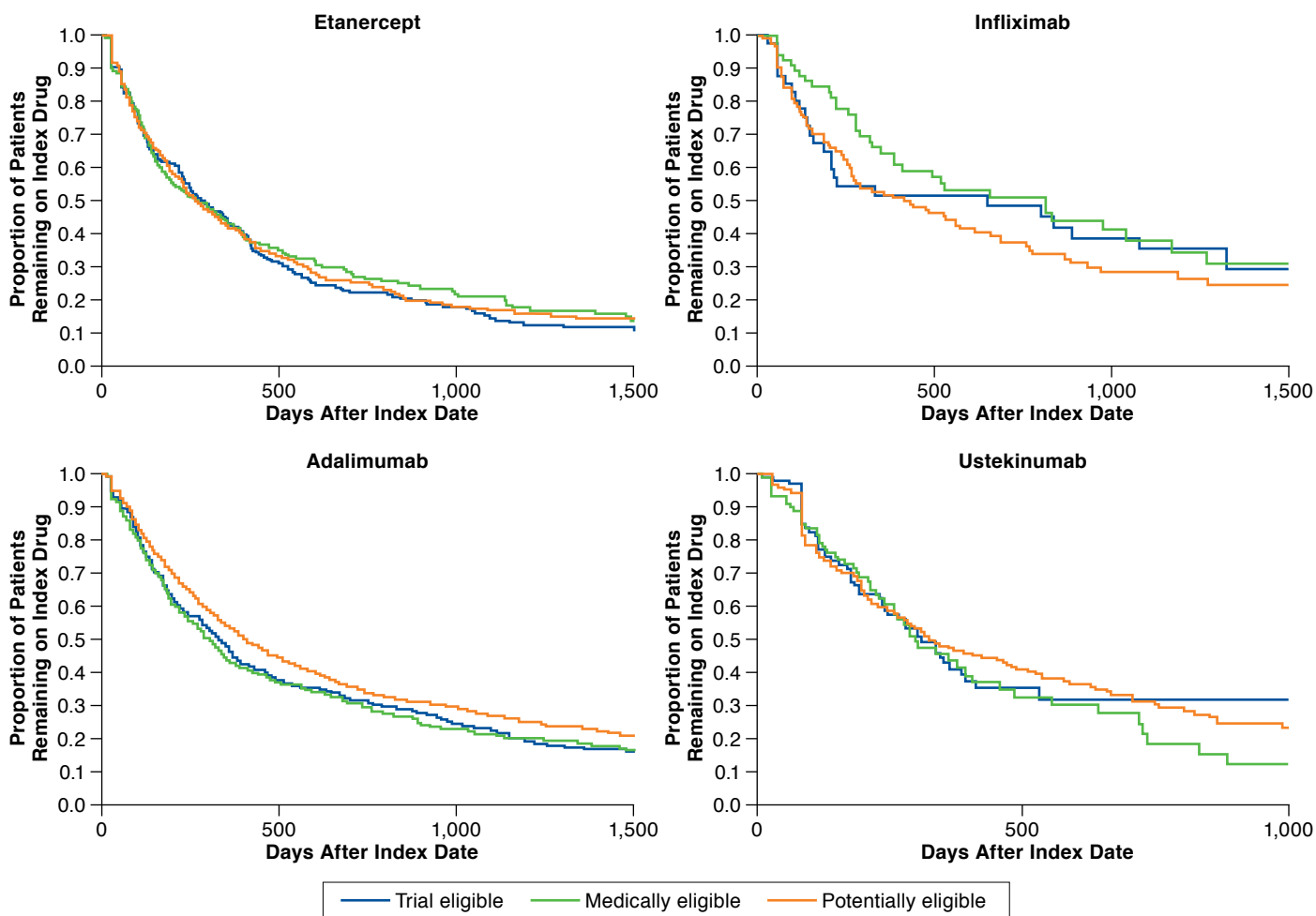
The algorithm used to identify patients with moderate-to-severe psoriasis demonstrated relatively good performance. A visit to a dermatologist in which a diagnosis of psoriasis was recorded, in combination with use of systemic therapy or phototherapy, identified a cohort in which approximately 83% of patients truly had moderate-to-severe psoriasis. The chart review revealed one important limitation that may be specific to the DoD database: patients undergoing phototherapy for conditions other than psoriasis sometimes had psoriasis entered as the diagnosis. Our study proceeded by excluding patients with no psoriasis diagnosis other than those recorded on phototherapy claims; further validation via additional chart reviews would help to determine the extent to which this should be part of the standard algorithm for identifying moderate-to-severe psoriasis.

Limitations

This study has some limitations that need to be considered. This real-world analysis used surrogates for biologic trial eligibility based on information available in medical claims. Some trial ineligibility criteria may have been erroneously reported in the claims data when the entry of a diagnosis code indicated a condition to be ruled out rather than a definite diagnosis. The prevalence of malignant disease, for example, seems high (13.8% of the full cohort). While some of the trial ineligibility criteria cannot be reliably identified in claims data (e.g., laboratory abnormalities), meaning that some patients may have been misclassified as trial-eligible, it is likely that the present analysis has resulted in a larger portion of patients misclassified as trial-ineligible. The proportion of patients deemed medically ineligible for RCT participation was consistent with

a previous study, which found that 29.8% of consecutive systemic- and biologic-treated psoriasis patients from dermatology departments in Spain would be ineligible due to age or existing medical conditions.[30]

Additional limitations of the study include the imperfect classification of psoriasis status and other diagnoses and the potential that patients may have received pharmacy-dispensed drugs without taking the supply as prescribed. In addition, utilization patterns for patients in the DoD's health plan may not be representative of all insured patients in the United States. Sample sizes, while large overall, were small for some subgroups, limiting the power for some comparisons.

■ Conclusions

This study represents a thorough comparison between large populations of patients who may be eligible for biologic trials and those who may be ineligible for the trials but could receive biologics in usual medical care. Many differences existed between these patient groups, most notably a higher prevalence of comorbidities among the trial-ineligible patients, but their treatment utilization patterns were largely similar. Future research should investigate the association between treatment patterns and subsequent health outcomes to determine whether patients ineligible for trials show differences from their trial-eligible counterparts with respect to treatment effectiveness or adverse events.

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