High rates of stopping or switching biological medications in veterans with rheumatoid arthritis

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Abstract

Objectives

To define the characteristics of a population of veterans with rheumatoid arthritis (RA) who have stopped or switched their first biologic agent, and to assess if measures of disease activity are predictors in the decision to alter the regimen.

Methods

A retrospective analysis of the VA electronic medical record system identified RA patient demographic and disease activity parameters from 1999 to 2007. Demographic data included age, race/ethnicity, sex, and tobacco use. Disease-specific data included date of RA onset, past DMARD therapies, prednisone use, as well as the disease activity score (DAS-28) and the health assessment questionnaire (HAQ) at each clinic visit. The use of six biologicals (infliximab, etanercept, adalimumab, abatacept, rituximab, anakinra) was identified in order to compare those who continued with the medication to those discontinuing or switching to another biological. Descriptive and parametric statistics were applied to define differences between the two groups.

Results

Of 454 RA patients identified, 212 have been on a biologic agent at one point in time, and 100 patients (47%) had either stopped or switched their first biologic agent. Among these 100 patients, the most common reasons for stopping or switching a biologic agent were adverse events (in 48%) and inefficacy (43%) Adverse events included malignancies (23% of 48 patients), rash (23%), infections (18.8%), and cardiac complications (18.8%). When comparing the 100 patients versus the 112 that did not stop or switch their first agent, the DAS-28 correlated significantly with a change of regimen with an OR 2.1 ($p<0.001$). The HAQ score had an OR of 2.0 ($p<0.04$).

Conclusion

RA patients who continue taking their initial biologic medication have similar age, RA disease duration, ethnicity, and smoking status to those requiring switching or discontinuation. The DAS28 and HAQ scores significantly correlated with stopping or switching of a first biologic agent. Adverse event rates were high and their distributions differed in this population compared to previous studies of younger Caucasian females.

Key words

Rheumatoid arthritis, anti-TNF-α medication, biologic therapy, registries, adverse events.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that primarily affects synovial tissues (1). It classically causes symmetrical polyarthritis of small and large synovial joints, and presents between the ages of 30 and 50 years of age (2). RA is responsible for 250,000 hospitalisations and 9 million physician visits in the US each year (2). During the last few decades, several new therapies and strategies have emerged to attenuate the joint-destroying inflammation that has been associated with rheumatoid arthritis (1). The use of combination disease modifying anti-rheumatic drugs (DMARD) in RA such as methotrexate and hydroxychloroquine has improved outcomes (1). Although DMARDs play an integral role in the treatment of RA, the increased research into the pathophysiology of this disease has led to the development of biologic agents as another therapeutic strategy. Targeting cytokines such as TNF-α and IL-1, or modulating B cells and T cells, has provided new, effective treatments (1-7).

The tumour necrosis factor alpha inhibitors (TNF-α) are biologic agents that have made an enormous impact on the treatment of RA. TNF-α has been found to be an important cytokine in mediating inflammation in rheumatoid arthritis patients (4). During the time of the current study there were three TNF-α inhibitors commercially available: infliximab, etanercept, and adalimumab (1). Another biologic agent that has been used is the IL-1 inhibitor, anakinra (1, 5). Usage of anakinra has decreased dramatically over the last decade as its efficacy data have only been marginally significant (1, 5).

Other biologics in use include those that target B- and T-cell pathways. Rituximab is a genetically-engineered chimeric monoclonal antibody that recognises CD-20+ B-cells. It depletes subpopulations of peripheral B cells through complement-dependent cytotoxicity, and promotes apoptosis (6). It has also been shown to improve ACR-20, -50, and -70 scores as well as decreasing radiographic progression (6). Abatacept is a soluble, recombinant, fully human fusion protein composed of the extracellular and the Fc domains of human CTLA4 and IgG1, respectively. It has been modified to prevent complement fixation. Abatacept serves to inhibit T cell co-stimulation, thus attenuating T cell-mediated immune responses (7). In clinical trials, abatacept has also been shown to significantly reduce RA disease activity and improve quality of life measures (7).

Though the biologic agents have extensively improved morbidity and mortality outcomes in up to 65% of RA patients (8), each of these agents will leave subpopulations of patients that may discontinue therapy due to various reasons such as adverse events. After stopping therapy, switching to another biologic agent is one option. Several studies that have shown that switching to a second biologic agent after failure of the first biologic agent can recapture a beneficial clinical response or avoid side effects encountered with previous therapy (4, 8-14).

One study from the STURE registry showed that patients who had been on either infliximab or etanercept that switched to the other agent had similar clinical efficacy in terms of DAS 28 scores when the first agent was discontinued due to adverse events or clinical inefficacy (14). Another study of 37 patients who had discontinued infliximab due to adverse events and switched to etanercept did not show any statistical worsening of DAS 44 scores after changing to etanercept at week 24 (11). A large UK cohort of 6739 patients with RA identified 856 patients who switched from their first TNF-α inhibitor. Of the patients that switched, 73% were still taking their second anti-TNF-α therapy at a mean of 6 months. Sixty-five percent of the patients switched due to inefficacy versus 35% due to an adverse event (12). Other trials have also shown that replacing anti TNF-α therapy with a biologic targeting a completely different mechanistic pathway, such as rituximab or abatacept, is also clinically effective. The REFLEX trial showed that utilising rituximab therapy after failing at least one TNF-α inhibitor due to inefficacy resulted in statistically significant ACR-20, -50, and -70 responses (6). Another trial using EULAR criteria also confirmed similar findings (15).

Most of the trials examining discontinuation of anti-TNF-α drugs found that the primary reason for switching or stopping a biologic agent is due to inefficacy rather than adverse events (12, 14). These studies typically use TNF-α inhibitors as their first biologic agent (12, 14). The goal of the current study is to observe the characteristics of patients enrolled in a longitudinal study of RA that have either stopped or switched their first biologic agent. The Dallas population of military veterans with RA tends to be older, male, and have more baseline co-morbidities compared to RA patients outside of the VA system (16). Given the demographics of this RA population, the clinical characteristics of this population at the time of biologic agent switch may be different from a national RA population. This retrospective study identifies these characteristics and compares different disease activity parameters such as DAS-28 and HAQ scores to see if these parameters can correlate with switching or stopping of biologic agents.

Methods

Study sample

All RA patients treated at the VA Medical Center in Dallas met the American College of Rheumatology (ACR) diagnostic criteria for RA (17). This study includes baseline and longitudinal clinical data collected and recorded during the process of routine rheumatologic care. A longitudinal registry of RA patients has received Institutional Review Board (IRB) approval and all study subjects provide informed written consent prior to enrollment.

At enrollment, subjects provided the following data: socio-demographics (self-reported race/ethnicity, sex, date of birth, and educational level), tobacco use, dates of RA diagnosis and symptom onset, and receipt of past disease-modifying anti-rheumatic drugs (DMARDs). The following clinical parameters were recorded at each clinic visit: tender and swollen joint counts (0-28), erythrocyte sedimentation rate (ESR, mm/hr), C-reactive protein levels (CRP), and a ten-item modified Health Assessment Questionnaire (HAQ; range 0-3). A three-variable Disease Activity Score (DAS)-28 is calculated as a composite score of tender and swollen joint counts and ESR (19). For this study, all patients ever receiving a biologic agent for RA were considered for inclusion. The clinical parameters were recorded during the time of subjects' switch from one biologic agent to another, or for the subjects who did not switch their biologic agent, at the most recent visit.

In order to compare the extent to which subjects with varying levels of RA disease activity differed by whether or not they changed biologic agents, each subject's DAS score was categorised into one of four categories: 0 to 2.6 = "Remission" (n=47), 2.61 to 3.2 = "Low Disease Activity" (n=38), 3.21 to 5.1 = "Moderate Disease Activity" (n=77), and over 5.1 = "High Disease Activity" (n=34). These score ranges are based on past findings that such cutoffs are indicative of varying levels of disease activity (13).

Statistical analysis

Continuous parameters were reported as mean ± SD, and discrete parameters were reported as a percent (%). Continuous parameters were compared with one-way ANOVA or the Kruskal-Wallis Test and discrete parameters were compared with the Pearson chi-square test. The association of select baseline variables (DAS, gender, smoking history, erosions, nodules, C-reactive protein levels, prednisone use, methotrexate use, and HAQ) with the incidence of switching from or stopping a biologic agent was analysed using logistic regression analyses. All analyses were performed with SAS 9.1 and SPSS 14.0 for Windows.

Results

A total of 212 RA subjects with mean age of 63 ± 11 years, enrolled in a longitudinal RA registry were included in the present study. The characteristics of the study sample are shown in Table I. Subjects were primarily men (88%), and most were Caucasian (79%). There were no significant differences in age between the subjects who switched their biologic agent and those who did not (mean age 64 versus 62 years, respectively), nor were there significant differences in RA disease duration (12 years versus 10 years, respectively), gender, ethnicity, or smoking history.

Almost half of the study sample (47%) switched or stopped their first biologic agent that was being used. Within this group, 27% stopped using a biologic

Table I. Descriptive statistics of study variables.

Variable	Subjects who did not switch (n=112)	Subjects who switched/stopped (n=100)	*p*-value
Age (years)	61.9 ± 11.3	64.2 ± 10.9	0.15
RA disease duration (years)	10.2 ± 10.9	12.4 ± 10	0.13
Ethnicity, n (%)			
White	85 (75.9%)	82 (82%)	
Black	18 (16.1%)	10 (10%)	
Hispanic	8 (7.1%)	4 (4%)	
Other	1 (0.9%)	2 (2%)	0.37
Smoking			
Ever smoked	86 (76.8%)	84 (84%)	
Never smoked	25 (22.3%)	15 (15%)	0.18
Rheumatoid factor	100 (89.3%)	93 (93%)	0.35
aCCP	82 (73.2%)	79 (79%)	0.33
Morning stiffness	109 (97.3%)	99 (99%)	0.37
Nodules	64 (57.1%)	58 (58%)	0.90
Erosions	109 (97.3%)	99 (99%)	0.37
DMARD use	109 (97.3%)	99 (99%)	0.37
Methotrexate use	109 (97.3%)	99 (99%)	0.37
Prednisone use	65 (58%)	76 (76%)	0.01
Disease Activity Score (DAS)	3.1 ± 1.1	4.3 ± 1.5	<0.001
HAQ	0.9 ± .6	1.3 ± .6	<0.001
C-reactive protein levels	1.0 ± 1.6	1.6 ± 2.2	0.03

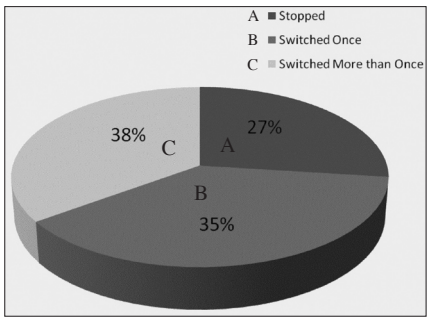

Fig. 1. Proportions of stopping and switching biologic agents.

agent completely, while 38% switched to another biologic agent once and 35% switched more than once (Fig. 1). Table II presents the initial biologic used in this population, as well as the second biologics used in those patients who switched. The most prominent reason to stop or switch biologic agents was adverse events in 48%, followed by inefficacy (43%), social reasons (6%), and clinical remission (3%) (Fig. 2A). The need to switch or stop the biologic for an adverse event occurred regardless of DAS-28 level (44% had DAS ≤3.2), while inefficacy was accompanied by a higher DAS-28 in most cases (DAS ≥3.21 in 84%). Of the study sample with adverse events, 23% stopped biologics due to malignancy. The overall malignancy rate was 5.1% in the combined study and control groups with no malignancies reported in the control group (Fig. 2B). There were 3 lymphomas and 8 solid tumour malignancies observed in the study group. The solid tumours consisted of lung cancer, colon cancer, recurrent basal cell carcinoma,

Table II. Initial and second biologic agents.

Initial agent	n (%)
Etanercept	51 (51%)
Infliximab	31 (31%)
Adalimumab	14 (14%)
Anakinra	4 (4%)
Total patients	100
Second agent	
Adalimumab	28 (38.5%)
Infliximab	20 (27.4%)
Etanercept	13 (17.8%)
Anakinra	7 (9.6%)
Abatacept	4 (5.5%)
Rituximab	1 (1.4%)
Total patients	73

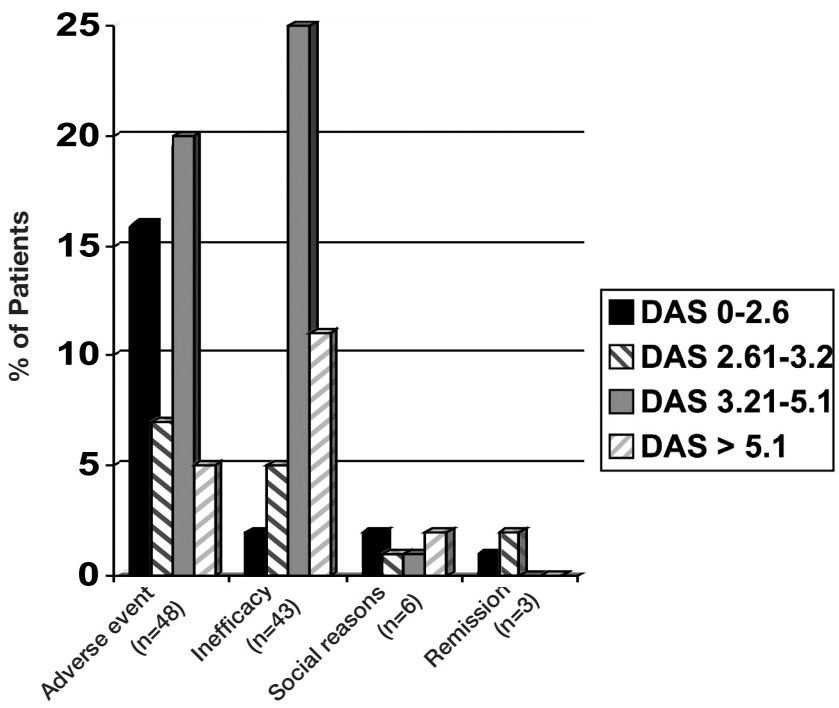

Fig. 2A. Reasons patients switched from or stopped their first biologic agent.

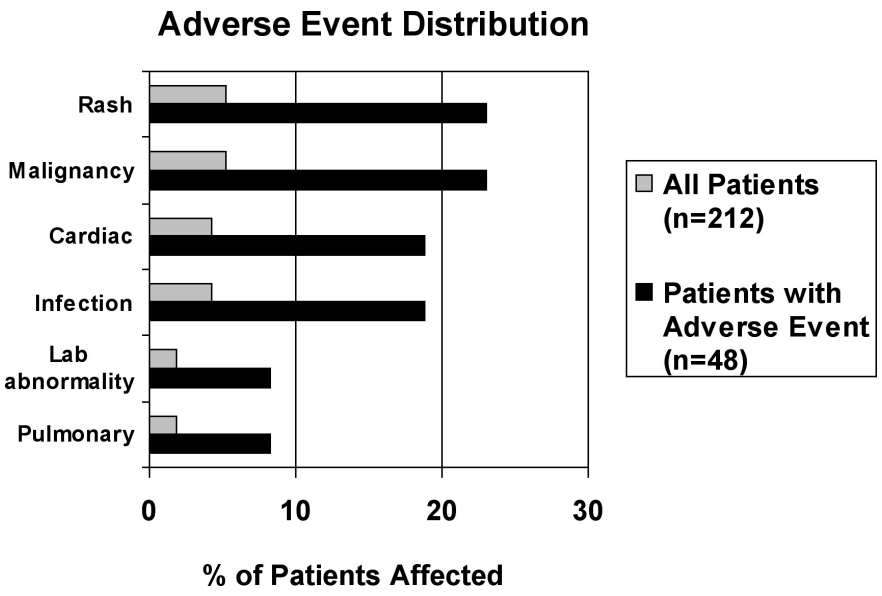

Fig. 2B. Adverse event distribution.

renal cell carcinoma, recurrent melanoma, and head and neck cancer. A cardiac adverse event (in those stopping: CHF in 3, arrhythmia in 1; in those switching: CHF in 3, chest pain in 2) accounted for 18.8% of the study sample with adverse events and for 4.2% of the entire study group of 212 patients. Rash accounted for 23% of the adverse event group and 5.1% of the population. Serious or recurrent infections accounted for 18.8% of the patients with adverse events (stopping biologics: 5 bacterial, 2 atypical mycobacterial, 1 fungal and viral; switching biologics: 1 bacterial pneumonia), and 4.2% of the overall RA population exposed to biologic agents. Patients who developed a malignancy received their biologic medications for a mean of 1028.0 days (SD 720.1 days), compared to those patients who experienced infectious

(365.1 days, SD 329.1), skin (541.0 days, SD 696.6), or cardiac (606.9 days, SD 749.5) side effects. By comparison, patients who continued their TNF-α inhibitors without side effect had received their drug for a mean of 1238 days (SD 676) by the end of the study. The mean age for those developing a malignancy was 74.4 years, while the entire group of those stopping or switching biologics had a mean age of 64.2 years.

Thirteen of the most common co-morbidities were analysed in the studied population (Fig. 3). The three most common were hypertension, hyperlipidemia, and osteopenia/osteoporosis. Four comorbidities were found in a significantly higher percentage of patients who stopped or switched their biologic: hypertension, osteopenia/osteoporosis, diabetes, and anemia. Of note, the prevalence of obesity, hyperlipidemia, ischemic heart disease, and COPD were not statistically different between the studied groups.

Of the 212 subjects, 208 (98%) had a valid DAS score collected at the time of switch or stop for the study sample or at their most recent patient encounter in the control group. Compared to subjects who remained on their initially prescribed biologic agent, significantly more subjects who switched their biologic agent exhibited high disease activity (31% *vs*. 7.5%; $\chi^2(3) = 36.5$, $p<.001$; Fig. 4). There were no significant differences between the two groups in the presence of rheumatoid nodules, rheumatoid factor, DMARD use, erosions or methotrexate use (Table I). However, significantly more subjects who stopped or switched their biologic agent were using prednisone at the time of the switch or stop, or in absence of a switch, at the time of last visit (76% *vs*. 65%; $p<0.01$). Among patients taking prednisone, the average dose of prednisone used during the last 3 months of observation was similar between the two groups: 9.7 mg/day (SD±8.5) for those stopping or switching, and 8.9 mg/day (SD±11.0) for those continuing on biologic. Of the 8 patients in the high disease activity group who did not switch biologic medication, four had had recent infections (URI, sinusitis, or otitis) leading to erratic dosing of the biologic but not long-term treatment failure, and four had been urged to change medication but made their decision only after the study ended. By comparison, patients who stopped or switched biologics in the setting of low disease activity had a variety of reasons for making a change: cancer (4), inefficacy (2), skin rash (2), social (2), infection (1), GI intolerance (1), hemolytic anemia (1), and remission (1).

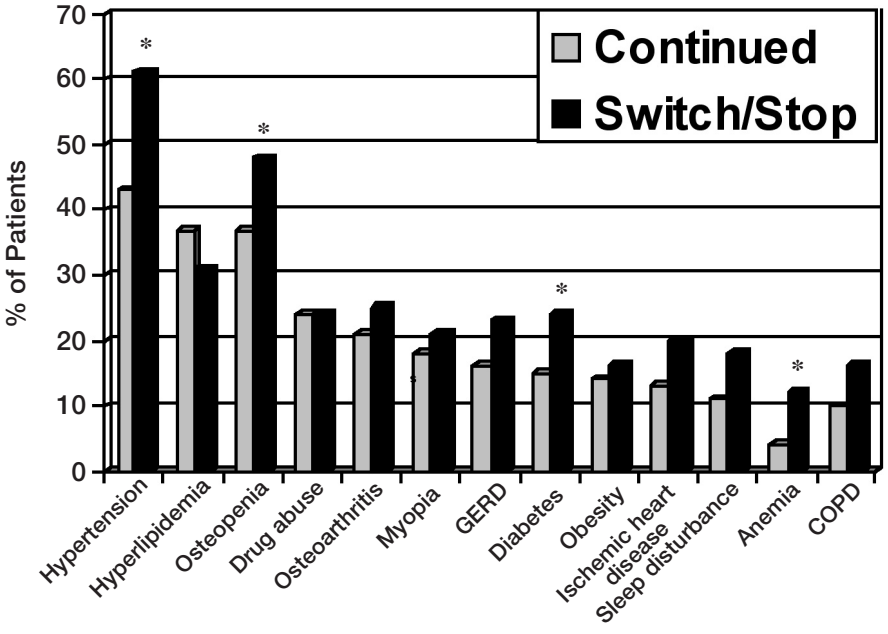

Fig. 3. Comorbidities. *Statistically significant.

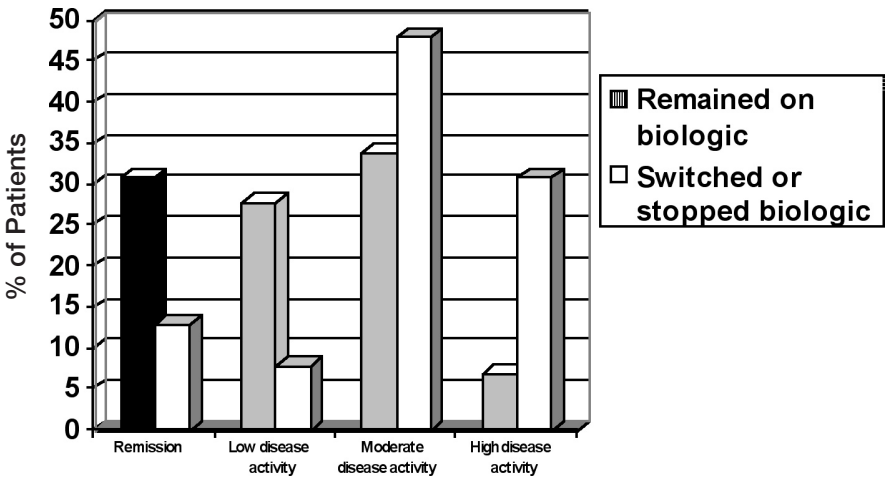

Fig. 4. Biologic agent changes by DAS category.

Subjects who switched agents also had significantly higher DAS, HAQ scores and C-reactive protein levels ($p<0.05$) (Table I). Logistic regression analysis indicated that DAS and HAQ scores were significantly associated with switching, independent of traditional risk factors such as gender, smoking history, disease duration, erosions, nodules, C-reactive protein levels, prednisone use, and methotrexate use. (Table III). For every one point increase in either the DAS or the HAQ score, patients were twice as likely to switch or stop a biologic agent (OR=2.1, $p<0.001$, 95% CI: 1.4 to 2.9; OR=2.0, 95% CI: 1.03–3.88, respectively).

Discussion

The concept of switching or stopping a first biologic agent is not new in the treatment of RA. Up to one third of RA patients have had to switch off their first anti TNF-α agent either due to

Table III. Adjusted odds ratios of predictors of biologic switching or discontinuation.

Predictor	Odds ratio	*p*-value	95% Confidence interval
DAS	2.1	<0.001	1.4–2.9
HAQ	2.0	0.04	1–3.9
Gender	0.8	0.74	0.3–2.7
Smoking history	1.7	0.33	0.6–4.9
Erosions	2.1	0.08	0.1–5
Nodules	0.7	0.40	0.3–1.6
C-reactive protein	1.0	0.91	0.8–1.3
Methotrexate use	1.4	0.38	0.7–3.1
Prednisone use	1.6	0.24	0.7–3.4
Disease duration	1.0	0.08	1–1.1

adverse events or inefficacy (14, 19), and the switch of medication can result in a renewed clinical response and, in most cases, no increased risk of adverse events (20). Using the UK Cohort data, 35% of the 6739 patients who started anti-TNF-α agents discontinued their anti-TNF-α medication (12). Fifteen percent of the patients in the UK Cohort that switched anti-TNF-α agents did so due to adverse events (14). Another registry in Spain, the BIOBADASER, illustrated an adverse event rate of 46% as a reason for anti-TNF-α discontinuation (13).Our study analyses a unique RA population from an RA registry of American veterans who are predominantly male, older, and with significant co-morbidity profiles. Forty-seven percent of this veteran population who had been on a biologic agent had discontinued their biologic agent.

Age by itself has been studied as a risk factor in the use of etanercept. When reviewing the experience of clinical trial participants, Bathon *et al*. found that RA patients aged ≥65 years taking etanercept had similar adverse event rates to those on placebo or methotrexate (21). Similarly, a review of etanercept safety in RA, ankylosing spondylitis, and psoriatic arthritis clinical trials revealed no increase in adverse events in those age >65, and death rates consistent with that expected for the age. (22). However, such clinical trial enrollees are carefully selected to exclude potentially serious comorbidities and are therefore not strictly comparable to the veteran population of the current study, who were predominantly male and had only two criteria for study entry: RA diagnosis and use of a biologic medication.

In the current study, forty-eight percent of the patients that discontinued their first biologic agent did so due to adverse events. Of the study sample that experienced adverse events while on biologic agents, malignancy and rash followed by cardiac events, infections, pulmonary disease, and lab manifestations, respectively, were the most common adverse event reasons to switch or stop a biologic agent. Though this is a small population of 100 patients, the distribution of adverse events differs from studies outside of our veteran population. Previous studies have shown infection, drug reactions, and rash to be the most common adverse events. (5, 15, 22-26). Nevertheless, a previous study demonstrated that the rate of serious infections requiring hospitalisation was not increased in patients ≥65 years old starting anti-TNF-α therapy compared to those starting methotrexate or other DMARDs (27).

Malignancy and rash were the two most common adverse event reasons to switch or stop an anti-TNF-α agent. Malignancy accounted for 23% of the adverse event group of the study sample and 5.1% of the total number of patients exposed to biologic agents in this study. These results are markedly higher than those of other studies (28, 29). A study analysed data from 9 RA clinical trials and calculated a malignancy rate of 0.8% for patients exposed to anti-TNF-α agents (28). This trial identified 24 malignancies out of 3493 patients exposed to at least one dose of anti-TNF-α agent. (28). In the UK National Cohort Study, the rate of malignancy for patients on TNF-α inhibitors with adverse events that led to discontinuation was only 3%, versus 23% in our group (12). In our group, we report 8 solid tumour malignancies and 3 lymphomas among the 212 who had received a biologic agent at the VA, and all malignancies occurred in patients who then stopped the biologic therapy. The increased rate may reflect the higher age and increased risk factors such as tobacco abuse or other environmental exposures. The length of exposure to biologic medication did not appear as a risk factor, since patients developing a malignancy while on biologic medication had been on the treatment for a mean of 1028 days, while the group of patients who were able to continue their TNF-α inhibitors without side effects had taken the medication a mean of 1238 days. The current study was not designed to evaluate for causality for such adverse events. Roughly 80.1% of the population exposed to biologic agents had a history of tobacco abuse. Of the study sample that switched biologic agents, 84.8% of the 100 patients had a history of tobacco abuse. Previous studies have shown that tobacco abuse worsens RA activity (30), which may indirectly contribute to either a switch or stop of a biologic agent. Our statistical analysis, however, did not reveal a significant difference between the two groups regarding tobacco abuse.

The increased tobacco abuse combined with baseline cardiovascular morbidity may also explain the relatively high cardiovascular event rate among biologic agent users. Cardiac events accounted for 18.8% of the adverse event group of the study sample and 4.2% of the total group of patients. The South Sweden study group looked at anti-TNF-α agents and first cardiac event. 531 out of 983 RA patients had received anti-TNF-α agents infliximab or etanercept. The study found 13 cardiac events in the anti-TNF-α treated group out of 656 patient years, which is a lower rate than seen in our population (29). Heart failure, chest pain, and ischemic heart disease only accounted for 3% combined adverse event rate in patients who switched off their first TNF-α agent from the UK registry study (12). A study of Medicare beneficiaries concluded that elderly RA

patients taking TNF-α inhibitors have a hazard ratio of 1.7 for hospitalisation for heart failure, and for those with a prior episode of heart failure, a hazard ratio of 4.19 for death (31). It is well-established that the VA population has elevated cardiovascular morbidity rates (32). Another trial analyzing 292 veteran males with RA also showed that this group of patients is at increased risk for a major cardiac adverse event (16). Nevertheless, cardiovascular disease may be under-recognised in rheumatoid arthritis populations (and therefore not recorded as a co-morbidity), as shown by elevated numbers of silent MIs and sudden death (33). In our examination of co-morbidities in the current study, diagnosed ischemic heart disease showed only a trend of higher incidence in patients stopping or switching their biologics, while hypertension and diabetes, two common cardiovascular risk factors, were statistically more common in those stopping or switching biologics. In addition, previous trials of TNF-α inhibitor initiation typically had a younger age population and fewer co-morbidities (5, 15, 23-25, 34). The average ages in our study and control group populations were 61 and 64 years, respectively. Increased age has been a well-documented risk factor for both cardiovascular events and malignancy.

Another interesting finding was that 35% of the 100 patients that stopped or switched their first biologic agent have switched multiple times. This implies that multiple switching may be necessary to accomplish optimal control in this population. The South Sweden study looked at ACR 20 responses in patients on their third anti-TNF-α agent and compared the group to first time switchers. 337 first time switchers and 36 second time switchers were included in this study. ACR-20 on the new agent was 51% in the first time switching group versus 35% in the second time switching group (19). The results also imply that different regimens targeting different immunologic pathways may be needed to optimise RA control.

Importantly, we demonstrate that the DAS 28 and HAQ scores are significantly associated with switching or stopping biologic medication (Table III, Fig. 4). The findings that DAS28 significantly correlates with the switch or stop of a biologic agent enhances previous reports of the usefulness of the DAS 28 score. One study assessed 511 patients suffering from RA who were treated with infliximab at 3mg/kg every 8 weeks. At week 22, 474 patients were still in follow up and 102 patients were not optimally responding and received a dose increase. This study confirmed that rising DAS28 scores correlated with a physician's decision to increase infliximab dosage (35). Even individual components of the DAS28 have shown similar correlation as the full DAS28 in this setting (35), which was relevant to the clinicians' situation in our study, where tender and swollen joint counts were available to shape decisions on ongoing therapy, while the third component of the DAS28, the ESR, was at times not back from the lab until after completion of the clinical visit. It is noteworthy, however, that the DAS28 may not necessarily capture all disease activity. In a study of 161 patients with RA, 57 patients met the defined clinical remission criteria of DAS28<2.68. Four out of 57 patients, or 7%, still had both tender and swollen joints (36). On the other hand, our study illustrated that increased DAS28 scores significantly correlate with a stop or switch of a biologic agent compared to those that did not stop or switch with an OR of 2.1 and a $p<0.001$.

The HAQ score also correlated with biologic stopping or switching, but to a lesser extent than the DAS28 score. The OR was 2.0 with a $p<0.04$ (Table III). A previous study has shown that the HAQ reflects disease activity (37). The current study finds that the HAQ is also a useful tool and correlates significantly with biologic agent change.

Surprisingly, erosions did not have a statistically significant correlation with stopping or switching a TNF-α agent (Table III). Erosions are known to correlate with disease activity (38), and several studies have shown that biologic agents retard erosive damage to joints (5, 23-26, 34). Therefore, the presence of new or worsening erosions would have been expected to influence a physician's decision to continue with current biologic therapy. A larger study sample of RA patients with erosions may be needed to re-evaluate this parameter.

Our study also illustrates that CRP scores were higher in the group that switched biologic agents than the group who did not switch. This finding is consistent with the use of CRP as a non-specific inflammatory marker. We also observe that the group that switched was more likely to be on prednisone than the group that did not switch biologic agents, although both groups used similar average doses. This again may reflect increased disease activity and lack of efficacy of the biologic agent in the group that switched.

Our original statistical analysis included categories of age, minority status, RF status and CCP status. We removed these variables because they are not known to be influential in a physician's decision to stop or switch a biologic agent. Under the initial regression, RF, anti-CCP, age, and minority status did not statistically predict the stop or switch of a TNF-α agent as expected. Categories added include HAQ score and the concomitant use of steroids. It was hypothesised that the requirement of concomitant medication such as prednisone may indicate that a current regimen is suboptimal.

The main limitation of this study is the limited sample size and the model as a retrospective observational study. In addition, there were 18 patients that were excluded from the study due to inaccurate records. The data reflect the time period between 1999 and December 2007. As more biologic agents have become commercially available, certain earlier biologic agents such as infliximab and etanercept may not necessarily be the initial agent of choice. This study indicated that etanercept followed by infliximab were the two most common initial agents of choice that were used to treat rheumatoid arthritis. The increased availability of other biologic agents may influence the rate of switching in the future as further research goes into optimal sequencing of biologic regimens. For example, infusions have generally had higher adverse event rates than injections, which may

influence the use of injections as an initial agent (39). Finally, our registry of veterans with RA limits the population to a predominantly Caucasian, elderly, and male population. Thus, the results of this study may not be directly comparable to previous clinical trials focusing on female RA patients in their fifties. However, it becomes a strength of this study that it establishes the Veterans Affairs population with RA as a unique, real-world population of RA patients on biologic agents who have a response rate and side effect incidence different from previously-studied populations.

Conclusion

This study demonstrates elevated rates of stopping or switching biologic medication in a unique veteran population whose characteristics are notable for older age, male gender, high rates of smoking, and multiple co-morbidities. Adverse events including malignancy and cardiovascular events were present at high rates while patients took biologic agents, and even those who could continue biologics by changing to a different medication showed a high rate of switching multiple times. In addition, the DAS28 and HAQ scores of disease activity correlated in a statistically significant analysis with the switch or stop of a biologic agent. The findings in this study characterise older male veterans with multiple co-morbidities as particularly susceptible to side effects requiring discontinuation of biologic therapies.

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