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Patient-Reported Outcomes Following Biologic Therapy in a Sample of Adults with Rheumatoid Arthritis Recruited from Community-Based Rheumatologists

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Abstract

OBJECTIVE—Examine self-reported symptoms and functioning in a community-based sample of persons with RA who and did not initiate treatment with biologics.

METHOD—Data were from annual telephone interviews (1998–2003) with a longitudinal observational cohort identified through community rheumatologists. Self-reported function and symptoms of subjects who initiated biologic therapy (etanercept or infliximab) and reported consistent use at 2 annual interviews (n=64; “continuous use”, CON) were compared to those with no biologic use (n=183) and those who initiated biologic therapy but discontinued use (n=42, DISCON), at one year prior to initiation of therapy (baseline; 1998 for comparison group), and years 1 and 2 of therapy (1999 and 2000 for comparison group).

RESULTS—At baseline, subjects taking biologics reported significantly worse function and symptoms on all measures except fatigue and pain severity. After two years, significant differences in HAQ remained, but there were no other significant differences between biologic non-users and CON. DISCON exhibited significantly greater pain severity and more painful joints than non-users. Improvements from baseline in number of painful joints (CON: 33.4% vs. non-users: 16.2%, p=.004), number of swollen joints (38.4% vs. 18.7%, p=.003), and morning stiffness (27.3% vs. 10.4%, p=.001) were more frequent in CON than non-users. Differences between non-users and DISCON were noted only for number of swollen joints (36.4% vs. 18.7%, p=.02).

CONCLUSIONS—Results suggest that biologic treatment was initiated based on severe disease. Over an average of 17 months of treatment, differences in some, but not all, symptoms between CON and non-users narrowed to statistical non-significance.

Clinical trials of biologic agents have established the efficacy of these agents in improving outcomes among individuals with moderate to severe rheumatoid arthritis (1–3). Results of these trials are usually based on ACR 20/50/70 responder criteria or EULAR improvement criteria, which include some patient-reported outcomes, but patient-reported outcomes have not traditionally been the primary focus of clinical trials. More recently, some studies have begun to focus on patient-reported outcomes such as joint pain, pain severity, fatigue, and function (4–6).

A limited number of these trials have evaluated results beyond one year. For example, of the trials evaluated by Chen and colleagues for a systematic review of the effectiveness of various biologic agents, only 2 of 11 trials of etanercept extended beyond 12 months, and the longest noted trials of infliximab were 54 weeks (for 4 of 9 trials)(1). Similarly, Gartlehner noted in another systematic review of 26 trials of biologic agents that the longest trial was 52 weeks (7).

In addition, patients enrolled in clinical trials are selected based on very strict inclusion and exclusion criteria and treatment is defined by the clinical trial protocol. Patients are assigned to treatments randomly to assess the efficacy of the treatment being studied accurately and to minimize differences between treatment groups. However, in community practice, treatment assignment is not random and care is not as strictly controlled, so effectiveness may differ from the efficacy seen in clinical trials.

In 1998, two biologic agents, etanercept and infliximab were approved for the first time for the treatment of individuals with moderate to severe RA. Given the high cost of these agents, it is important to assess how treatment is being allocated and whether individuals on treatment long-term are receiving meaningful benefits from treatment. Some community-based studies suggest that patients who receive biologic agents have worse function and pain than those who do not (6).

The purpose of this analysis was to examine self-reported symptoms and functioning of persons with RA treated by community rheumatologists who initiated biologic agents, and changes in symptoms and function after up to two years of use, compared to a group of individuals from the same cohort who did not use biologic agents.

Methods

Overview

Data were drawn from a cohort of individuals with RA who are interviewed by telephone annually. Disease-related characteristics of individuals who reported initiation of biologic therapy (etanercept or infliximab) at one interview and reported consistent use at the following interview (n = 64) were compared to those with no use of biologic agents (n = 183) and those who initiated biologic therapy but discontinued use (n = 42). For the treatment groups, the year prior to initiation of therapy was considered the baseline year, the first year biologic treatment was reported was year 1, and the subsequent follow-up year was year 2. For the comparison group, 1998 was used as the baseline year, 1999 as year 1, and 2000 as year 2. Comparisons of symptoms and functioning were made between the groups at each time point. Improvement scores, defined a change from baseline by at least 0.5 standard deviation, were also calculated, and analyses compared the frequency of improvement among the three groups.

Subjects

The sample for the present study was drawn from five waves of the UCSF Rheumatoid Arthritis (RA) Panel Study, covering the years 1998 through 2003. The UCSF RA Panel was constructed in 1982 from a random sample of rheumatologists practicing in Northern California. Participants were recruited from lists maintained by participating rheumatologists of all persons with RA presenting to their offices over a one-month period and expressing an interest in participating in the study. The original RA Panel consisted of 822 patients who were enrolled between June 1982 and July 1983. There were subsequently four additional enrollment periods in 1989–90, 1995, 1999, and 2003, during which 203, 131, 122, and 169 individuals were enrolled, respectively. Retention from year to year has averaged 93%; the 7% attrition includes deaths. The principal data source for the RA Panel is an annual telephone interview that includes questions on demographics, medications, RA symptoms, comorbidities, and functioning. The study was approved by the UCSF Committee on Human Research.

Variables

Primary independent variable: Use of biologic agents—Medication use is regularly assessed as part of the RA Panel telephone interview. Participants are asked if they have used any of a list of medications during the preceding year. For each of the study years, they were asked if they had taken Enbrel (or etanercept) or Remicade (or infliximab) for at least one month in the past year. Reported use of either etanercept or infliximab constituted use of biologic agents. Use of biologic agents was determined for each year.

Dependent variables: Self-reported symptoms and functioning—Panel members are regularly queried about functioning and symptoms as part of the annual telephone interview. Functioning was assessed using the Health Assessment Questionnaire (HAQ) (8). The HAQ was developed specifically to assess functioning among individuals with arthritis. HAQ scores range from 0 to 3, with higher scores representing more severe functional problems.

The following symptom measures were also assessed:

- Pain severity. Panel members were asked to rate the severity of their pain on a scale of 0 (no pain) to 100 (very severe pain) (8).
- Number of painful joints/joint groups, from a list of 17 (9).
- Number of swollen joints/joint groups, from a list of 14 (9).
- Duration of morning stiffness, dichotomized to less than one hour versus one hour or longer.
- Severity of fatigue, rated as no fatigue, very mild, mild, moderate, severe, or very severe fatigue. Based on the distribution of responses, fatigue ratings were dichotomized to severe or very severe fatigue versus all other responses.

Covariates—All multivariate analyses controlled for age, sex, years of education, baseline or 1998 number of comorbid conditions from a list of seven conditions (hypertension, heart disease, stroke or neurological condition, diabetes, lung disease, and kidney disease), and duration of RA.

Analysis

Subjects who initiated biologic therapy (etanercept or infliximab) were compared to those with no use of biologic agents. Initiation of therapy was defined as a report of using one of the biologic agents, with no previous use of biologic therapy. Subjects could report initiation of therapy in any of four years (1999, 2000, 2001, or 2002). The year prior to initiation of therapy was defined as the baseline year. Data from three years were examined: baseline and years one and two after initiation of therapy. Individuals who reported initiation of biologic therapy in year 1 and reported continuous use at the year 2 interview were included in the "continuous use" group (n = 64). Individuals who reported initiation of biologic therapy in year 1 but did not report continuous use at the year 2 interview were included in the "discontinued" group (n = 42). The comparison group consisted of individuals who reported no use of biologic agents during any of the analysis years (1998 through 2003; n = 183). For the comparison group, 1998 was used as the baseline year, 1999 as year 1, and 2000 as year 2.

For these analyses, only individuals who were interviewed in 1998 (baseline year for analysis) and remained in the Panel for at least two additional years were included. Individuals who initiated biologic agents but were lost to follow-up before their year 2 interview were excluded (n = 4).

At each time point (baseline, year 1, and year 2), self-reported symptoms and functioning were compared among the three treatment groups (no use, discontinued, and continuous use). Bivariate analyses (i.e., analyses of variance [ANOVAs] and chi-square analyses) were first conducted, followed by multiple linear and logistic regression analyses that controlled for age, sex, education, number of comorbid conditions, and duration of RA.

For a secondary set of analyses, improvement scores were computed. Improvement was defined for HAQ, pain rating, and numbers of painful and swollen joints as a change from baseline by one half standard deviation or more, a proxy for clinically meaningful improvement (10). For the two binary symptom measures, morning stiffness and fatigue, improvement was defined as moving from the more severe group (e.g., severe or very severe fatigue; morning stiffness of one hour or longer) to the less severe group (e.g., no fatigue or mild or moderate fatigue; morning stiffness of less than one hour's duration). Chi-square analyses were conducted to determine whether there were differences in the frequency of improvement among the treatment groups. Multiple logistic regression analyses were then performed to determine if differences among the groups existed after controlling for age, sex, education, number of comorbid conditions, and RA duration. Some improvement might be expected even in individuals with no changes in treatment over the study period as a result of normal fluctuations in disease or gradual responses to therapy. Thus, the frequency of improvement in the no-biologic group is viewed in these analyses as a "background" rate of improvement.

Results

Overall, 84% of the subjects were female, mean age was 61 years, and mean duration of RA was 21 years (Table 1). Just under one half (42.9%) of the subjects had at least one comorbid condition.

Individuals who received biologic therapies were younger than those who did not (58.7 and 59.1 years compared to 62.5 years, $p = 0.05$), but there were no significant differences among the groups in sex, education, number of comorbid conditions, or disease duration.

Use of etanercept was more common than use of infliximab. Overall, 56 individuals reported use of etanercept only, 34 reported use of infliximab only, and 16 reported use of both biologics over the study period. Among continuous users, 61% used etanercept only, 31% used infliximab only, and 8% used both biologics. In contrast, among discontinuers, 40% used etanercept only, 33% used infliximab only, and 26% used both.

Baseline

In bivariate analyses, at baseline, function was significantly worse for both biologic groups (HAQ 1.21 for both biologic groups vs. 0.90 for non-users, $p=0.001$; Table 2). Other symptom measures (number of painful joints, number of swollen joints, and duration of morning stiffness) were also significantly worse in the biologic groups, with the exception of fatigue, for which no differences were noted, and severity of pain rating, for which the difference was marginal. Adjustment for age, sex, education, number of comorbidities, and duration of RA did not substantively change the results from the baseline comparisons.

Follow-up

At the year 1 assessment, there was only a slight difference in the mean length of time on biologics for the discontinued and continuous use groups (4.6 [SD 3.3] months for the discontinued group and 6.1 [SD 3.5] months for the continuous use group). The biologic groups still reported worse symptoms than the non-users, with significant differences between the no biologic group and the two biologic groups in HAQ, number of painful

joints and number of swollen joints, and again, a marginal but not statistically significant difference in pain severity. However, there was no longer a statistically significant difference between the treatment groups in duration of morning stiffness.

At the year 2 assessment, the mean total length of time on biologics was 8.3 (SD 5.6) months for the discontinued group and 17.0 (SD 4.7) months for the continuous use group. Bivariate analyses revealed that significant differences remained between both biologic groups and the no biologic group in HAQ. There were no significant differences between the continuous use group and the no biologic group in any of the symptom measuers. The discontinued group, however, exhibited significantly greater pain severity and more painful joints than the no-biologic group. Adjustment for age, sex, education, comorbidities, and duration of RA yielded slightly different results in that the number of swollen joints was also significantly greater in the discontinued group than in the no-biologic group.

Improvement scores

At year 1, after adjusting for covariates, individuals in the continuous use biologic group were significantly more likely than those in the no-biologic group to exhibit improvement from baseline in pain severity rating (35.3% improved in biologic group vs. 21.5% in no-biologic group, p=.03), number of swollen joints (43.5 vs. 21.1, p=.001), and duration of morning stiffness (25.7% vs. 9.3%, p=.002) (Table 3). The discontinued group, which had a similar amount of treatment time at year 1, also exhibited a significantly greater proportion of individuals who improved in HAQ (29.1% vs. 15.4%, p=.04), number of swollen joints (47.3%, p = .001) and duration of morning stiffness (22.0%, p=.04), compared to the no biologic group. The proportions of individuals who had improvements in number of painful joints and fatigue rating did not differ significantly between the groups.

At year 2, after adjustment for covariates, the continuous use group was more likely than the non-biologic group to exhibit improvements from baseline in number of painful joints (33.4% vs. 16.2%, p=.004), number of swollen joints (38.4% vs. 18.7%, p=.003), and duration of morning stiffness (27.3% vs. 10.4%, p=.001). In comparison, a significant difference from the no-biologic group was noted for the discontinued group only for number of swollen joints (38.4% vs. 18.7%, p=.02).

Discussion

Results suggest that among patients of community-based rheumatologists, treatment with biologic agents was initiated based on severe disease. Individuals with RA who were treated with biologic agents had significantly worse functioning and more severe symptoms prior to initiation of treatment. Other community-based studies have also noted this. For example, Wolfe (6) noted that patients who received treatment with biologic agents were younger and had worse baseline HAQ scores and pain.

We found that by year 2, differences between the continuous users and non-users in pain severity, number of painful joints, and number of swollen joints had narrowed to statistical non-significance. For this group of individuals who began the study period with significantly greater symptoms levels than the non-users, reaching a non-significant difference in symptoms may represent an important change, in spite of the fact that function remained significantly worse in the biologic group.

With regard to HAQ score over time, it was found that HAQ score for the non-biologic group was fairly stable, whereas for the biologic group the score decreased slightly (year 1) and then returned to baseline levels (year 2). The different patterns are worth noting for two reasons. First, for the non-biologic group, increase of the HAQ score on average was smaller

than the previously reported 0.02–0.03/year by Welsing et al (11). Second, for the biologic group, the change of HAQ score (decreased at year 1 and then regressed to baseline level at year 2) demonstrated the effect of biologic treatment on function despite the fact that in late RA (average disease duration of 20 years in this study), functional capacity is most associated with joint damage (11). The results are comparable to early findings that patients with established RA exhibit less improvement in HAQ score after initiation of biologic therapy (12).

The secondary analyses focusing on improvement showed that after initial treatment, individuals in the biologic treatment groups were more likely to demonstrate meaningful improvement, defined as a decrease in symptom severity rating of one-half standard deviation or more. It may not be surprising that individuals who received new treatments (the biologic groups) experienced more improvements than individuals who did not (non-user group). However, we assumed that even in the non-user group, some percentage of individuals would experience improvement. We compared the biologic groups' frequency of improvement to the non-user group's, considering the non-user group's frequency as a "background" rate of improvement. At the year 1 assessment, when the time on biologics was similar for the discontinued and continuous use groups, greater proportions of both biologic groups exhibited improvement from baseline in number of swollen joints and duration of morning stiffness. By the year 2 assessment, however, when those in the discontinued group had stopped taking the biologics, a significantly greater proportion of the continuous use group exhibited meaningful improvements in number of painful joints, number of swollen joints, and duration of morning stiffness, compared to the no-biologic group. In contrast, the discontinued group exhibited a greater improvement only in the number of swollen joints.

We found no differences in the prevalence of severe fatigue between the groups at any point, consistent with the findings reported by Wolfe (13). In clinical trial patients, Moreland noted improvements in fatigue among those treated with biologic agents (4). Farahani also noted differences in fatigue between patients treated and not treated with biologic agents after six months of treatment; at 12 months, however, those differences had disappeared (5). Differences in findings may be attributed to differences in the fatigue measure (single-item vs. four-item vitality battery from the SF-36 (14)) or the patient populations (community-based sample vs. clinical trials cohorts; differences in disease duration); for example, Moreland found fewer individuals with established RA achieved clinically meaningful improvement than did individuals with early RA (4).

This study has important strengths and limitations to consider. The two-year follow-up period of the current study is longer than most clinical trials examining the outcomes of biologic therapies. Data were obtained from a cohort of individuals with RA recruited from community-based rheumatologists rather than a clinical trial population, which should enhance the heterogeneity of the study sample and broaden the generalizability of the results. However, the average duration of RA was 20 years, which may limit the ability to generalize results to individuals with early onset RA. All subjects were recruited from rheumatology practices and thus may be different from individuals who do not obtain care from rheumatologists. This limitation may be outweighed by the diagnostic certainty resulting from the recruitment source.

There is a potential for bias in both reports of treatments and symptoms; however, the symptom report measures used have been well validated, and in the past, reports of utilization have closely corresponded with utilization noted in medical records. Although we used a fairly standard method to estimate "clinically meaningful" improvement (10), our definition may have lacked precision. We do not have information regarding the reasons that

patients did not start a biologic agent. It is possible that physicians may have wished to prescribe such agents for some individuals, but access or payment issues precluded use. Finally, we do not have information as to why individuals in the discontinued group stopped treatment although the reason for discontinuation (e.g., access vs. side effects) could have resulted in variations in outcomes.

Conclusion

In a cohort of individuals recruited through community-based rheumatologists, persons with RA who were selected for treatment with biologic agents had significantly worse functioning and more severe symptoms, suggesting that biologics were being reserved for individuals with more severe disease. Over two observation periods (an average length of treatment of 17 months) following initiation of biologic therapy, some, but not all of the differences in symptoms between individuals treated continuously with biologic agents and non-users narrowed and no longer reached statistical significance, representing what is probably an important change in symptoms. In contrast, individuals who initiated treatment with biologic agents but did not continue use maintained high levels of symptoms at the second follow-up period. In addition, individuals who continued use of biologic agent over the two-year study period were significantly more likely to demonstrate meaningful improvement in most symptom measures than non-users of biologic agents, whereas, individuals who initiated biologic treatment but did not continue use did not achieve the same rates of improvement.

This study shows that, while individuals selected for treatment with biologic agents exhibited more severe disease characteristics prior to initiation of therapy, those who received extended treatment with such therapy experienced a reduction in symptoms, leading to a narrowing of differences compared to individuals who did not receive biologic treatment. Individuals who received biologic agents for a shorter period of time did not achieve the same results, and their symptoms remained significantly more severe; however, the reasons for treatment discontinuation are not known.

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Table 1

Characteristics of study sample

	Total (n = 289)	No biologic (n = 183)	Biologic, discontinued (n = 42)	Biologic, completed (n = 64)	p*
Female, % (n)	84.0 (241)	83.6 (153)	82.5 (33)	85.9 (55)	.88
Age, years; mean (SD)	61.2 (12.1)	62.5 (11.1)	58.7 (13.6) *a*	59.1 (13.2) *a*	.052
Education, years; mean (SD)	13.7 (2.6)	13.7 (2.6)	13.8 (3.0)	13.8 (2.2)	.95
Number of comorbidities; % (n)					.97
0	57.1 (165)	56.3 (103)	59.5 (25)	57.8 (37)	
1	30.5 (88)	30.6 (56)	26.2 (11)	32.8 (21)	
2 or more	12.5 (36)	13.1 (24)	14.3 (6)	9.4 (6)	
Disease duration, years; mean (SD)	20.7 (9.4)	20.9 (9.4)	20.7 (8.9)	20.3 (10.0)	.93

*p-value from chi-square analysis or t-tests comparing no biologic vs biologic groups.

*a*Significantly different from no biologic group (from post hoc means test)

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Table 2

Year-to-Year Differences between Biologic and No Biologic Groups

		Bivariate			Adjusted*		
	Biologic	**Baseline**	**Year 1**	**Year 2**	**Baseline**	**Year 1**	**Year 2**
HAQ	No	0.90 (0.68)§	0.92 (0.68)	0.92 (0.67)	0.89	0.90	0.89
	Continuous use	1.21 (0.72)a	1.16 (0.72)a	1.20 (0.73)a	1.22 (.0004)	1.18 (.002)	1.22 (.0004)
	Discontinued	1.21 (0.60)a	1.15 (0.62)	1.18 (0.60)	1.22 (.0024)	1.15 (.02)	1.20 (.005)
	p†	0.001	.02	.005			
Severity of pain rating	No	25.1 (30.4)§	22.3 (27.0)	25.2 (27.1)	24.6	21.9	25.1
	Continuous use	33.1 (26.3)	28.0 (24.3)	30.5 (26.7)	32.9 (.05)	28.3 (.10)	30.8 (.14)
	Discontinued	34.4 (25.8)	31.5 (28.7)	36.5 (28.1)a	33.0 (.09)	31.2 (.05)	37.0 (.01)
	p†	0.06	.07	.04			
Number of painful joints/ joint groups	No	3.4 (4.4)§	3.2 (4.1)	3.9 (4.3)	3.4	3.2	3.9
	Continuous use	5.2 (4.2)a	5.2 (4.3)a	4.8 (4.3)	5.2 (.006)	5.1 (.002)	4.8 (.18)
	Discontinued	6.3 (5.1)a	5.5 (5.3)a	5.9 (4.6)a	6.1 (.0005)	5.4 (.003)	5.9 (.008)
	p†	0.0001	.0005	.03			
Number of swollen joints/joint groups	No	2.2 (3.1)§	1.8 (2.8)	2.3 (3.1)	2.2	1.8	2.3
	Continuous use	3.3 (3.2) a	2.5 (2.6)	2.8 (3.2)	3.2 (.02)	2.4 (.11)	2.8 (.23)
	Discontinued	4.5 (3.7) a	3.3 (3.4)a	3.5 (3.4)	4.4 (<.0001)	3.2 (.004)	3.5 (.02)
	p†	0.0001	.006	.06			
Duration of morning stiffness > 1 hour	No	23.0 (42)**	19.7 (36)	18.0 (33)	22.9	19.3	17.9
	Continuous use	34.4 (22)	15.6 (10)	15.6 (10)	34.2 (.07)	16.1 (.53)	15.9 (.70)
	Discontinued	42.9 (18)	23.8 (10)	30.0 (12)	40.6(.02)	20.8 (.81)	30.4 (.08)
	p¶	0.02	0.57	0.16			
Severe/very severe fatigue	No	21.3 (39)**	17.5 (32)	19.1 (35)	21.1	17.4	18.7
	Continuous use	18.2(11)	26.6 (17)	20.3 (13)	17.4(.52)	26.4 (.10)	20.6 (.72)
	Discontinued	26.2 (11)	31.0 (13)	25.0 (10)	25.7 (.49)	28.0 (.11)	26.0 (.27)
	p¶	0.54	0.08	0.70			

[*] Adjusted mean/percentage (p-value from multiple regression, with no biologic group as reference), adjusting for age, sex, education, number of comorbidities at baseline, and duration of RA. For “duration of morning stiffness” and “severe/very severe fatigue,” p-values are from multiple logistic regression analyses, controlling for the same covariates.

[†] p-value from ANOVA comparing groups

[§] Mean (standard deviation)

[¶] p-value from chi-square analysis comparing treatment groups

[**] % (n)

[a] Significantly different from no biologic group (from post hoc means test)

Table 3

Improvement from Baseline

		Bivariate		Adjusted*	
	Biologic	**Year 1**	**Year 2**	**Year 1**	**Year 2**
HAQ	No	15.9	12.6	15.4	12.3
	Completed	23.4	21.9	22.2 (.23)	21.4 (.08)
	Discontinued	28.6	22.5	29.1 (.04)	22.2 (.12)
	p†	.11	.11		
Severity of pain rating	No	21.9	21.6	21.5	21.3
	Completed	35.9	32.8	35.3 (.03)	31.8 (.10)
	Discontinued	31.0	17.5	27.0 (.47)	16.7 (.52)
	p	.07	.12		
Number of painful joints/joint groups	No	22.4	16.4	21.7	16.2
	Completed	31.3	32.8	29.9 (.17)	33.4 (.004)
	Discontinued	35.7	20.0	32.1 (.18)	20.2 (.55)
	p	.12	.02		
Number of swollen joints/joint groups	No	21.9	19.7	21.1	18.7
	Completed	43.8	39.1	43.5 (.001)	38.4 (.003)
	Discontinued	47.6	375	47.3 (.001)	36.4 (.02)
	p	.0002	.002		
Duration of morning stiffness > 1 hour	No	9.8	10.9	9.3	10.4
	Completed	26.6	28.1	25.7 (.002)	27.3 (.001)
	Discontinued	21.4	19.1	22.0 (.04)	14.7 (.52)
	p	.003	.004		
Severe/very severe fatigue	No	9.8	10.9	9.4	10.5
	Completed	4.7	9.4	4.2 (.19)	9.0 (.68)
	Discontinued	11.9	14.3	11.9 (.70)	9.5 (.80)
	p	.36	.73		

*Adjusted percentages calculated from multiple linear regression analyses, adjusting for age, sex, education, number of comorbidities at baseline, and duration of RA. P-values are from multiple logistic regression analyses, controlling for the same covariates.

†p-value from chi-square analysis comparing biologic and no biologic groups