

Differences in Longitudinal Disease and Treatment Characteristics of Patients with Rheumatoid Arthritis Replying and Not Replying to a Postal Questionnaire. Experience from a Biologics Register in Southern Sweden

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ABSTRACT. *Objective.* Studies on patients not answering postal questionnaires are scarce. We assessed the demographics and longitudinal disease and treatment characteristics of patients with rheumatoid arthritis (RA) in a Swedish biologics register who replied and who did not reply to a postal questionnaire.

Methods. In the South Swedish Arthritis Treatment Group register, we have detailed disease severity characteristics at baseline and at followup for rheumatology patients taking biologic drugs. In 2005 a questionnaire on smoking, comorbidities, education, and ethnicity was sent to 1234 RA patients who had started their first biologic drug.

Results. In total, 989 subjects (80%) answered the questionnaire. The 245 (20%) who did not answer generally had more severe RA [higher Disease Activity Score, worse Health Assessment Questionnaire score, higher visual analog scale scores for general health and pain at baseline and at followup, and stopped the drug treatment more frequently (72% vs 53%; $p = 0.0001$)]. There were no statistically significant differences in gender and disease duration between those who replied and those who did not reply, but in general the patients who did not reply were younger.

Conclusion. Patients with RA in a Swedish biologics register not replying to a postal questionnaire had more severe RA and stopped biological drug treatment more frequently. Thus a detailed analysis of prospectively collected data can clarify selection bias introduced by subjects who do not answer a postal questionnaire, which may influence the validity and interpretation of results from postal survey studies. (J Rheumatol First Release May 1 2009; doi:10.3899/jrheum.081027)

Key Indexing Terms:

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Studies on patients not answering postal questionnaires are scarce, due to the inherent problem of not receiving the required questionnaire information. Regarding patients with chronic rheumatological diseases, little is known about factors such as course of disease and treatment success in those who choose not to reply to a postal survey^{1,2}. It is usually not possible to characterize individuals who do not reply, except for demographics and disease-specific characteristics at baseline.

We investigated the patient-derived selection bias introduced by individuals not answering a postal questionnaire on smoking, comorbidities, education, and ethnicity in patients with rheumatoid arthritis (RA) who started their first biological drug. We used the South Swedish Arthritis Treatment Group (SSATG) register, which contains prospectively collected baseline and followup data on disease severity and treatment outcome^{3,4}.

MATERIALS AND METHODS

Rheumatologists in 12 hospitals and 5 private practices in southern Sweden contribute to the SSATG register. The aim is to register all patients with rheumatological diseases who are prescribed biological drugs. Data are collected using a structured clinical protocol designed for drug monitoring^{3,4}. Earlier validation against pharmaceutical sales showed that the register covers about 90% of the prescription of biological drugs in the region, where the population structure is representative for the whole of Sweden⁴.

For the study, we used information in the SSATG register from March 1999 through September 2005. A questionnaire was sent to 1234 patients in the SSATG register who were above the age of 18 years in 2005 (March through July) and had started their first biological drug (Figure 1). The questionnaire contained questions on education, ethnicity (immigrant/non-immigrant), smoking history, use of smokeless tobacco or other nicotine products, and comorbidities based on the patient's own assessment (high blood pressure, cardiovascular disease, pulmonary disease, diabetes, neurological disease, cancer, stomach ulcer, kidney disease, eye disease, and/or psychiatric disease). The questionnaire was sent to all patients initiating biologic therapy regardless of presence of followup data. One postal reminder was sent to patients who did not answer the questionnaire. The followup was the same for patients who answered the questionnaire and those who did not, i.e., from March 1999 to September 2005.

The diagnosis of RA was determined clinically by the local rheumatologist. No formal level of disease activity is required in the Swedish Society for Rheumatology guidelines for biological treatment. The guidelines do, however, state that the patient should have at least partial failure with or intolerance to previous methotrexate treatment. Methotrexate could have been tried alone or in combination with other disease-modifying antirheumatic drugs (DMARD). Disease activity is evaluated at inclusion, at 3, 6, and 12 months, and every 6–12 months thereafter. Missing followup data are requested from the treating physician every 6 to 12 months. The variables collected include number of swollen joints (28 joint count; SWJ), number of tender joints (28 joint count; TJC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and the Health Assessment Questionnaire (HAQ)⁵ and visual analog scales (VAS) for pain and general health. Disease Activity Score (28 joint count; DAS28) is also calculated (UMC Sint Radboud Hospital, Nijmegen, The Netherlands; www.das-score.nl).

Statistics. SPSS version 15.0 was used for the statistical analyses, and all

tests were 2-tailed. Chi-square test, t test, and Kaplan-Meier survival analysis were used when appropriate, and we considered a p value ≤ 0.05 statistically significant.

The study was approved by the ethics committee of Lund University.

RESULTS

Nine hundred eighty-nine of 1234 patients with RA starting their first biological drug returned the questionnaire. Sixty-eight percent answered the first questionnaire, and a further 12% the reminder, giving an overall reply frequency of 80% (Figure 1). The 245 patients (20%) who did not answer the questionnaire differed with regard to a number of disease-specific characteristics at baseline (Table 1). At baseline, i.e., at initiation of first anti-tumor necrosis factor treatment, the subjects who did not answer were generally younger and had a significantly lower number of ongoing DMARD, higher DAS28, a higher number of tender joints (28-joint index), higher VAS global and VAS pain scores, and higher HAQ score at baseline. Moreover, DAS28 scores at 3, 6, and 12 months' followup were significantly higher for those who did not reply (DAS28 at 3 months, 4.0 vs 3.7, p = 0.005; at 6 months, 4.0 vs 3.6, p = 0.005; at 12 months, 4.0 vs 3.4, p = 0.0001). Thus, the patients who did not answer the questionnaire had significantly higher disease activity at both baseline and followup. However, there were no significant differences in gender and baseline disease duration between those who replied and those who did not reply.

The mean followup time from the start of the biological treatment to the issue of the questionnaire (June 2005) was the same for patients answering the questionnaire (39.4 mo) and those not answering (39.2 mo). The response rate between different inclusion years was similar (range 74% to 81%).

Table 1. Baseline demographics and disease activity of patients who answered and did not answer the questionnaire. Values are mean (SD) unless stated otherwise.

Demographics and Disease Activity	Not Answered, n = 245	Answered, n = 989	p
Age, yrs	54 (14)	56 (13)	0.02
Women, n (%)	182 (74)	780 (79)	0.12
Disease duration, yrs	13 (10)	13 (9.9)	0.29
Previous DMARD, no.	3.5 (2.0)	3.6 (2.0)	0.81
Ongoing DMARD, no.	0.8 (0.6)	0.9 (0.6)	0.004
DAS28	5.8 (1.2)	5.6 (1.1)	0.03
Swollen 28 joint count	9.8 (5.6)	10 (5.9)	0.57
Tender 28 joint count	9.9 (7.1)	8.8 (6.4)	0.02
VAS global, mm	66 (22)	62 (22)	0.02
VAS pain, mm	66 (22)	62 (22)	0.006
HAQ	1.5 (0.7)	1.4 (0.6)	0.0001
ESR, mm	40 (26)	36 (25)	0.08
CRP, mg/l	31 (30)	34 (35)	0.36

DMARD: disease-modifying anti-rheumatic drug, VAS: visual analog scale, HAQ: Health Assessment Questionnaire, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, DAS28: disease activity score (28 joints).

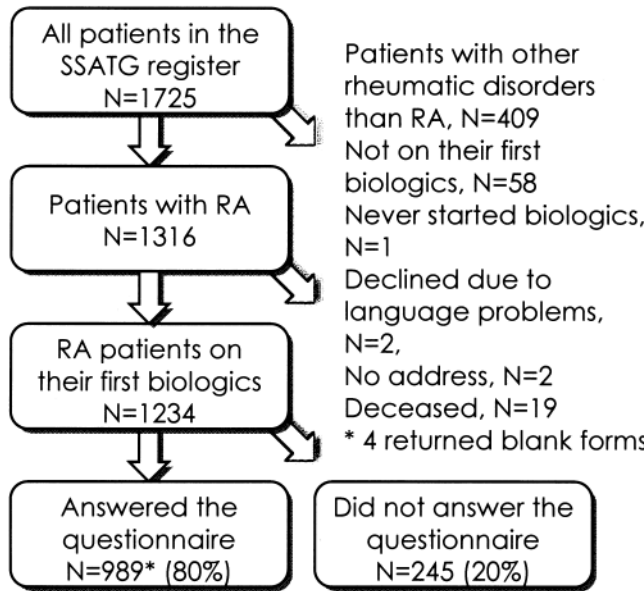


Figure 1. The progress of the study.

Patients who did not answer the questionnaire had worse drug survival (Figure 2). A total of 521 of the 989 patients who replied (53%) stopped treatment, in contrast to 177 (72%) of the 245 who did not reply ($p = 0.0001$). Of the patients who answered the questionnaire, 298 (30%) stopped because of an adverse event, whereas 106 (43%) of those who did not answer stopped because of an adverse event ($p = 0.0001$, log-rank 0.034). Stopping treatment due to inefficacy was similar between patients answering and not answering the questionnaire ($p = 0.298$).

DISCUSSION

This is the first study to report demographics and disease and treatment characteristics of patients with RA taking biologics not replying to a postal questionnaire. That patients who did not answer the questionnaire generally had higher disease activity, both at baseline and at followup, illustrates a selection bias introduced by the patients. Moreover, these patients would not have been identified if only gender and disease duration had been used to differentiate between those who replied and those who did not. Our findings of patients stopping due to an adverse event must be interpreted with caution, since in the observational setting overall reason for stopping is the most important issue⁶. Our findings highlight the importance of a thorough analysis of those not replying in studies involving postal questionnaires. Also, our study emphasizes the importance of reminder questionnaires, as a further 12% answered after this procedure.

In view of the actual results, the patients not replying appear to represent RA patients with some characteristics known to have less good response to therapy using biological drugs — for example, poor HAQ score^{6,7}. The size of the bias introduced by those who have not responded is obviously affected by the proportion that has answered the survey. In our study, with a response rate of 80%, the propor-

tion that stopped treatment was 53% for those answering the survey, and would have been 57% if we had included those not answering. If we assume a reply frequency of only 60%, the proportion of patients stopping treatment would rise to 61%. These differences remain modest regarding this particular issue. Even so, it is important to realize that those who do not answer a survey may differ in several aspects. This is perhaps often disregarded when interpreting survey results, but is important when discussing their generalizability.

There have been very few studies on the effect of not answering postal questionnaires in the field of rheumatology. In a Finnish study, patients who did not answer a postal questionnaire on health status in RA were found to have higher mortality rates than those who did in a 2-year followup of both patients with RA and study subjects in an age and sex-matched community control group². The patients who did not respond were younger, as in our study, and were more often men². Patients not answering a postal survey on smoking had higher mortality in an Italian study⁸. In a study from the United States on attrition (patient dropout) in 11 databanks involving 6346 patients with RA who had been followed for 32,823 person-years, it was found that smaller, inner city-based and university-based databanks had higher dropout rates and thus are biased by retaining older, more educated Caucasian patients. Lower age, lower level of education, and non-Caucasian race was predictive of dropping out. The level of disability, gender, and disease duration was not predictive of dropping out¹. Patients who do not participate in studies often have lower socioeconomic status, lower education, poorer health, younger age, and are more often men⁹.

A detailed analysis of the characteristics of patients with RA starting their first biological drug who were sent a postal questionnaire on smoking, comorbidities, education, and ethnicity revealed significant differences between patients who responded and those who did not, which may affect the validity of the results. These differences would not have been detected by examination of gender and disease duration alone.

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REFERENCES

1. Krishnan E, Murtagh K, Bruce B, Cline D, Singh G, Fries JF. Attrition bias in rheumatoid arthritis databanks: a case study of 6346 patients in 11 databanks and 65,649 administrations of the Health Assessment Questionnaire. *J Rheumatol* 2004;31:1320-6.
2. Kauppi M, Sokka T, Hannonen P. Survey nonresponse is associated with increased mortality in patients with rheumatoid arthritis and in a community population. *J Rheumatol* 2005;32:807-10.
3. Geborek P, Saxne T. Clinical protocol for monitoring of targeted therapies in rheumatoid arthritis. *Rheumatology* 2000;39:1159-61.
4. Geborek P, Nitelius E, Noltorp S, et al. Population based studies of

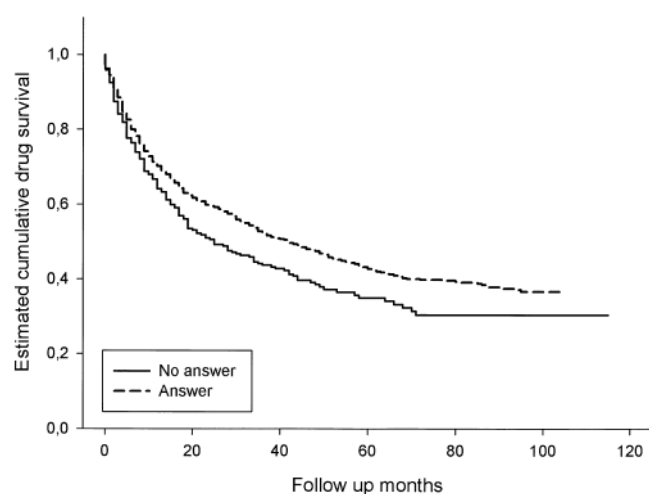


Figure 2. Kaplan-Meier curves for drug survival for the patients who answered and those who did not answer the questionnaire. Log-rank $p = 0.015$.

- biological antirheumatic drug use in southern Sweden: comparison with pharmaceutical sales. *Ann Rheum Dis* 2005;64:1805-7.
5. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137-45.
 6. Kristensen LE, Saxne T, Nilsson JA, Geborek P. Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. *Arthritis Res Ther* 2006;8:R174.
 7. Hyrich KL, Watson KD, Silman AJ, Symmons DP. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Rheumatology* 2006;45:1558-65.
 8. Barchielli A, Balzi D. Nine-year follow-up of a survey on smoking habits in Florence (Italy): higher mortality among non-responders. *Int J Epidemiol* 2002;31:1038-42.
 9. Bergstrand R, Vedin A, Wilhelmsson C, Wilhelmsen L. Bias due to non-participation and heterogenous sub-groups in population surveys. *J Chronic Dis* 1983;36:725-8.