EQ-5D utility, response and drug survival in rheumatoid arthritis patients on biologic monotherapy: A prospective observational study of patients registered in the south Swedish SSATG registry

Tanja Schjødt Jørgensen1 *, Carl Turesson2,3, Meliha Kapetanovic3,4, Martin Englund5, Aleksandra Turkiewicz5, Robin Christensen1, Henning Bliddal1, Pierre Geborek3,4, Lars Erik Kristensen1,2

1 The Parker Institute, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark, 2 Rheumatology, Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden, 3 Department of Clinical Sciences, Lund, Section of Rheumatology Lund University and Skåne University Hospital, Lund, Sweden, 4 Rheumatology, Department of Clinical Science, Lund University, Lund, Sweden, 5 Clinical Epidemiology Unit, Orthopaedics, Department of Clinical Sciences, Lund University, Lund, Sweden

* Tanja.Schjoedt.Joergensen@regionh.dk

Abstract

Objectives
Biologic agents have dramatically changed treatment of rheumatoid arthritis (RA). To date only scarce head-to-head data exist especially when the biological therapies are given as monotherapy without concomitant disease modifying drugs (DMARDs). Thus the objective of the current study is to evaluate treatment response of all available biological therapies with special focus on utility (EQ-5D-3L) and drug survival of biologic DMARDs (bDMARDs) prescribed as monotherapy in RA patients in southern Sweden.

Materials and methods
All RA patients registered in a regional database as initiating bDMARD as monotherapy, i.e. without concomitant conventional synthetic DMARDs (csDMARDs), from 1st of January 2006 through 31st of December 2012, were included. Patients were followed from initiation of the first dose of bDMARD monotherapy treatment until withdrawal from treatment, loss of follow-up or 31st of December 2012. Descriptive statistics for utility (EQ-5D-3L), effectiveness, and drug survival of bDMARD monotherapy were calculated.

Results
During the study period, a total of 554 patients were registered in SSATG as initiating bDMARD monotherapy. Most of the patients were women (81%), with a mean age of 57 years. The average disease duration was more than 12 years, and on average the patients had previously been treated with approximately four different csDMARDs. Fifty-five percent
of the patients were initiating their first bDMARD, 26% their second, and 19% their third or more. At baseline the average EQ-5D-3L was 0.34. Most patients had moderate to high disease activity, with a mean DAS28 of 5.0, and were substantially disabled, with an average HAQ score of 1.4. At 6 months’ follow-up, the EQ-5D-3L in patients still on the biologic drug had increased by mean 0.23 (SD 0.4) with no differences between type of bDMARD (p = 0.49). The mean change in EQ-5D-3L ranged from 0.11 (rituximab and infliximab) to 0.42 (tocilizumab). Although the changes were numerically different, no distinct pattern favored any particular bDMARD for EQ-5D-3L (p = 0.49) or other clinical outcomes. Overall, DAS28 defined remission and low disease activity were achieved in 20% and 43% of patients, respectively. Drug survival rates were statistically significantly different between bDMARDs (p = 0.01), with the highest rates observed for rituximab, followed by etanercept. After failing first course of anti-TNF, patients switching to another mode of action had significantly higher drug survival than those switching to a second course of anti-TNF therapy (p = 0.02).

Conclusions
Utility (EQ-5D-3L) increased after 6 months of all bDMARD treatments in monotherapy, indicating improvement of patients’ quality of life. After failure of anti-TNF treatment in monotherapy, switching to another mode of action may be associated with better drug survival than starting a second TNF-inhibitor.

Introduction
Rheumatoid arthritis (RA) patients should be treated as early as possible with disease-modifying anti-rheumatic drugs (DMARDs) to improve the disease course [1]. Methotrexate (MTX) is considered the anchor drug in RA, both on the basis of its efficacy and safety as monotherapy, as well as its ability to increase the efficacy of biologic agents when used in combination [2–5].

It is estimated that between 10 and 30% of RA patients are MTX-intolerant and discontinuation is common in clinical practice [6]. Adverse effects from MTX include ulcerative stomatitis, leukopenia, liver toxicity, nausea and abdominal distress [7]. Thus, there are many reasons for discontinuation of MTX during biologic DMARD (bDMARD) therapy or initiating at least some of the bDMARDs as monotherapy. For those patients who are in need of treatment with a bDMARD and cannot tolerate MTX, bDMARD monotherapy may be a good option. Effectiveness and drug adherence of monotherapy with bDMARD has previously been described in a cohort study of patients with RA registered in the Danish DANBIO registry [8].

It is well known that RA has significant socioeconomic impact defined as health loss associated with diseases including both morbidity and mortality [9]. The Global Burden of Disease studies [10, 11] have recently addressed the challenges faced by the healthcare systems and, in this context, the cost-effectiveness of treating RA is highly impacted by modern therapies [12]. Thus, it can be claimed that rheumatologists need to show responsibility and consider economic implications when choosing between treatment options or modalities with comparable efficacy and safety. With growing numbers of biosimilar bDMARDs in the field of rheumatology, cost considerations by rheumatologists will become increasingly important [13]. In addition, stakeholders such as payers and administrators have to consider individual and societal...
implications (i.e. work disability and loss of productivity) of RA when making guidelines or treatment recommendations regarding the use and implementation of bDMARDs.

However, little is known about utility gain in clinical practice. Moreover, reports from independent cohorts in a similar clinical setting are lacking. The aim of this study was to investigate the frequency and type of bDMARDs used in monotherapy in a representative sample of patients with RA. Further, to evaluate and compare treatment response with special focus on utility (EQ-5D) and tolerability (drug adherence) among the different bDMARDs. For this purpose, we used the regional register held by the Southern Sweden Arthritis Treatment Group (SSATG), which covers more than 90% of rheumatology patients treated with bDMARDs [14] in southern Sweden setting, and can be considered representative of patients with RA who are treated in routine care.

Materials and methods

Eligibility criteria, data summaries, and statistical analyses were based on a predefined protocol, which can be accessed through the first author. The outcomes were utility (EQ-5D-3L) gain, disease activity score in 28 joints (DAS28) remission, DAS28 defined low disease activity (LDA), the American College of Rheumatology response criteria 20%, 50%, 70% (ACR20, ACR50, ACR70) after 6 months of follow-up, and drug adherence.

Study design, setting, and participants

RA patients who were registered in the SSATG database [14] as receiving initiation of treatment with any bDMARD without concomitant conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD) therapy (i.e., monotherapy) in the period from 1st of January 2006 through 31st of December 2012 were included in the present study. There was no formal definition of the initiation date of bDMARD monotherapy. The initiation date was based on the decision of the treating physician, and most of the patients were exposed and intolerable to csDMARDs prior to the bDMARD monotherapy initiation. A minority (about 3%) of the patients had contra-indications for csDMARDs and was initiated directly on bDMARD monotherapy. The patients were continuously enrolled and were monitored in the SSATG register at baseline and during treatment. The patients were seen in the clinics at individual time points. Patients were followed from initiation of the first dose of bDMARD monotherapy treatment until withdrawal from treatment, loss of follow-up or 31st of December 2012. Drug survival were retrieved from data recorded on withdrawals from treatment, which were routinely recorded by the treating physicians and classified as being due to adverse events, lack of response/inefficacy, or miscellaneous reasons such as pregnancies, patient decisions, poor compliance, and other unspecified causes. No formal criteria were required to terminate treatment, and the decision was based on the judgment of the treating physician.

The study sample included RA patients on monotherapy from bio-initiation and throughout the study period, whereas patients who became on monotherapy after cessation of concomitant csDMARD were excluded. A random sample of 50 patients from the SSATG database was validated by TSJ with respect to monotherapy timelines for date of onset (first dose bDMARD administered), dosage for the bDMARD monotherapy, and—in cases of withdrawal—the date of first missing dose. The validation showed complete data recording except for 1 patient (2%) with misrecorded termination date with monotherapy.

The regional ethics board of the University of Lund approved linkage of laboratory and clinical data used for this study (No. 379/2011). Informed consent was not required for the present study, as the study was part of a quality ensuring data recording process of routine clinical care, where all data handling was anonymous.
Variables

At the time of inclusion in the SSATG register, the following core data were recorded: diagnosis, year of disease onset, previous csDMARD treatment, and previous bDMARD treatment. At treatment start (baseline) and at follow-up, utility gain (EQ-5D-3L based on British tariff to improve external validity) was calculated [15, 16] on those still on the biologic drug (EQ-5D-3L only exist on patients still on the drug). The EQ-5D is a five-dimensional health state classification. The five dimensions are mobility, self-care, usual activities, pain/discomfort and anxiety/depression. It is a preference-based measure that can be regarded as a continuous outcome scored on a -0.59 to 1.00 scale, with 1.00 indicating ‘full health’ and 0 representing dead [17]. The negative EQ-5D scores represent certain health states valued as worse than dead.

In addition, the following clinical data were registered: DAS28 remission, LDA, health assessment questionnaire score (HAQ), patient-scored visual analogue scales for pain (VAS-pain), general health (VASglobal), physician’s global assessment of disease activity scored on a visual analogue scale, 28 tender and swollen joint count, low disease activity, CDAI, SDAI and C-reactive protein (CRP). DAS28, CDAI, and ACR20, ACR50, and ACR70 responses compared to baseline were calculated at 6 months of follow-up. Patients were considered in remission with a DAS28 score less than 2.6, and LDA was defined as DAS28 less than 3.2 at follow-up.

Statistical analyses

In the analysis the first monotherapy treatment for each patient during the study period was included (i.e. each patient was included once). Data were analyzed by Kruskal-Wallis test for between-group comparisons regarding continuous variables, whereas a Chi-square test was used for categorical variables. The Wilcoxon signed rank test was used to assess changes in EQ-5D from baseline to the 6 month follow-up. For the discrete treatment outcomes, both per-protocol and ITT-adjusted data (using the LUNDEX [18]) are given. The LUNDEX adjustment is an ITT methodology developed for the observational setting to account both for withdrawals from therapy and for missing response recordings at certain points of follow-up [18]. Drug survival data were illustrated by Kaplan Meier plots and further statistically analysed with log-rank statistics for comparing different treatments. Level of significance was chosen to be two-sided \( p < 0.05 \).

Results

During the study period, a total of 554 patients were registered in SSATG as initiating bDMARD monotherapy, as seen in Fig 1.

At baseline most of the patients were women (81%), with a mean age of 57 years. The average disease duration was more than 12 years, and on average the patients had previously been treated with approximately four different csDMARDs. Fifty-five percent of the patients were initiating their first bDMARD, 26% their second, and 19% their third or more. As presented in Table 1, the average utility or preference-based measure of health (EQ-5D-3L) was 0.34. At the time of inclusion, most patients had moderate to high disease activity, with mean scores for DAS28 of 5.0, CDAI of 28.7, and SDAI of 31.1, and were substantially disabled, with an average HAQ score of 1.4 (Table 1).

Of the 554 patients in monotherapy, adalimumab (25.6%), etanercept (39.2%), rituximab (11.2%), and infliximab (9.0%) were the 4 most prevalent bDMARDs administrated (Fig 1).
Utility measure of health

At 6 months' follow-up, the EQ-5D-3L in patients still on the biologic drug increased by mean 0.23 (SD 0.4) (p < 0.001), indicating improvement of patients' quality of life. The mean change in EQ-5D-3L ranged from 0.11 (rituximab and infliximab) to 0.42 (tocilizumab) (Table 2). Although the increases in EQ-5D-3L were numerically different, there was no statistically significant difference across the various bDMARDs (Table 2). There were no major differences in sex (83% vs 78% females; p = 0.24), age (mean: 59.2 years vs 59.3 years; p = 0.37), disease duration (mean: 15.6 years vs 14.4 years; p = 0.55), and DAS28 (mean: 5.1 vs 4.9; p = 0.16) between patients reporting EQ-5D data and those with missing data.

Treatment responses

At 6 months' follow-up, the crude DAS28 remission rates ranged from 0% (abatacept) to 27% (adalimumab); LDA ranged from 27% (abatacept) to 67% (tocilizumab); ACR20 response rate from 67% (abatacept and infliximab) to 90% (golimumab); ACR50 response rate from 22% (tocilizumab) to 67% (certolizumab); and ACR70 response rate from 0% (abatacept and golimumab) to 33% (certolizumab). Improvements of more than 0.3 in HAQ ranged from 18% (rituximab) to 44% (certolizumab) (Table 2). Although the rates were numerically different, these differences were not statistically significant (Table 2).
Table 1. Baseline characteristics and disease activity of patients in the study population according to treatment.

| Characteristics | Abatacept (n = 22) | Adalimumab (n = 142) | Certolizumab (n = 21) | Etanercept (n = 217) | Golimumab (n = 50) | Infliximab (n = 50) | Rituimab (n = 62) | Tocilizumab (n = 22) | Total (n = 554) |
|-----------------|-------------------|----------------------|-----------------------|----------------------|-------------------|-------------------|----------------|-------------------|-----------------|
| **Female sex, no. (%)** | 19 (86%) | 22 | 116 (82%) | 142 | 19 (86%) | 21 | 175 (81%) | 217 | 14 (78%) | 18 | 446 (81%) | 554 |
| **Age, years** | 53.0 (13.2) | 21 | 57.2 (15.4) | 140 | 52.0 (14.1) | 21 | 56.0 (14.4) | 216 | 59.5 (10.7) | 18 | 58.6 (12.9) | 47 | 57.5 (13.8) | 22 | 57.0 (14.2) | 547 |
| **Disease duration, year** | 11.2 (9.5) | 21 | 11.7 (10.6) | 140 | 10.3 (9.3) | 21 | 12.6 (11.7) | 216 | 11.5 (9.7) | 18 | 18.5 (16.2) | 47 | 13.6 (12.7) | 22 | 12.7 (9.5) | 547 |
| **No. of previous DMARDs** | 7.3 (3.4) | 22 | 3.5 (2.1) | 142 | 4.4 (2.5) | 21 | 3.2 (2.2) | 216 | 3.9 (3.3) | 18 | 3.4 (2.0) | 50 | 5.6 (3.3) | 61 | 3.8 (2.6) | 550 |
| **No. of previous biologics** | 2.6 (1.4) | 22 | 0.6 (0.7) | 142 | 0.7 (1.0) | 21 | 0.4 (0.8) | 217 | 0.8 (1.0) | 18 | 0.4 (0.8) | 50 | 1.5 (1.3) | 61 | 1.6 (1.5) | 22 | 1 (NA)* | 243 |
| **Swollen joint count: 0–28** | 6.0 (4.0;12.0) | 21 | 7.0 (3.0;11.0) | 140 | 6.0 (4.8;9.3) | 21 | 7.0 (3.0;12.0) | 195 | 9.0 (5.0;11.75) | 18 | 7.0 (2.0;10.5) | 45 | 5.0 (2.5;11.0) | 61 | 5.5 (3.25;9.75) | 20 | 7.0 (18.5;36.6) | 496 |
| **Tender joint count: 0–28** | 12.0 (8.0;24.0) | 21 | 8.0 (4.0;14.0) | 140 | 7.0 (2.0;12.0) | 21 | 7.0 (3.0;13.0) | 195 | 7.5 (4.0;11.5) | 18 | 7.0 (4.0;12.5) | 45 | 7.0 (2.0;14.0) | 61 | 6.0 (3.25;10.0) | 20 | 8.0 (3.0;13.0) | 495 |
| **C-reactive protein, mg/L** | 39.0 (40.7) | 22 | 27.4 (35.6) | 126 | 20.4 (31.8) | 21 | 19.1 (43.1) | 201 | 31.9 (43.1) | 19 | 26.2 (32.1) | 45 | 22.2 (26.6) | 61 | 35.6 (38.6) | 20 | 24.1 (30.7) | 510 |
| **Erythrocyte sedimentation rate, mm/hour** | 41.2 (26.4) | 22 | 36.3 (27.5) | 126 | 36.3 (25.6) | 21 | 27.9 (22.4) | 196 | 35.9 (25.4) | 12 | 36.3 (23.9) | 41 | 32.0 (25.0) | 61 | 44.4 (27.5) | 19 | 32.9 (25.1)* | 489 |
| **Patient global assessment, 0–100 mm VAS** | 67.4 (22.9) | 22 | 63.5 (22.6) | 126 | 59.3 (23.0) | 21 | 62.9 (22.4) | 200 | 60.5 (26.0) | 16 | 64.0 (21.8) | 43 | 60.0 (23.1) | 57 | 69.1 (23.5) | 19 | 63.0 (22.6) | 520 |
| **Doctors global assessment (5-grade Likert scale)** | 75.7 (26.0) | 22 | 72.2 (24.0) | 140 | 70.3 (23.0) | 21 | 72.3 (2.0) | 200 | 73.6 (2.0) | 16 | 60.8 (2.0) | 45 | 73.6 (0.7) | 61 | 62.3 (2.0) | 20 | 2.2 (0.7) | 495 |
| **Patient pain assessment, 0–100 mm VAS** | 70.4 (20.8) | 22 | 66.0 (23.4) | 140 | 62.1 (23.0) | 21 | 62.8 (22.4) | 201 | 58.8 (27.9) | 16 | 65.3 (20.5) | 43 | 56.4 (24.0) | 57 | 67.6 (16.2) | 19 | 63.4 (22.7) | 503 |
| **EQ-5D** | 0.19 (0.3) | 17 | 0.37 (0.4) | 92 | NA | 0 | 0.32 (0.4) | 158 | 0.59 (NA) | 1 | 0.42 (0.4) | 36 | 0.38 (0.3) | 30 | 0.15 (0.3) | 4 | 0.34 (0.4) | 338 |
| **HAQ score, 0–3** | 1.7 (0.5) | 22 | 1.4 (0.7) | 140 | 1.4 (0.8) | 21 | 1.3 (0.7) | 200 | 1.3 (0.8) | 16 | 1.5 (0.8) | 42 | 1.5 (0.7) | 57 | 1.4 (0.6) | 17 | 1.4 (0.4) | 497 |
| **CDAI** | 16.7 (11.2) | 22 | 15.2 (12.5) | 140 | 14.8 (12.5) | 21 | 14.6 (12.5) | 200 | 14.6 (12.5) | 16 | 14.6 (12.5) | 42 | 14.6 (12.5) | 57 | 14.6 (12.5) | 17 | 14.6 (12.5) | 497 |
| **SDAI** | 39.8 (17.0) | 22 | 31.6 (13.9) | 140 | 28.6 (12.1) | 21 | 30.8 (14.6) | 189 | 32.5 (12.1) | 16 | 29.9 (13.6) | 41 | 29.4 (15.1) | 57 | 30.0 (11.9) | 19 | 31.1 (14.3) | 477 |
| **DAS28** | 5.7 (13.0) | 22 | 5.1 (1.3) | 142 | 4.7 (1.2) | 21 | 4.9 (1.3) | 190 | 5.1 (1.0) | 16 | 5.0 (1.3) | 41 | 4.8 (1.4) | 57 | 5.1 (1.0) | 19 | 5.0 (1.3) | 478 |

Data are given as mean and standard deviation (SD) or median and interquartile [Q1;Q3] unless otherwise indicated.

*Statistical significant difference between the different biologic agents (p<0.05)

doi:10.1371/journal.pone.0169946.t001
Table 2. Utility gain and effectiveness of different biologics at 6 months follow-up.

| Characteristics | Abatacept (n = 14) | Adalimumab (n = 91) | Certolizumab (n = 13) | Etanercept (n = 166) | Golimumab (n = 36) | Infliximab (n = 50) | Rituximab (n = 15) | Total (n = 398) | P-value |
|----------------|-------------------|---------------------|----------------------|---------------------|-------------------|-------------------|------------------|-------------------|---------|
| ΔEQ-5D N       | 6                 | 36                  | 0                    | 91                  | 0                 | 21                | 15               | 2                 | 171*    |
| ΔEQ-5D (0.4)   | 0.16 (0.4)        | 0.13 (0.4)          | NA                   | 0.31 (0.3)          | NA                | 0.11 (0.5)        | 0.11 (0.3)       | 0.42 (0.5)        | 0.23 (0.4) | 0.493   |
| DAS28 remission N | 11               | 83                  | 10                   | 148                 | 13                | 35                | 38               | 15                | 353     |
| Remission, no (%) | 0 (0%)           | 22 (27%)            | 2 (20%)              | 34 (23%)            | 3 (3%)            | 7 (18%)           | 3 (20%)          | 72 (20%)*         |          |
| LUNDEX corrected (%) | 0%               | 18%                 | 13%                  | 18%                 | 13%               | 2%                | 15%              | 12%               | 13%     | 0.098   |
| DAS28 N        | 11               | 83                  | 10                   | 148                 | 13                | 35                | 38               | 15                | 353     |
| ΔDAS28 N       | 4.5 (0.17)        | 3.7 (1.5)           | 3.5 (1.4)            | 3.5 (1.3)           | 3.7 (1.3)         | 4.2 (1.1)         | 3.7 (1.6)        | 3.3 (1.1)         | 3.7 (1.4) | 0.052   |
| DAS28 low disease activity (LDA) N | 11               | 83                  | 10                   | 148                 | 13                | 35                | 38               | 15                | 353     |
| LDA, no (%)    | 3 (27%)           | 37 (45%)            | 5 (50%)              | 65 (44%)            | 4 (31%)           | 12 (34%)          | 15 (40%)         | 10 (67%)          | 151 (43%) |
| LUNDEX corrected (%) | 17%              | 29%                 | 32%                  | 34%                 | 18%               | 22%               | 33%              | 39%               | 28%     | 0.428   |
| CDAI N         | 11               | 82                  | 10                   | 147                 | 13                | 36                | 38               | 15                | 352     |
| ΔCDAI N        | -11.6 (8.8)       | 12.8 (15.0)         | -16.0 (12.5)         | -14.8 (14.1)        | -15.0 (14.8)      | -10.8 (13.0)      | -12.6 (13.1)     | -13.1 (10.3)      | -13.6 (13.8) | 0.533   |
| HAQ improvement N | 12               | 72                  | 9                    | 139                 | 13                | 32                | 35               | 13                | 326     |
| Improvement >0.3, no (%) | 5 (42%)          | 21 (29%)            | 4 (44%)              | 45 (35%)            | 3 (30%)           | 9 (31%)           | 6 (18%)          | 2 (20%)           | 95 (31%) | 0.599   |
| LUNDEX corrected (%) | 27%              | 19%                 | 28%                  | 27%                 | 17%               | 20%               | 15%              | 12%               | 20%     |         |
| ACR response N | 9                 | 51                  | 4                    | 88                  | 10                | 29                | 33               | 10                | 304     |
| ACR20, no (%)  | 6 (67%)           | 44 (86%)            | 3 (75%)              | 76 (86%)            | 9 (90%)           | 14 (67%)          | 18 (75%)         | 9 (82%)           | 180 (83%) | 0.338   |
| LUNDEX corrected (%) | 43%              | 56%                 | 47%                  | 67%                 | 52%               | 43%               | 62%              | 48%               | 54%     |         |
| ACR50, no (%)  | 7                 | 43                  | 3                    | 69                  | 5                 | 19                | 20               | 9                 | 175     |
| LUNDEX corrected (%) | 2 (29%)          | 25 (58%)            | 2 (67%)              | 45 (65%)            | 3 (60%)           | 9 (47%)           | 9 (45%)          | 2 (22%)           | 97 (55%) | 0.165   |
| ACR70, no (%)  | 5                 | 32                  | 3                    | 56                  | 3                 | 17                | 16               | 9                 | 141     |
| LUNDEX corrected (%) | 0 (0%)           | 10 (31%)            | 1 (33%)              | 14 (25%)            | 0 (0%)            | 2 (12%)           | 1 (6%)           | 2 (22%)           | 30 (21%) | 0.345   |

N is the number of patients with complete recording of the particular outcome. ΔEQ-5D, ΔDAS28, ΔCDAI and ΔACR are given as mean and standard deviation (SD). DAS28 remission, LDA, HAQ and ACR responses are given as no. and percent (%).

* The overall change from 0 to 6 months in EQ-5D was highly significant; p<0.001.

doi:10.1371/journal.pone.0169946.t002
Overall, the crude mean change in DAS28 after 6 months was -1.4 and for CDAI -13.6 (Table 2). For DAS28 remission, the crude and LUNDEX corrected rates were 20% and 13%, respectively, and for LDA the crude and LUNDEX corrected rates were 43% and 28%, respectively. The crude and LUNDEX corrected response rates for ACR20/50/70 were 83%/55%/ 21% and 54%/36%/14%, respectively (Table 2).

**Drug survival, stratified by bDMARD**

A total of 156 patients withdrew from treatment during the 6 months’ follow-up (Fig 1). The overall drug survival rates were significantly different between the bDMARDs (p = 0.01). Rituximab showed statistically significantly better drug survival than etanercept (p = 0.05), whereas etanercept showed statistically significantly better drug survival rates compared to both infliximab and adalimumab (Fig 2). The estimated overall drug survival was approximately 65% after 6 months, declining to approximately 55% after 2 years, with the exception of abatacept, certolizumab, golimumab and tocilizumab having low number of patients and a short follow-up time (Fig 2).

![Drug survival, stratified by drug](https://example.com/figure2.png)

**Fig 2. Drug survival, stratified by drug.** The graph for the Kaplan-Meier estimated survival has been censored when the number at risk was below 10. The number of patients on a drug at different time points is listed below the figure.

doi:10.1371/journal.pone.0169946.g002
Drug survival in bDMARD switchers, anti-TNF vs. other modes of action

The estimated drug survival rates were statistically significantly different when comparing anti-TNF switchers to other modes of action switchers (OMA switchers) (p = 0.02; Fig 3). There was no statistically significant difference between anti-TNF naïve patients and OMA switchers (p = 0.30) (Fig 3). The observed drug survival rates were similar irrespective of the number of biologic treatments the patients had received previously (p = 0.41; Fig 4).

There were no statistically significant differences between anti-TNF naïve patients, anti-TNF switchers, and OMA switchers regarding change in EQ-5D-3L, DAS28, HAQ, CDAI, and the crude and LUNDEX corrected ACR response rates (Table 3) at 6 months follow-up.

Discussion

In the present study, based on the data from the south Swedish SSATG registry, we found that the most common drugs used as biologic monotherapy were adalimumab, etanercept, and rituximab. One of our main findings was that in RA patients receiving bDMARD monotherapy, utility or preference-based health (EQ-5D-3L) on average nearly doubled after 6 months of treatment with a bDMARD, indicating improvement of patients’ quality of health [19, 20]. Whether the absolute changes are clinically important remains to be validated in the RA population. Although the changes were numerically different, no distinct pattern favored any
particular bDMARD regarding change in health utility (EQ-5D-3L), remission and ACR response criteria. Furthermore, the estimated survival rates were generally lower than seen in combination therapy [21]. In addition, the survival rates seemed more favorable for rituximab than for etanercept, whereas, etanercept showed significantly better drug survival rates compared to both infliximab and adalimumab when given in monotherapy. On the other hand, LUNDEX corrected treatment response rates and proportions achieving DAS28 defined remission or low disease activity were not substantially different in patients treated with rituximab, etanercept and adalimumab.

The observed increase in health utility is in line with the utility gain found in an observational study by Gülfe et al. [22] and in RCTs of biologic therapy in patients with RA receiving concomitant csDMARDs [23, 24]. Comparison of change in utility score between bDMARD monotherapy group and combination therapy group would be a clinically important issue to investigate. However, with regard to background csDMARD usage this imposes an immense confounding by indication, as these different patient groups are very heterogeneous in the clinical setting [21]. Furthermore, this was not the scope of the current study, and must be addressed in future studies.

EQ-5D was chosen as utility outcome because of its simplicity, patient acceptability and well-established utilities. This adds important knowledge from a societal or payers perspective.
This being said, EQ-5D is well suited for measuring health-related quality of life, including dimensions such as pain, mobility, self-care and usual activities, all of which are important in inflammatory joint diseases. However, EQ-5D entails several subjective judgments made by the patients, wherefore it has major limitations for clinical monitoring and has to be complemented with more objective measures before making decisions regarding the start or change of bDMARD treatment.

Significantly better drug survival rates for etanercept compared to both infliximab and adalimumab have previously been shown in independent RA cohorts treated with csDMARDs combination therapy [21, 25, 26], but it is to our knowledge the first time that this is demonstrated in a unique monotherapy cohort. The finding that rituximab should be even less likely to be discontinued is novel and could in part be due to methodologic issues. For example, the pattern of administration with long inter-infusion times for rituximab probably contributes to artificially improved drug survival in this analysis. As the study included more than four years of follow-up, these patterns may also reflect true differences between bDMARDs in terms of long term efficacy and safety. Of note, rituximab is often administered at a later state in the treatment algorithm, wherefore limitation in the remaining treatment options might inflate

### Table 3. Utility gain and effectiveness of anti-TNF naïve, anti-TNF switchers and other modes of action (OMA) bDMARDS 6 months follow-up.

|                      | Anti-TNF naïve (n = 269) | Anti-TNF switchers (n = 160) | Other modes of action (OMA) (n = 83) | P-value |
|----------------------|--------------------------|-----------------------------|-------------------------------------|---------|
| ΔEQ-5D               |                          |                             |                                     |         |
| N                    | 58                       | 31                          | 9                                   |         |
|                      | 0.28 (0.3)               | 0.25 (0.4)                  | 0.14 (0.3)                          | 0.379   |
| ΔDAS28               |                          |                             |                                     |         |
| N                    | 93                       | 41                          | 27                                  |         |
|                      | -1.6 (1.4)               | -1.6 (1.3)                  | -1.7 (1.1)                          | 0.897   |
| ΔCDAI                |                          |                             |                                     |         |
| N                    | 94                       | 45                          | 27                                  |         |
|                      | -15.4 (13.2)             | -16.4 (11.7)                | -15.6 (11.7)                        | 0.680   |
| ΔHAQ                 |                          |                             |                                     |         |
| N                    | 93                       | 44                          | 25                                  |         |
|                      | -0.3 (0.6)               | -0.3 (0.5)                  | -0.1 (0.5)                          | 0.100   |
| ACR response         |                          |                             |                                     |         |
| N                    | 189                      | 82                          | 51                                  |         |
| ACR20, no (%)        | 105 (56%)                | 37 (45%)                    | 25 (49%)                            | 0.261   |
| LUNDEX corrected (%) | 41%                      | 29%                         | 36%                                 |         |
| N                    | 189                      | 82                          | 51                                  |         |
| ACR50, no (%)        | 61 (32%)                 | 20 (24%)                    | 11 (22%)                            | 0.202   |
| LUNDEX corrected (%) | 13%                      | 15%                         | 16%                                 |         |
| N                    | 189                      | 82                          | 51                                  |         |
| ACR70, no (%)        | 61 (32%)                 | 20 (24%)                    | 11 (22%)                            | 0.202   |
| LUNDEX corrected (%) | 13%                      | 15%                         | 16%                                 |         |

N is the number of patients with complete recording of the particular outcome. ΔEQ5D, ΔDAS28, ΔCDAI, and ΔHAQ are given as mean and standard deviation (SD). ACR responses are given as no. and percent (%).

doi:10.1371/journal.pone.0169946.t003
the drug survival rate in favor of rituximab. Future studies are needed to confirm our finding and explore the underlying mechanisms.

Surprisingly, we found that when switching to OMA after anti-TNF failure the drug adherence was as good as when treated with an anti-TNF as 1st course. However, switching to a 2nd anti-TNF showed significantly inferior drug survival rates compared to bDMARDs with other modes of action. Recently, an observational study comparing rituximab to anti-TNF in combination therapy also showed superiority when switching to OMA compared to another anti-TNF [27]. Thus our results suggest that bDMARDs with other modes of action could be considered as the first choice for patients not tolerating csDMARDs and who have had an inadequate response to their first anti-TNF agent. It should be noted, that the favorable effect of OMA is primarily driven by rituximab.

The clinical remission and response rates in the present study are comparable with results from a study in the Danish DANBIO registry [8] showing somewhat lower overall remission and response rates than in previously published studies in bDMARD therapy combined with MTX [21, 25, 28–33].

The overall retention rate after 6 months was approximately 65%, declining to approximately 55% after 2 years, which is lower than the result observed in the DANBIO registry [8] and generally lower than previously published studies on combination therapy [21, 26, 29–32]. The reason for the discrepancies in drug survival between SSATG and DANBIO might be due to various reasons such as differences in the data capturing, regional prescription policies, and the fact that the DANBIO report also included patients starting out in combination therapy, but who withdrew from csDMARD during the course of the particular bDMARD.

In line with the monotherapy study from DANBIO [8], the survival rates found in the present study were independent of previous treatments. Patients who were in their 2nd or 3rd line of bDMARD as monotherapy adhered to the treatment as long as those who were on their first biologic agent on monotherapy. This finding is in contrast with data from other registries on RA patients in combination therapy [34, 35], showing that drug survival in switchers was lower than in anti-TNF naïve [34, 36] and an increased risk of withdrawing from the second treatment for the same reason as the first, regardless of whether it was due to inefficacy or adverse events [35]. Other possibilities might be the pooling of anti-TNF bDMARDs and bDMARDs with other modes of action in the present analysis which may have influenced the drug survival in either direction for switchers, or that adherence to monotherapy depends more on other factors (e.g., patients’ age and comorbidities).

Limitations and strengths

The non-randomized observational design of this study has limitations such as possible bias regarding patient selection, assignment of treatment, baseline disparities between groups and missing data. The patient background features and conditions were different, so one could argue whether direct comparisons for outcomes among biologic agents is appropriate. Confounding by indication is an issue in the current study, being the inherent problem with all observational studies. Thus, we have faded the role of direct comparison by grouping the different agents in larger groups (anti-TNF’s and OMA) in the main analysis performed. Moreover, regression-analysis was performed to compensate for confounding, however, residual confounding always remains a problem in the observational study setting.

The Swedish national bDMARD registry [37] demonstrated that patients with many comorbidities might have been channeled to non-TNF bDMARDs hampering the effectiveness of these drugs. Moreover, TNF inhibition has previously been first line treatment in RA, wherefore non-anti-TNF agents have been used more extensively as 2nd or 3rd line treatment,
potentially deflating the response to these bDMARDs. This being said, summary disease characteristics in this study were similar across different treatments, suggesting a limited potential role of such confounding. Furthermore, decisions to start or stop therapy as well as concomitant DMARDs were based solely on clinical practice and experience of treating physicians, with national guidelines as a support.

Major strengths of the present study include access to prospectively recorded, routinely collected registry data on biologic treatment. Observational data like ours are more generally applicable as a reference for health economic modeling than randomized controlled trial data, which are derived from highly selected patients. Observational studies remain important contributors of information from daily clinical practice.

Conclusions
This observational study showed that utility (EQ-5D-3L) significantly increased after 6 months of treatment with a bDMARD when applied in monotherapy, indicating improvement of patients’ quality of life. Although there were numerical differences between bDMARDs in terms of utility gain and clinical response, no distinct pattern favored any particular bDMARD when used as monotherapy for RA. Survival rates were more favorable for rituximab than for etanercept, whereas etanercept showed significantly better drug survival rates compared to both infliximab and adalimumab. Furthermore, after anti-TNF failure, switching to a 2nd anti-TNF drug showed significantly inferior drug survival rates compared starting one of the bDMARDs with other modes of action.

Acknowledgments
This study was supported by a core grant from the Oak Foundation (OCAY-13-309), NordForsk, The Swedish Rheumatism Association, The Swedish Research Council and Lund University. The sponsors had no role in the design, collection, analysis or interpretation of data; in drafting of the manuscript or in the decision to submit the manuscript for publication.

Author Contributions
Conceptualization: TSJ CT RC LEK.
Data curation: TSJ LEK.
Formal analysis: TSJ LEK.
Funding acquisition: LEK.
Investigation: TSJ LEK.
Methodology: TSJ CT RC LEK.
Project administration: TSJ LEK.
Resources: TSJ LEK.
Software: TSJ LEK.
Supervision: LEK.
Validation: TSJ LEK.
Visualization: TSJ LEK CT ME MK AT RC HB PG.
Writing – original draft: TSJ LEK CT ME MK AT RC HB PG.
Writing – review & editing: TSJ LEK CT ME MK AT RC HB PG.

References

1. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. Lancet 2007; 370:1861–74. doi: 10.1016/S0140-6736(07)60784-3 PMID: 17570481

2. Nixon RM, Bansback N, Brennan A. Using mixed treatment comparisons and meta-regression to perform indirect comparisons to estimate the efficacy of biologic treatments in rheumatoid arthritis. Stat Med 2007; 26:1237–54. doi: 10.1002/sim.2624 PMID: 16900557

3. Lie E, van der Heijde D, Uhlig T, Mikkelsen K, Kalstad S, Kaufmann C, et al. Treatment strategies in patients with rheumatoid arthritis for whom methotrexate monotherapy has failed: data from the NORDMARD register. Ann Rheum Dis 2011; 70:2103–10. doi: 10.1136/ard.2011.152363 PMID: 21875874

4. Kristensen LE, Christensen R, Bliddal H, Geborek P, Danneskiold-Samsoe B, Saxne T. The number needed to treat for adalimumab, etanercept, and infliximab based on ACR50 response in three randomized controlled trials on established rheumatoid arthritis: a systematic literature review. Scand J Rheumatol 2007; 36:411–7. doi: 10.1080/03009740701607067 PMID: 18092260

5. Kristensen LE, Jakobsen AK, Bartels EM, Geborek P, Bliddal H, Saxne T, et al. The number needed to treat for second-generation biologics when treating established rheumatoid arthritis: a systematic quantitative review of randomized controlled trials. Scand J Rheumatol 2011; 40:1–7. doi: 10.3109/03009742.2010.491834 PMID: 20950126

6. Yazici Y, Shi N, John A. Utilization of biologic agents in rheumatoid arthritis in the United States: analysis of prescribing patterns in 16,752 newly diagnosed patients and patients new to biologic therapy. Bull NYU Hosp J Dis 2008; 66:77–85. PMID: 18537774

7. Salliot C and van der HD. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis 2009; 68:1100–4. doi: 10.1136/ard.2008.093690 PMID: 19060002

8. Jorgensen TS, Kristensen LE, Christensen R, Bliddal H, Lorenzen T, Hansen MS, et al. Effectiveness and drug adherence of biologic monotherapies in routine care of patients with rheumatoid arthritis: a cohort study of patients registered in the Danish biometrics registry. Rheumatology (Oxford) 2015.

9. Lundkvist J, Kastang F, Kobelt G. The burden of rheumatoid arthritis and access to treatment: health burden and costs. Eur J Health Econ 2008; 8 Suppl 2:S49–S60.

10. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380:2197–223. doi: 10.1016/S0140-6736(12)61689-4 PMID: 23245608

11. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380:2163–96. doi: 10.1016/S0140-6736(12)61729-2 PMID: 23245607

12. Kobelt G and Jonsson B. The burden of rheumatoid arthritis and access to treatment: outcome and cost-utility of treatments. Eur J Health Econ 2008; 8 Suppl 2:95–106.

13. Dorner T, Strand V, Castaneda-Hernandez G, Ferraccioli G, Isaacs JD, Kvien TK, et al. The role of biologics in the treatment of rheumatoid arthritis: a systematic review of the literature. Rheumatology (Oxford) 2015.

14. Geborek P, Nitelius E, Noltorp S, Petri H, Jacobsson L, Larsson L, et al. Population based studies of biologic antirheumatic drug use in southern Sweden: comparison with pharmaceutical sales. Ann Rheum Dis 2005; 64:1805–7. doi: 10.1136/ard.2005.036715 PMID: 16284356

15. Kay J, Morgacheva O, Messing SP, Kremer JM, Greenberg JD, Reed GW, et al. Clinical disease activity and acute phase reactant levels are discordant among patients with active rheumatoid arthritis: acute phase reactant levels correlate separately to predicting outcome at one year. Arthritis Res Ther 2014; 16:R40. doi: 10.1186/ar4468 PMID: 24485007

16. Karlsson JA, Nilsson JA, Neovius M, Kristenssen LE, Guille A, Saxne T, et al. National EQ-5D tariffs and quality-adjusted life-year estimation: comparison of UK, US and Danish utilities in south Swedish rheumatoid arthritis patients. Ann Rheum Dis 2011; 70:2163–6. doi: 10.1136/ard.2011.153437 PMID: 21859684

17. Walters SJ and Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res 2005; 14:1523–32. PMID: 16110932

18. Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid
Utility during biological monotherapy in patients with rheumatoid arthritis

Kim SK, Kim SH, Jo MW, Lee SI. Estimation of minimally important differences in the EQ-5D and SF-6D indices and their utility in stroke. Health Qual Life Outcomes 2015; 13:32. doi: 10.1186/s12955-015-0227-3 PMID: 25889191

Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007; 5:70. doi: 10.1186/1477-7525-5-70 PMID: 18154669

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. doi: 10.1186/ar2084 PMID: 17121678

Gulfe A, Kristensen LE, Saxne T, Jacobsson LT, Peterson IF, Geborek P. Rapid and sustained health utility gain in anti-tumour necrosis factor-treated inflammatory arthritis: observational data during 7 years in southern Sweden. Ann Rheum Dis 2010; 69:352–7. doi: 10.1136/ard.2008.103473 PMID: 19282310

Van Riel PL, Taggart AJ, Sany J, Gaubitz M, Nab HW, Pedersen R, et al. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. Ann Rheum Dis 2006; 65:1478–83. doi: 10.1136/ard.2005.043299 PMID: 16464988

Van Riel PL, Freundlich B, MacPeek D, Pedersen R, Foehl JR, Singh A, et al. Patient-reported health outcomes in a trial of etanercept monotherapy versus combination therapy with etanercept and methotrexate for rheumatoid arthritis: the ADORE trial. Ann Rheum Dis 2008; 67:1104–10. doi: 10.1136/ard.2006.068585 PMID: 17666447

Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, et al. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. Arthritis Rheum 2010; 62:22–32. doi: 10.1002/art.27227 PMID: 20039405

Neovius M, Arkema EV, Otsson H, Eriksson JK, Kristensen LE, Simard JF, et al. Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab. Ann Rheum Dis 2013.

Emery P, Gottenberg JE, Rubbert-Roth A, Sarzi-Puttini P, Choquette D, Taboada VM, et al. Rituximab versus an alternative TNF Inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study. Ann Rheum Dis 2014.

Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998; 41:1552–63. doi: 10.1002/1529-0131(199809)41:9<1552::AID-ART5>3.0.CO;2-W PMID: 9751087

Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006; 54:26–37. doi: 10.1002/art.21519 PMID: 16385520

van der HD, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum 2006; 54:1063–74. doi: 10.1002/art.21655 PMID: 16572441

Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al. Golimumab, a human antibody to tumour necrosis factor (alpha) given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis 2009; 68:789–96. doi: 10.1136/ard.2008.099010 PMID: 19066176

Fleischmann R, Vencovsky J, van Vollenhoven RF, Borenstein D, Box J, Coteur G, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis 2009; 68:805–11. doi: 10.1136/ard.2008.099291 PMID: 19015206

Jeffers HC, Ostergaard M, Glintborg B, Krogh NS, Foged H, Tarp U, et al. Efficacy of abatacept and tocolizumab in patients with rheumatoid arthritis treated in clinical practice: results from the nationwide Danish DANBIO registry. Ann Rheum Dis 2011; 70:1216–22. doi: 10.1136/ard.2010.140129 PMID: 21551512
34. Gomez-Reino JJ and Carmona L. Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. Arthritis Res Ther 2006; 8:R29. doi: 10.1186/ar1881 PMID: 16507128

35. Hyrich KL, Lunt M, Watson KD, Symmons DP, Silman AJ; British Society for Rheumatology Biologics Register. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. Arthritis Rheum 2007; 56:13–20. doi: 10.1002/art.22331 PMID: 17195186

36. Chatzidionysiou K, Askling J, Eriksson J, Kristensen LE, van Vollenhoven R; ARTIS group. Effectiveness of TNF inhibitor switch in RA: results from the national Swedish register. Ann Rheum Dis 2015; 74:890–6. doi: 10.1136/annrheumdis-2013-204714 PMID: 24431398

37. Askling J, Ernestam S, Forsblad-d’Elia H, van Vollenhoven R, Jacobsson L, Turesson L, et al. Which RA patients end up starting which biologic? A nationwide assessment of differential channelling to biologic treatments in Sweden 2006–2011. Ann Rheum Dis 2013; 72(Suppl3):455.