Treatment Continuation in Patients Receiving Biologics or Conventional DMARD Therapy

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Abstract

Objective: To compare drug survival rates in patients with rheumatoid arthritis (RA) who start on a biologic agent to a control group of patients with a change in DMARD therapy after previous DMARD failure.

Patients and Methods: Patients with RA enrolled in the German biologics register between May 2001 and September 2003 were included in the study. Data were available for 511 patients treated with etanercept (ETA), 343 treated with infliximab (INF), 70 treated with anakinra (ANAK), and 599 controls. Propensity scores were used to select a sub-sample of patients from the control group who were likely to be treated with biologics because of their disease severity, as well as comparable INF and ETA cases.

Results: Treatment continuation after 12 months was similar for ETA (68.6%, (95% CI: 62% - 75%)) and INF (65.4%, (58% - 73%)) but was significantly lower for ANAK (59% (41% - 77%)). Treatment continuation tended to be higher for patients treated with combinations of biologics and DMARDs than for those treated with INF or ETA alone. Patients treated with biologics were significantly more severely ill than those in the control group and had more previous DMARD failures. After adjustment for baseline differences, the continuation rates were significantly higher in patients treated with biologics than in comparable control patients treated with leflunomide (LEF) or LEF/methotrexate (MTX).

Conclusion: Treatment continuation of biologics in clinical practice is lower than in randomized clinical trials but higher than in comparable controls treated with conventional DMARDs.

Key Words. Biologics register, drug survival

Running Title. Treatment continuation with biologics
Introduction

Cytokine inhibitors have opened up new and promising treatment options in rheumatoid arthritis (RA). Randomised clinical trials have demonstrated the efficacy of cytokine inhibitors in reducing inflammation as well as inhibiting joint destruction in active RA, in particular in patients not responding to conventional disease-modifying antirheumatic drugs (DMARDs) (1-5).

Although trial-based evidence and clinical experience to date are encouraging, there is still insufficient information on the long-term safety and continuing efficacy of biologic agents in the general population with RA and in high-risk patient groups (e.g. patients with serious co-morbidity). Concerns have been raised regarding the risk of reactivation of tuberculosis, an increase in other serious infections, and rare but serious events, such as drug-induced lupus or demyelinating disease, as well as the unknown risk of malignancies.

Long-term observational studies on patients treated with biologics have a number of specific strengths. They represent the full spectrum of patients undergoing treatment, including those who would be excluded from clinical trials due to severe co-morbidity. They allow comparison of different treatments and treatment regimens (including off-label use) within one study, and - due to their long-term approach – they present the outcomes of exposure to multiple drugs (administered concomitantly or subsequently). Additionally, they provide information on the cost-effectiveness of new treatments in real-life clinical practice.

Various European countries have established long-term registers of patients treated with biologics. The German register has enrolled an inherent control group, which consists of patients with a change of conventional DMARD therapy because of inadequate disease control or with poor tolerability of at least one previous DMARD. These patients have been followed-up with the same protocol as the patients treated with biologics. This will allow to compare the results in the biologics groups with the overall risks of the disease and its present treatment.

This paper addresses the following questions:

- What is the baseline clinical status of patients with a new start on a biologic therapy in Germany compared with a control group of patients with at least one failure on conventional DMARD therapy?
- What is the drug survival rate over the first 12 months in patients receiving the various biologic agents and in the sub-samples of the control group?

We report data from the German biologics register for patients enrolled up to 1 September 2003. At that point in time, data were available in the biologics group for patients initially treated with etanercept, infliximab or anakinra. Patients in the adalimumab group are not included in this analysis due to the later start of enrolment.
Patients and Methods

Background: In 2001, the German Society of Rheumatology issued a guideline on the prescription of biologic therapies (6) recommending that patients who have failed to respond to or not tolerated at least two DMARDs, including MTX, should be treated with cytokine inhibitors. In conjunction with this recommendation the German Society of Rheumatology invited all rheumatologists to contribute to a national register. The Epidemiology Unit at the German Rheumatism Research Center was charged with maintaining the register, and an advisory board was established by the German Society of Rheumatology. The objectives of this prospective cohort study (known as RABBiT, which is the German acronym for: rheumatoid arthritis - observation of biologic therapy) are to describe the long-term effectiveness of treatment with biologic agents with regard to treatment continuation and clinical outcomes, to study the long-term hazards of treatment with cytokine inhibitors and to establish the direct and indirect costs of biologic therapy versus conventional DMARD therapy.

Patients: Patients aged 18 to 75 meeting the American College of Rheumatology (ACR) criteria for RA were eligible as “cases” if a new treatment with infliximab, etanercept, anakinra (since January 2003) was started and as “controls” if a conventional DMARD therapy was started after failure of at least one previous therapy. Patients could also be enrolled in the control group if another DMARD was added to an existing therapy. Patients were required to give written informed consent at the time of enrolment. The study protocol was approved by the ethics committee of the Charité Hospital, University of Berlin and, where necessary, by the local ethics committee of the participating rheumatology unit.

Patient recruitment is ongoing. In the following analyses patients enrolled up to 1 September 2003 were included. All follow-up data available to March 2004 were used.

Procedures. Each rheumatologist agreeing to participate was provided with the study protocol, study information and informed consent documents for the patients, as well as case report forms. The study protocol stipulates that treatment decisions were not to be influenced by the principal investigators, the scientific advisory board or the pharmaceutical companies sponsoring the register. For reasons of full transparency, all participating rheumatologists received a copy of the contract between the German Rheumatism Research Center and the four pharmaceutical companies. The contract specifies that full responsibility for the conduct of the study, data ownership and publication rights are in the hands of the principal investigators.

Assessments. At each visit, the treating rheumatologist recorded a 28-joint count of tender (TJC) and swollen (SJC) joints, erythrocyte sedimentation rate (ESR; Westergren method), C-reactive protein (CRP), morning stiffness, DMARD and/or biologic therapy including details of start/end, reasons for treatment termination, concomitant therapies with glucocorticoids, NSAIDs, and adverse events. In addition, patients assessed their pain, general health or fatigue on numerical rating scales from 0 to 10 and reported sociodemographic details. Furthermore the Hannover Functional Status Questionnaire (Funktionsfragebogen Hannover, FFbH) was to be completed every 6 months. This instrument is comparable to the HAQ (Health Assessment Questionnaire) and scores can be transformed from one questionnaire to the other (7). The disease activity score based on 28-joint counts (DAS28) was calculated (8). The case report forms were sent by fax to the study center. Queries were sent back in the case of incomplete or inconsistent data. The minimum valid data asked for in every case includes the baseline characteristics, and at follow up the start and end of DMARD and/or biologic therapy, reasons for treatment termination and detailed descriptions of adverse events.

Statistics. The chi-squared test and the non-parametric Kruskal-Wallis test were used to compare the baseline characteristics of the patients. The Kaplan-Meier method was applied to calculate the probability of treatment continuation. Three of these survival analyses were performed for each drug. The first analysis considered treatment termination in total due to adverse events, lack of efficacy, or miscellaneous causes such as noncompliance. In the
second analysis, only those treatment terminations were considered where adverse events were cited as at least one reason for stopping. In the third analysis, the same procedure was followed for lack of efficacy. Treatment terminations due to partial remission were calculated as censored data. Only the continuation of the new treatment applied at study entry was investigated. The following treatment episodes were not considered. Different Kaplan-Meier curves were compared using the log-rank test. The corresponding 95% confidence intervals (CI) of the continuation rates were estimated by the Hall-Wellner method. Cox proportional hazard models were used to investigate the effect of possible risk factors on treatment termination (number of previous DMARDs, rheumatoid factor, DAS28, SJC, TJC, FFbH, disease duration, age, and sex).

As patients in the control group and those in the biologics groups differed significantly in their baseline characteristics, propensity scores were calculated in order to select a more comparable subgroup of patients from the control group. Multivariate logistic regression was applied to estimate the likelihood (propensity score) of being treated with TNF inhibitors (infliximab or etanercept). The following baseline characteristics were included in the multivariate logistic regression analysis: age, number of previous DMARDs, DAS28, and FFbH. Each of these variables discriminated significantly between cases and controls. Twenty-seven out of 120 patients treated at study entry with leflunomide (LEF) alone and 21/141 patients treated with LEF and MTX but only 6/121 patients treated with MTX alone fulfilled the criterion of a propensity score >50% of being treated with TNF inhibitors. We therefore used the 48 patients from the LEF subgroups as fulfilling the above-mentioned criterion for the comparisons.
Results
Between 1 May 2001 and 1 September 2003 a total of 1,523 patients from 109 centres were entered into the RABBIT database. In this population, 599 patients had a change in their conventional DMARD therapy (control group), and 511 patients started treatment with etanercept (ETA), 343 with infliximab (INF) and 70 with anakinra (ANAK).

Patient characteristics. Table 1 shows the baseline clinical status of patients treated with the individual biologic drugs compared with patients in the control group. Two large subgroups of the control group (leflunomide alone (LEF) or leflunomide plus methotrexate (LEF/MTX)) are displayed separately. In patients treated with biologics, the mean age in all groups was 54, and mean disease duration ranged from 9 to 13 years. The patients had very active disease with a mean of more than 10 swollen joints and elevated ESR and CRP. DAS28 and functional status were similar in the biologics groups. Patients in all three groups had a long treatment history with DMARDs. The vast majority had been treated with MTX before, and about three quarters with LEF. Other DMARDs such as sulphasalazine or antimalarials had been tried in a great number of patients, leading to an average number of previous DMARDs of 3.9 to 4.2.

Table 1: Baseline characteristics of patients receiving biologics and in the control groups (SD: standard deviation; IQR: interquartile range)
Patients in the control group had significantly shorter disease duration (p<0.001), a lower prevalence of erosive disease and a lower mean DAS28 (5.4 compared to 6.0 and 6.1, p<0.001) than those in the biologics groups. Patients treated with LEF or LEF/MTX had a higher number of previous DMARD failures (p<0.001), a higher DAS28 (p=0.002) and a higher prevalence of erosive disease (p=0.001) than the other patients in the control group. Therefore they were more suitable than the rest of the control group in terms of comparability with the patients in the biologics groups.

The major difference between the biologics and the control groups was the number of previous DMARD failures: patients receiving biologics had almost two more DMARD failures on average. Most had previous experience with MTX plus a variety of other DMARDs. In addition, only 1.4 to 4.2% of the patients in the control group had been treated with a biologic agent before compared with 30% of those receiving ANAK, 16.4% receiving INF and 9.2% receiving ETA.

**DMARD therapy in combination with biologics.** Although INF is approved for use in combination with MTX, 10.5% of the patients were treated with INF alone at study entry and approximately one quarter of the patients were treated in combination with another DMARD (Table 2). More than half of the ETA patients were concomitantly treated with conventional DMARDs. In 6.7% of the INF patients and 4.7% of the ETA patients, two or three DMARDs were prescribed in addition to the biologic agent.

<table>
<thead>
<tr>
<th>DMARDs currently (%)</th>
<th>Etanercept (%)</th>
<th>Infliximab (%)</th>
<th>Anakinra (%)</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No DMARD</td>
<td>49.7</td>
<td>10.5</td>
<td>30.0</td>
<td>n.a.</td>
</tr>
<tr>
<td>MTX alone</td>
<td>32.7</td>
<td>63.8</td>
<td>60.0</td>
<td>20.2</td>
</tr>
<tr>
<td>LEF alone</td>
<td>7.8</td>
<td>13.4</td>
<td>5.7</td>
<td>20.0</td>
</tr>
<tr>
<td>Other single therapy</td>
<td>3.3</td>
<td>1.7</td>
<td>1.4</td>
<td>4.7</td>
</tr>
<tr>
<td>Combination MTX + LEF</td>
<td>1.8</td>
<td>3.8</td>
<td>1.4</td>
<td>23.5</td>
</tr>
<tr>
<td>Other combination of 2 DMARDs</td>
<td>3.5</td>
<td>4.7</td>
<td>1.4</td>
<td>24.0</td>
</tr>
<tr>
<td>Combination of 3 DMARDs</td>
<td>1.2</td>
<td>2.0</td>
<td>0.0</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Table 2. Current prescription of DMARDs in patients receiving biologics and in the control groups

**Treatment continuation.** Similar drug survival rates were found for ETA (69%, (CI: 62%; 75%)) and INF (65% (58%; 73%)) for the first 12 months of observation (Figure 1). The survival rates for ANAK (59% (41%; 77%)) were significantly lower (p=0.004 ANAK vs. ETA, p=0.03 ANAK vs. INF).

Significant predictors of premature treatment termination were number of previous DMARDs (hazard ratio (HR)=1.09, CI:(1.01;1.18)), rheumatoid factor (HR=1.53 (1.09;2.16) and higher age (HR=1.01 (1.00;1.02)) but not DAS28, TJC, or SJC at baseline.

The drug survival rates for ETA in combination with MTX or another DMARD tended to be higher (p=0.11 and p=0.07) than for ETA alone (Table 3). In the INF group this difference between single and combination therapy was even more apparent. Following adjustment for risk factors of premature treatment termination mentioned above, the hazard ratio (HR) of treatment termination for INF alone in comparison to INF/MTX was 1.9 (1.1; 3.1). For ETA alone versus ETA/DMARD the HR was 1.3 (0.9;1.8).

Reasons for treatment termination were specified by the rheumatologist in nearly all cases (288/290) where treatment with a biologic agent was discontinued. In 28 cases (12 with INF, 15 with ETA, and 1 with ANAK, total 9.8%) more than one reason (lack of efficacy, adverse event, non-compliance) was reported.

Table 3 shows the drug survival rates for the three biologics alone or in combination with DMARDs after 6 and 12 months, taking specific reasons for discontinuation into account. When only terminations due to adverse events were considered, the continuation rates after
12 months ranged from 81.3% for INF (total) to 87.4% for ETA (total). The rates of treatment terminations due to lack of efficacy were very similar for INF and ETA in combination with MTX or other DMARD but lower for ANAK and INF alone. The probability of discontinuation due to other reasons was very low. Furthermore, in 2 cases receiving ETA, 7 cases receiving INF and 1 case receiving ANAK, treatment was stopped due to partial remission. In 8 of these 10 cases, treatment with MTX or LEF was continued.

### Table 3: Treatment continuation of biologics in percent of patients. 95% confidence intervals are given in parentheses.

<table>
<thead>
<tr>
<th></th>
<th>Treatment continuation after six months</th>
<th>Treatment continuation after 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Adverse events ¹</td>
</tr>
<tr>
<td>ETA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>alone</td>
<td>254</td>
<td>71.2 (62.7;79.7)</td>
</tr>
<tr>
<td>+ MTX</td>
<td>167</td>
<td>82.3 (72.2;92.5)</td>
</tr>
<tr>
<td>+ other DMARD</td>
<td>90</td>
<td>84.0 (71.8;96.2)</td>
</tr>
<tr>
<td>total</td>
<td>511</td>
<td>77.2 (71.0;83.3)</td>
</tr>
</tbody>
</table>

| INF      |       |                  |                   |       |                  |                   |
| alone    | 36    | 67.1 (44.0;90.3) | 83.2 (63.3;100)   | 77.7 (54.5;100) | 44.2 (15.9;72.5) | 73.0 (51.1;94.9) | 55.0 (24.9;85.2) |
| + MTX    | 219   | 77.0 (68.6;85.4) | 85.5 (78.5;92.6) | 90.3 (83.2;97.3) | 66.2 (57.4;75.1) | 81.8 (74.5;89.1) | 82.1 (74.6;89.5) |
| + other DMARD | 88 | 80.1 (65.6;94.6) | 90.1 (76.8;100) | 87.9 (73.7;100) | 72.1 (56.8;87.6) | 83.4 (69.1;97.6) | 85.5 (70.9;100) |
| total    | 343   | 76.7 (69.5;83.8) | 86.4 (80.0;92.8) | 88.3 (81.8;94.8) | 65.4 (57.7;73.0) | 81.3 (74.6;88.0) | 80.2 (73.3;87.2) |

| ANAK     |       |                  |                   |       |                  |                   |
| total    | 70    | 66.2 (49.5;83.0) | 83.7 (74.3;93.2) | 79.1 (62.0;96.2) | 59.0 (41.0;77.0) | 83.7 (74.3;93.2) | 70.4 (51.6;89.3) |

1: Only includes termination due to adverse events 2: Only includes termination due to lack of efficacy

Controls treated with LEF or LEF/MTX did not differ significantly in their treatment continuation rates: LEF 76.5% and LEF/MTX 72.7% after 6 months; LEF 67.8% and LEF/MTX 62.4% after 12 months, p=0.28. In both groups the major reasons for treatment termination were adverse events (27.6%) and lack of efficacy (13.2%).

However, these patients were not fully comparable with the patients treated with biologics. We therefore generated propensity scores that predicted the start of a biologic treatment (see Methods). This procedure identified 48 controls receiving LEF or LEF/MTX who had a high likelihood of treatment with biologics, based on their clinical status at study entry. These patients had baseline characteristics similar to 563 patients treated with TNF inhibitors (ETA n=350, INF n=213) who also met the criterion of a propensity score > 50% (Table 4). The two groups differed significantly only in terms of the numbers of previous DMARDs (4.6 vs. 3.9).

### Table 4: Subgroups of patients with propensity score > 50% for treatment with biologics (see Methods).

<table>
<thead>
<tr>
<th></th>
<th>Etanercept or infliximab</th>
<th>Leflunomide</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>563</td>
<td>48</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>52.7 (12.5)</td>
<td>53.2 (11.1)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>78.2</td>
<td>87.5</td>
</tr>
<tr>
<td>Disease duration (yr), median (IQR)</td>
<td>10 (6 – 17)</td>
<td>12 (6 – 19)</td>
</tr>
<tr>
<td>Rheumatoid factor positive (%)</td>
<td>83.3</td>
<td>81.3</td>
</tr>
<tr>
<td>Erosive disease (%)</td>
<td>89.3</td>
<td>85.4</td>
</tr>
<tr>
<td>Swollen joint count, mean (SD)</td>
<td>11.6 (6.3)</td>
<td>10.9 (5.6)</td>
</tr>
<tr>
<td>Tender joint count, mean (SD)</td>
<td>14.4 (7.3)</td>
<td>14.4 (6.1)</td>
</tr>
<tr>
<td>ESR mm/hr, median (IQR)</td>
<td>38 (22 – 58)</td>
<td>30 (20 – 50)</td>
</tr>
<tr>
<td>CRP mg/L, median, (IQR)</td>
<td>23 (8 – 52)</td>
<td>16 (9 – 42)</td>
</tr>
<tr>
<td>DAS28, mean (SD)</td>
<td>6.4 (1.1)</td>
<td>6.4 (0.9)</td>
</tr>
<tr>
<td>FFbH, mean (SD)</td>
<td>49.1 (22.6)</td>
<td>50.4 (21.4)</td>
</tr>
<tr>
<td>Number of previous DMARDs</td>
<td>4.6 (1.5)</td>
<td>3.9 (1.2)</td>
</tr>
</tbody>
</table>


Nevertheless, the patients in the LEF subgroup had lower treatment continuation rates (64.1% after 6 months, 51.0% after 12 months) than patients receiving TNF inhibitors (Figure 2, p= 0.058). This result was confirmed in a Cox regression analysis taking risk factors for premature treatment termination into account. Following adjustment for age, rheumatoid factor, and number of previous DMARDs, there was a significantly increased hazard ratio of 1.7 (p=0.025) for treatment termination with LEF by comparison with INF/ETA.
Discussion

Even though rheumatologists today have access to far more effective drugs compared with a decade ago, a cure remains elusive and all available agents have to be given continuously in order to suppress inflammation and joint destruction. It is known that a majority of patients respond well to MTX therapy, which has high drug survival rates (9). However, if MTX alone is insufficient or not tolerated, other therapeutic options have to be chosen. Much less is known about the long-term survival of the new drugs which are given in the risk group of patients with MTX failure.

The aim of this study was to compare treatment continuation rates of patients with RA treated in daily rheumatologic practice with one of the cytokine inhibitors ETA, INF or ANAK or with LEF or a combination of MTX and LEF over the first 12 months. In order to select controls as similar as possible to the patients treated with biologics, attention was focused exclusively on those patients in the control group who needed more effective therapy than MTX alone or who had intolerance to MTX.

Not unexpectedly, drug survival over one year in our observational data was lower than in the major randomised clinical trials. In the ATTRACT trial (2) drug survival of INF plus MTX was 73%. The TEMPO trial (10) showed drug survival of 76% for ETA alone and 84% for ETA plus MTX. For ANAK, drug survival over 24 weeks was 78% in the 1mg/kg/day group in the study by Cohen et al. (11). Leflunomide alone had a drug survival rate of 80% over 24 weeks in the study by Dougados et al. (12) and 77% in the study of Kremer et al. (13). One possible explanation for the higher treatment continuation in clinical trials relates to the nature of the clinical trial and the wish of both the investigator and the patient to persist whereas in real life they may decide to stop the drug or to change over.

The most important risk factor for treatment termination in our data was a high number of previous treatment failures. Two or more treatment failures have not been used as an inclusion criterion in clinical trials but are a cue for starting biologic therapy in clinical practice.

Therefore, the differences against clinical trials are unsurprising because our data reflect routine day-to-day care in contrast to randomised trials with their rigorous protocols and restricted patient inclusion criteria. Reports from everyday rheumatology practice reveal data that resemble our own findings far more closely than those from randomised trials. In the Netherlands, Flendrie et al. found one-year drug survival rates of 66% for INF and 74% for ETA (14) in patients treated with a biologic for the first time: these findings are very similar to our data for INF (65%) and higher than those for ETA (69% in our study). Chung et al. reported one-year survival rates for INF of 71% from an inception cohort in Canada (15), and this compares well with our data. The higher efficacy of ETA in combination with MTX than of ETA alone reported by van Vollenhoven et al. (16) from the Stockholm TNF-alpha registry is in agreement with our finding of higher continuation rates in ETA combination therapy.

It has to be kept in mind that treatment cessation is subject to within-physician variation. This is especially true for the reasons given in patients who experienced a relative lack of efficacy as well as an adverse drug reaction. Therefore, the total treatment continuation rates are more important than the rates for the various reasons. Furthermore, it is important to note that the physicians enrolled patients for all groups simultaneously. This allows comparisons between patients treated with INF or ETA and those receiving conventional DMARD if the differences in the patient characteristics are taken into account.

Geborek et al. (17) found very low drug survival rates for LEF of about 40% after 12 months in a comparable register of patients with previous DMARD failures, our data indicated relatively better performance for LEF. However, after control for disease severity and other factors influencing drug survival, the TNF inhibitors in our data had higher continuation rates than LEF. The comparison of treatment survival in patients treated with LEF or LEF/MTX on the one hand and TNF inhibitors on the other using the propensity score method showed that adjustment for background risk is essential in order to put treatment results into context.
However, our results need further confirmation as they are based only on a rather small number of control patients.

This study is the first to show data on treatment continuation with various combinations of biologics and conventional DMARDs. The data suggest that combination of both ETA and INF with DMARDs such as MTX or LEF leads to higher treatment continuation. However, the data on combination with LEF or other DMARDs require confirmation by longer observation in the register and by other observational studies.

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Fig. 1: Probability of treatment continuation in patients receiving biologics
Fig. 2: Probability of treatment continuation in patients with an increased likelihood of being treated with TNF inhibitors (propensity score > 50%, see Methods)
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