Rheumatoid Arthritis

Do biologic drugs affect the need for and outcome of joint replacements in patients with rheumatoid arthritis? A register-based study

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A B S T R A C T

Objectives: The aim was to study the incidence of joint replacements among biologic drug and disease-modifying anti-rheumatic drug (DMARD) users as well as to investigate the plausible effect of biologic treatment on survival of prostheses in patients with Rheumatoid arthritis (RA).

Methods: The study population comprised 2 cohorts of patients [Register of biologic treatment in Finland (ROB-FIN) and the Central Finland RA database] from 1999 to 2010. Records of joint replacements performed in the study population between 1980 and 2010 were retrieved from the Finnish Arthroplasty Register. Propensity score matching was used to equalize patient characteristics between biologics and DMARD users. The incidence rates of primary and revision operations were compared between the 2 treatment groups. Kaplan–Meier survival analysis was used to analyze prosthesis survival.

Results: Of the 2102 biologics and 2710 DMARD users identified from the registries, 1587 were included in both groups after the matching. Median follow-up times were 3.1 and 8.0 years, respectively. There were more primary operations per 100 patient years in the biologics (3.89, CI 95% 3.41–4.41) vs. DMARD (2.63, 2.35–2.94) group but slightly fewer revisions (0.65, 0.46–0.88 vs. 0.83, 0.68–1.01). Biologics users were more likely to receive a joint replacement to small joints (p < 0.001). The survival of the prostheses installed during or prior to follow-up was similar in both treatment groups.

Conclusions: The use of biologic drugs did not reduce the need for joint replacement surgery in patients with a similar on-medication disease activity. Despite possibly lower rate of revisions among biologic users, the durability of prostheses was not improved.

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Background and objectives

Joint replacements are commonly used in the treatment of joint damage in patients with RA. An American cohort study of 1600 patients found that 25% of the patients with RA underwent joint replacement surgery during the follow-up period of 22 years [1]. A Norwegian study from 1994 to 2004 reported that while the rate of joint replacements done in patients with osteoarthritis (OA) increased, joint replacement surgeries due to rheumatic diseases declined [2]. Supporting these results, the age-standardized incidence rate of total joint replacements (TJR)
increased from 2 to an even 10 fold from 1986 to 2003 among OA patients in a Finnish country, but remained unchanged for RA patients [3].

Little information is available whether the introduction of biologic drugs in RA patients' treatment has affected the need for joint replacement surgery. The results from a single center in Brazil show a decrease in the numbers of TJRs that occurred simultaneously with widespread induction of biologic therapies, which is in line with a Japanese report [4,5]. A Swedish study found the incidence of hip replacements to be on decline while the need for knee replacements increased [6]. A Finnish study found no decrease in the rates of large joint replacements as a result of intensified treatment with traditional disease-modifying anti-rheumatic drugs (DMARD) [7]. A recently published meta-analysis looked into radiographic progression in RA and summarized that effective anti-rheumatic treatment slowed down the progression by 48–84% at 1 year [8]. Treatment effect of 2 DMARDs was comparable to combination treatment of a biological drug and methotrexate.

Survival of total hip replacements (THR) among the RA patients was found to be similar to OA patients [9], but in knee replacements, RA predisposes to periprosthetic infection [10]. A small proportion of patients require revision surgery, most commonly due to infection, dislocation or aseptic loosening [11]. DMARDs as well as biologic drugs aim to control the inflammation thus preventing the joint damage and premature need for joint replacement [8,12]; however, especially biologic drugs have been suspected to predispose to periprosthetic infections [13]. A review article published in 2007 recommended performing elective surgery before initiating biologic treatment while more recent guidelines advice withholding biologic treatment 1 week before and after the operation [14,15]. It remained uncertain whether sulfasalazine and leflunomide should be discontinued before surgery, whereas methotrexate and hydroxychloroquine were considered safer. In the study by Bongartz et al. [13], perioperative discontinuation of DMARDs and biologics did not statistically significantly reduce the risk of infection.

Our hypothesis was that the use of biological anti-rheumatic drugs reduces the need for joint replacement surgery by slowing down the progression of tissue damage caused by RA. Further, it was hypothesized that biological drugs may slow down aseptic loosening by suppressing the chronic foreign body inflammation-mediated “particle disease” and osteolytic processes around the prosthesis [16] and hence to prolong prosthesis survival. On the other hand, the risk of implant-related joint infections in prothetic joints might be increased.

The aims of our study were to describe the (1) incidence rate of joint replacement surgery among RA patients in Finland and find out if the use of biologics alter (2) the incidence rates of joint replacement surgeries and their revisions during follow-up, or (3) the survival of previously implanted prostheses in general or after stratification by joint, compared to use of DMARDs.

Patients and methods

Patients

Patient data were collected from 3 different sources: the Finnish register of biological treatment in Finland (ROB-FIN), the Central Finland RA database and the Finnish Arthroplasty Register (FAR). The nationwide ROB-FIN register has been maintained since 1999 by the Finnish Society for Rheumatology and includes only patients treated with biologic drugs. Data are collected by rheumatologist using pre-defined data-collection sheets, which are submitted to the register on a regular basis. Currently, over 4500 patients have given their consent to be registered. Approximately, half of the patients have been diagnosed with RA according to the American College of Rheumatology (ACR) 1987 criteria [17]. The estimated coverage is approximately 60% of the Finnish biologics users reported from 17 out of 20 hospital districts in Finland [18].

Data about patients treated with conventional DMARDs were collected from the Central Finland RA database from the Central Finland Central Hospital, Jyväskylä, Finland [19]. The database includes both patient-reported and serological data (the former being annually collected using questionnaires) on patients with RA who used DMARDs and biologics between 1999 and 2009.

The RA population obtained from these 2 sources was linked to the FAR register using the patients’ unique social security numbers to obtain data on their joint replacement operations [20]. FAR is a nationwide database, and its data are based on mandatory reporting by operating hospitals. FAR data have been collected since 1980 and the reporting has been mandatory since 1989 and currently it covers over 95% of all implantations made in Finland [20,21]. FAR is maintained by the Center for Health and Welfare of the Finnish Government (THL). The data on joint replacements were available for this study until November 9, 2010. An ethical consent for the study was granted by the ethical board for internal medicine in Helsinki University Central Hospital (HUCH), while the study approval was acquired from THL.

Biologic use was defined as any exposure to any of the 9 biologic drugs (anakinra, abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab and tocilizumab) approved for treatment of RA and available in Finland during the observation period. Follow-up was defined as the time between the first and last patient report, but truncated to end on November 9, 2010. If the patient had initially used DMARDs and later switched to biologics, only the time on biologics was counted into follow-up. To increase the power of the study, we did not stratify biologic drug users by individual substances. For DMARD users, the individual agents and their combinations used and duration of use were not recorded.

Matching

Due to the differences in patient characteristics in the DMARD and biologic groups, propensity score matching (PSM) was used to match the study groups [22]. A regression model was constructed to describe the unique propensity of each patient to be included in the intervention group without knowing their actual allocation. Variables included in the model were age, sex, time since diagnosis, Health Assessment Questionnaire (HAQ) score, patient global assessment using visual analog scale (0–100 mm), and the number of joint replacements prior to the current follow-up period. If HAQ and patient global assessment were available at more than one time point, their mean values were used. Each patient from the interventional biologics group was paired with a matched control DMARD patient. Patients were matched as long as the difference between the propensity scores did not exceed 0.01. Greedy matching was used, meaning that once a match was made, it was fixed. The differences in patient characteristics between study groups were compared before and after the PSM.

Statistical analyses

Data were analyzed using PASW 18.02 statistical data package (IBM, Armonk, NY) and R 2.14.2 with Epicalc add-on. Additional analyses were done with Microsoft Excel 2007 (Microsoft, Redmond, WA) and MatLab (MathWorks, Natick, MA). The results were analyzed using non-parametric methods, namely Mann–Whitney U-test for pair-wise comparisons and Pearson chi-square
for comparison of relative proportions while the confidence intervals for incidence rates were calculated via a Poisson distribution. The survival of replaced joints was studied using Kaplan–Meier survival analysis. The difference between survival plots was analyzed using log-rank test with Mantel–Cox method. The survival of joint replacements installed during the follow-up was analyzed from the date of surgery onwards, whereas the lifetime of joints implanted prior to the current follow-up were analyzed from the beginning of follow-up onwards. Endpoint in the survival analyses was either the first revision or in its absence, at the end of follow-up. Data were stratified for sub-analyses according to the operated joint and the reason for revision (as reported in FAR). The operated joints were divided into 3 groups: knees, hips, and other joints. Missing disease activity data were imputed by linear interpolation and a sensitivity analysis was performed to further investigate patients with missing data.

**Sensitivity analyses**

Because the patients in the biologic and DMARD groups originated from geographically separate areas, an additional analysis was performed to study an eventual bias caused by differences in the local treatment guidelines and healthcare resources. Biologic users from ROB-FIN were compared to biologic users from Central Finland RA database to find if there were any differences between the incidence rates of primary and revision joint replacement operations.

Additional sensitivity analyses were performed to investigate the eventual bias caused by differences in the duration of exposure (stratified by interquartile range) between biologic and DMARD users as well as to disclose an eventual effect of missing disease activity data (missing data vs. complete data) on incidence rates and outcomes of joint replacements.

**Results**

**Patients**

Overall, 2102 biologics users and 2710 DMARD users were identified from the 2 register sources (ROB-FIN and the Central Finland RA database) for the study. Majority of the biologic drug users came from the ROB-FIN register but 229 additional patients (not reported to ROB-FIN) were obtained from the Central Finland RA database. All 2710 control DMARD patients were obtained from the Central Finland RA database.

There were numerous differences in patient characteristics between DMARD and biologics users before matching (Table 1). Biologics users were more often females, were younger and had more joint replacements prior to follow-up. Patients in the biologics group also had a longer time from the diagnosis of RA to the initiation of follow-up and higher HAQ scores than their DMARD using comparators.

After PSM, the number of patients was reduced to 1587 in both groups while most differences in background data disappeared (Table 1). Despite matching the patient populations, small but statistically significant differences were observed in HAQ scores and time from RA diagnosis. One or more disease activity measurements were missing from 16.0% to 27.5% of biologics and DMARD users, respectively.

Follow-up period in the control group began 4.5 years earlier and ended 1 year earlier compared to biologics users. The median duration of follow-up periods in the biologics and DMARD groups were 3.1 (0.04–10.05) and 8.0 (0.02–12.94), respectively (Table 2). Thus, DMARD group accumulated nearly
appears lower in the biologics (0.65, 0.46–0.88) group than in the DMARD group (0.83, 0.68–1.01) (Table 4). The difference was mostly due to lower rates of hip and knee revisions (although there were no statistically significant differences) and in the rate of other joint revisions the situation was the opposite. There were no statistically significant differences between biologics and DMARD users in reasons for revision.

Results of the survival analyses

According to survival analysis, the patients using biologic drugs were more likely to receive at least 1 prosthesis to joints other than knee and hip during the follow-up period ($p < 0.001$, Fig. 1B). The difference in hip and knee operations between the treatments was not statistically significant ($p = 0.294$, Fig. 1A).

Due to uncertainties in linking primary operations to revisions, 2 primary operations were excluded from the survival analyses of revision operations. Thus, there were 238 and 310 primary operations in the biologics- and DMARD-groups, respectively. A revision was performed in 12 cases (5.0%) in biologics group, of which 3 (1.3%) were due to loosening and 1 due to infection (0.4%), while the corresponding figures for DMARD users were 19 (6.1%), 0 and 3 (1.0%), respectively. The survival of the joints replaced prior to follow-up appeared similar in biologics group compared to DMARD users both in hip and knee ($p = 0.450$) and other joints ($p = 0.571$) (Fig. 2A and B). The primary surgery had taken place 5.2 (median, range 0.1–25.0) and 5.3 (0.01–22.1) years before the follow-up in biologics and DMARD groups with no statistical difference ($p = 0.924$), respectively. The results for prostheses installed during follow-up suggested that while the biologics users might have better survival of hip and knee joint replacements ($p = 0.236$), the situation was reversed regarding other joints ($p = 0.278$) (Fig. 3A and B).

Results of the sensitivity analyses

The comparison between biologics users from ROB-FIN and the Central Finland RA database revealed no apparent geographical bias, as there were no statistically significant differences in rates of primary or revision operations between the nationwide and Jyväskylä county rates. Stratification by the length of exposure revealed that while biologics users with follow-up longer than 9.5 years (fourth quartile) have lower incidence rate of primary operations (2.27, CI 95% 1.61–3.12) compared to un-stratified results, this does not apply to patients on DMARDs (2.72, CI 95% 2.32–3.13). Patients with missing data had shorter follow-up times compared to patients with complete data with median follow-up times of 1.5–6.4 years, respectively. Biologic users with missing data had higher incidence rates of operations compared to complete cases, but only accounted for 8.1% of the patient years.
Discussion

Findings of this study

It is often supposed that the use of biologic drugs would considerably diminish the need for joint replacement [4–6]. Surprisingly, the incidence rate was not lower, but significantly higher among biologics users than in their matched DMARD user controls (Table 4). Survival analysis specifies that biologics users are less likely to survive without small joint replacement while the likelihood to undergo hip or knee replacement is unaffected (Fig. 1). Despite the rapid effect of effective anti-rheumatic treatment on radiologic progression of joint damage, the necessary time to obtain protective effect against joint replacement surgery may be longer than our follow-up time [8]. Patients using biologics experienced their first joint replacement 3.5 years earlier than their comparators on DMARDs. As patients who require biologics usually have aggressive RA, the joint destruction leading to joint replacement may have occurred before the initiation of biologics. Hence, the results with respect to need for joint replacement might be different if biologics were started very early in the course of RA.

Despite the higher rate of primary operations in the biologics group, the overall incidence of revisions appeared lower among the users of biologics than among DMARD users, suggesting that biologics might protect against the need for revision joint replacement. There was no difference between the biologics and DMARD groups in the rate of revisions performed for infection. Although evidence for increased risk of infection due to perioperative DMARD and biologics use is inconclusive, many antirheumatics are nevertheless recommended to be discontinued before the surgery [13,14].

The pathologic process in aseptic loosening is largely driven by wear debris from the prosthesis [16]. Phagocytic cells phagocytose wear debris which again gives rise to a chronic inflammatory host response against foreign bodies that eventually leads to

Table 4

Numbers of joint replacement operations in the matched populations during follow-up.

<table>
<thead>
<tr>
<th>Joint replacements</th>
<th>Incidence rate per 100 patient years (95% CI) a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Biologics</td>
</tr>
<tr>
<td>Primary operations</td>
<td>240</td>
</tr>
<tr>
<td>Hip</td>
<td>58 (24.2%)</td>
</tr>
<tr>
<td>Knee</td>
<td>101 (42.1%)</td>
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<tr>
<td>Other joints</td>
<td>81 (33.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for primary operation</th>
<th>Incidence rate per 100 patient years (95% CI) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>206 (85.8%)</td>
</tr>
<tr>
<td>Other arthritis</td>
<td>0</td>
</tr>
<tr>
<td>Primary osteoarthritis</td>
<td>28 (11.7%)</td>
</tr>
<tr>
<td>Secondary osteoarthritis</td>
<td>4 (1.7%)</td>
</tr>
<tr>
<td>Other reason</td>
<td>2 (0.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Revision operations</th>
<th>Incidence rate per 100 patient years (95% CI) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>40</td>
</tr>
<tr>
<td>Knee</td>
<td>17 (42.5%)</td>
</tr>
<tr>
<td>Other joints</td>
<td>7 (17.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for the revision</th>
<th>Incidence rate per 100 patient years (95% CI) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loosening</td>
<td>8 (20.0%)</td>
</tr>
<tr>
<td>Infection</td>
<td>6 (15.0%)</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Other reason or missing</th>
<th>Incidence rate per 100 patient years (95% CI) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other reason or missing</td>
<td>26 (65%)</td>
</tr>
</tbody>
</table>

* Poisson distribution.

Fig. 1. Kaplan–Meier survival plots indicating the percentage of patients without joint replacements to either (A) hip and knee or (B) other joints during the follow-up.
periprosthetic osteolysis and prosthesis loosening. Also tumor necrosis factor alpha is involved in the process [16] and it is suggested that biologics could slow down the osteolytic process. Although there was no statistically significant difference in the incidence of revisions and survival stratified by joints, there was a tendency indicating that knee and hip revisions would be less common among biologics vs. DMARD users while the situation was reversed regarding other joints (Fig. 3). This is in accordance with the above mentioned hypothesis: wear particles are a particular problem in the weight-bearing metal-on-polyethylene hip and knee joints (in Finland, metal-on-metal and ceramic-on-ceramic joint implants are rarely used), while this is not a clinical problem in e.g. the non-weight-bearing and flexible silicon (rubber) elastomer-based Swanson implants of the metacarpophalangeal joints [11,21]. The higher revision rate in DMARD group than in the biologic drug users could perhaps reflect greater bone destruction or poorer bone quality at the time of primary surgery. On the other hand, because inflammatory cytokines, such as TNF-α, are supposed to play a role in aseptic loosening and because the stimulate osteoclast activity, it could also be that the lower revision rates in the biologic users is due to inhibition of the chronic foreign body inflammation (particle disease). However, this is speculation because these aspects could not be studied in the current setting. Survival of prostheses was similar among the treatment groups although the results gave a weak hint of improvement among biologics users. The plausible improvement in survival of prostheses would be in line with the reduced incidence rate of revision operations.

Strengths and limitations

We combined and matched 2 cohorts of patients and acquired their joint replacement records from the nationwide FAR. Patients missing from the ROB-FIN with 60% coverage, but present in the

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**Fig. 2.** Survival without revisions in joint replacements either to (A) hip and knee or (B) other joints installed prior to follow-up.

**Fig. 3.** Survival without revisions in joint replacements either to (A) hip and knee or (B) other joints installed during follow-up.
Arthroplasty Register with ca. 100% coverage are not likely to form a bias. First, the national Current Care Guidelines define indications for THR, the National Health Insurance covers all citizens for the costs of the THR and the legally defined maximum waiting time for such an operation is 6 months, otherwise the operation is purchased and performed in the private sector at public cost.

Matching was quite successful although the minor difference between HAQ scores of the treatment arms remained statistically significant. The difference between median scores is unlikely to be clinically significant considering mean values were similar [23]. The CRP and ESR values could also have been used as a measure of disease activity but could not be included in the matching model because of too many missing values. At the cost of losing one-third of our patients, PSM enabled comparison of 2 originally heterogeneous groups. On the downside, the patients excluded from the biologics group were likely to be the ones with the most active disease condition, and therefore the largest number of joint replacement operations.

The duration of follow-up was shorter among patients with missing data compared to patients with complete data, suggesting that the data might be not missing at random. Despite the higher incidence rate of joint replacements among the biologics users with missing data, the subgroup only accounts for 8% of the patient years and thus, has only minor effect on the results of the study.

Median follow-up duration is vastly different between patients on biologics and those on DMARDS, and this issue is not cleared by the propensity score. Therefore, results were stratified by years of exposure. While the duration of exposure–response relationship was generally well established, biologic users with follow-up of over 9.5 years were an exception with lower incidence rate of revisions. While the finding may be confounded, the difference in follow-up durations could nevertheless, be considered an eventual source for bias. Although the follow-up period in biologics group is quite short (3.03 years in average) compared to DMARDs group it is to be emphasized that the incidence rate of revisions covers all previous joint replacement operations, even those which took place more than 10-15 years ago and were implanted between 1980 and 2010. Further, survival analyses technically enable an unbiased comparison between groups with unequal follow-up times.

We did not analyze individual biologic drugs separately due to a tendency to switch from one biologics to another, which would have led to even shorter follow-up periods. Medication data other than the actual use of biologics or DMARDs were not available in all control patients and therefore is not reported. Regardless of what treatment (DMARD or Biologic) the patient received, those with higher disease activity (disease not under control) at the initiation of the treatment might have more joint replacement surgeries. These data were lacking from the DMARD cohort. Therefore, the current study only compares the incidence rates and outcomes of joint replacements in groups with different treatment modes and in patients with apparently similar disease activities.

Our data do not explicitly reveal whether the use of biologics was discontinued for the joint replacement surgery, but published guidelines encourage a halt in the use of biologics at least 1 week prior and after operation [15]. We included all joint replacement operations in the analyses including those performed due to osteoarthritis as it may not be clear whether osteoarthritis was primary or secondary and because all patients in our population had been diagnosed with rheumatoid arthritis. Nevertheless, majority of primary operations were registered to be performed for RA.

Many countries lack comprehensive registries, which in part is the reason why this is the first report of its kind. Collecting data regarding DMARD users from a single county could have caused bias, but we observed no geographical differences in the incidence rates of joint replacements in the sensitivity analysis. Although the FAR covers nearly all primary and revision operations performed in Finland, it does not reliably detect infections that are treated non-operatively [10,20]. Moreover, the number of revision joint replacements was relatively low and therefore our analyses concerning different reasons for revision, particularly infections, should be considered preliminary. Although our cohort is likely to be a representative sample of Finnish RA population, the results may not be generalizable to other countries due to differences in the treatment guidelines.

Conclusions

We tested the assumption that the use of biologic drugs would diminish the need for joint replacement surgery in patients with RA. Contrary to our hypothesis the incidence rate of operations to joints other than hip was higher among biologics users while the incidence of revision operations, on the other hand, appeared lower in biologics users. Biologic anti-rheumatic drugs were not found to be associated with increased risk of infection. Despite possibly lower rate of revisions among biologic users, the durability of prostheses was not improved compared to DMARD users. The findings of the study should however, be viewed in light of the limitations and eventual sources for bias. Despite matching, the plausible difference in pre-treatment disease activity might be confounding the results. More research on the subject is needed and while a randomized controlled trial would provide the strongest evidence it may be not feasible considering the long-term outcomes.

Acknowledgments

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