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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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ABSTRACT

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.

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)

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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 prosthetic 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 biologics 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