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Impact of Etanercept Therapy on Disease Activity and Health-Related Quality of Life in Moderate Rheumatoid Arthritis Patients Population from a National British Observational Cohort

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ABSTRACT

Objectives: To describe a population with moderate rheumatoid arthritis (RA) before biologic initiation and assess change in disease status, health-related quality of life (HRQOL), and adverse events in etanercept (ETN)-treated patients. **Methods:** Data on adult patients with moderate RA (3.2 < Disease Activity Score in 28 Joints [DAS28] ≤ 5.1) were retrospectively analyzed from the British Society for Rheumatology Biologics Register comparing a nonbiologic-treated group (nBG) using at least one traditional disease-modifying antirheumatic drug to a biologic group (BG) treated with ETN. The HRQOL was assessed by using the Health Assessment Questionnaire disability index score. To mitigate confounding, we controlled for drivers of progression. Appropriate univariate, multivariate, and regression analyses were used. **Results:** A total of 1754 patients with RA were assessed (211 BG and 1543 nBG). Compared with the nBG, the BG tended toward higher disease activity, such as significantly higher tender joints and DAS28. The BG compared with the nBG had 1) a greater reduction in DAS28 and Health Assessment Questionnaire scores; 2) disease remission occurring more often (odds ratio = 2.7; $P = 0.006$); and 3) progression occurring in fewer patients (odds ratio = 0.3; $P = 0.002$). BG patients had a higher incidence of "other serious infection" and "other central nervous system–related events," with no significant differences in associated hospitalization rates or deaths. **Conclusions:** Among patients with moderate RA from a clinical practice registry, ETN-treated patients had significantly higher disease activity at the time of biologic initiation but significantly reduced disease activity and better HRQOL after 6 months compared with nBG patients, although the possibility of unmeasured confounding remains. The ETN group reported significantly higher incidences of "other serious infections" and "other central nervous system–related events" without higher hospitalization rates.

Keywords: etanercept, health-related quality of life, rheumatoid arthritis, treatment comparison.

Introduction

Historically, various immune-modulating agents have been used in patients with rheumatoid arthritis (RA); however, one had to be mindful of toxicities linked to idiosyncratic dosing of the therapy either alone or in combination therapy. Several recently completed randomized controlled trials demonstrate that an early and aggressive approach to treatment has emerged as a key intervention for controlling disease activity effectively and achieving optimal results [1,2]. More than two-thirds of European rheumatologists surveyed reported the presence of symptoms for less than 3 months as "early" RA. These same surveyed rheumatologists said that 50% of their patients are referred after 6 months of disease [3]. RA may initially be treated with nonpharmacologic or over-the-counter therapies, especially when the diagnosis is still in question. Once a diagnosis is suspected, primary care or other non-RA specialists may start with a high-dose nonsteroidal anti-inflammatory drug and steroids. Some may even begin one or more disease-modifying antirheumatic drug (DMARD) as they transition the patient to a specialist; yet this is not always the case. A biologic response modifier may be recommended by the specialist if active disease and inflammation persists despite high doses of one or more DMARDs, particularly in the presence of prognostically unfavorable factors [4]. In this case, an anti–tumor necrosis factor agents, such as etanercept, adalimumab, or infliximab, are usually recommended, along with methotrexate.

Previous work on the real-world burden of disease of patients with RA highlighted low health-related quality of life (HRQOL) at the time a decision is made to move past DMARDs onto biologic

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therapy [5]. Previous studies have shown that early aggressive management of RA has resulted in better clinical and radiographic outcomes [6]. Yet, the impact of biologics on clinical and patient-reported measures in patients with moderate RA remains unclear because there is limited data available in this population. Despite indications for treatment, the patient population with moderate RA is often not considered when assessing the impact of biologic therapy because of a perception of lower levels of disease burden.

The first objective of this study was to explore the clinical characteristics of patients with moderate RA, their real-world pathway from one treatment to the next treatment, and treatment outcomes through an analysis of longitudinal patient-level registry data. Specifically, we aimed to assess, at the time of RA therapy initiation, the baseline disease characteristics, sociodemographic characteristics, initial treatment profile, and quality of life of two cohorts of patients with moderate RA, one newly exposed to etanercept (Enbrel) and the other exposed to other nonbiologic therapies. The second objective of this study was to assess the change over time in disease characteristics, adverse events (AEs), treatment patterns, treatment, quality-of-life outcomes, and resource utilization within these two cohorts.

The National Institute for Health and Care Excellence guidance [7] states that only those patients who achieve an improvement of at least 2.1 points in the Disease Activity Score in 28 Joints (DAS28) after 6 months of etanercept therapy can remain on etanercept; thus, results pertaining to the 6-month follow-up will be emphasized in findings relative to 12- and 24-month findings.

Methods

Patient Population

This was a nonexperimental, retrospective cohort study that used anonymous UK patient-level data provided by the British Society for Rheumatology Biologics Register (BSRBR) [8]. The BSRBR, established in the United Kingdom in 2001, is a national prospective observational study that enrolled patients with RA initiated on biologic therapies (etanercept, infliximab, or adalimumab), thereby monitoring the long-term safety of biologic drugs and providing valuable information about their long-term effects. Recruitment of 4000 patients with RA treated with each of the three biologic drugs, along with 4000 biologic-naive patients with active RA receiving standard DMARD therapy, was targeted at the start of the study [9]. This target for the etanercept cohort was met in 2005, for the infliximab cohort in 2007, and for the adalimumab cohort in 2008. Before recruitment targets were achieved, it was estimated that more than 80% of the patients with RA treated with biologics were registered on the BSRBR out of the estimated 7% of the patients with RA treated with biologics in the United Kingdom [10].

Baseline Data

A standard baseline questionnaire was completed by the consultant or specialist nurse at enrollment for both biologic and DMARD cohorts. The questionnaire collected data on demographic characteristics; the 1987 American College of Rheumatology (ACR) criteria for RA; and clinical characteristics including previous joint replacement or surgery, systemic features, and components necessary to calculate the DAS28 (such as tender joint count, swollen joint count, erythrocyte sedimentation rate, C-reactive protein, and patient global visual analogue scale [VAS] score); details of all previous and current DMARD therapy; and comorbidities including hypertension, angina, stroke, and diabetes. The patients were also asked to complete a separate questionnaire collecting data on smoking habits, occupational history, as well as quality-of-life instruments such as the Health Assessment Questionnaire (HAQ) for British use [11] and the Medical Outcomes Study short-form 36 health survey (SF-36) (assessed by Physical Component Summary [PCS] score, Mental Component Summary [MCS] score, and vitality domain score).

Follow-Up Data

All patients with RA in both cohorts were followed for 5 years, during which follow-up took place every 6 months for the first 3 years and then annually for the next 2 years. At each follow-up visit, the clinician completed a questionnaire documenting changes to antirheumatic therapy, reasons for discontinuation, and current DAS28-related evaluations. The follow-up questionnaire also incorporated details of AEs including whether the AE was related to the biologic therapy and the outcome of the AE, such as hospitalization or death. For the first 3 years of the study, the patients completed a diary every 6 months that incorporated information on any new medical diagnoses/illness, new drugs, and hospital admissions. Also, information was collected from patients regarding HAQ and SF-36 questionnaires. Furthermore, all patients were flagged with the UK Office for National Statistics, which provided information on mortality including the cause of death [9].

Inclusion and Exclusion Criteria

From previously published BSRBR criteria [12], patients with moderate RA as defined by a DAS28 (>3.2 and ≤ 5.1) and age 18 years and more at the time of diagnosis were eligible for inclusion in the analysis. The study compared two groups: 1) The biologic group (BG)—Patients with moderate RA newly starting therapy with a biologic (etanercept/Enbrel). These patients may or may not be treated with nonbiologic DMARDs before initiating treatment with etanercept for RA. 2) The nonbiologic group (nBG)—Patients were selected if they had moderate RA, were receiving a DMARD, had no history of exposure to biologic therapies, and were felt to have moderately active disease. New use of a nonbiologic DMARD was not required for comparator patients.

Statistical Analyses

All study subjects with moderate RA satisfying the inclusion/exclusion criteria were considered for analysis. For postbaseline treatment comparisons of the BG and the nBG, intent-to-treat analysis was performed in which the treatment assigned at the baseline was used irrespective of the treatment received during the observational period.

Baseline sociodemographic characteristics, disease characteristics, initial treatment profile, baseline DAS28-related evaluations, and HRQOL were compared between the BG and nBG patients. Continuous variables were compared using the two-sample t test, whereas categorical variables were evaluated using the chi-square test or the Fisher exact test as appropriate.

Change in DAS28-related evaluations and HRQOL from baseline to 6-, 12-, and 24- month follow-up visits was evaluated using analysis of covariance between the BG and nBG patients. Assessment of change in DMARD therapy and development of AEs at 6-, 12-, and 24-month follow-up visits between the two groups was carried out using the chi-square test or the Fisher exact test as appropriate.

Improvement in RA defined by ACR criteria (ACR20 $\geq$20% improvement in tender joint count, $\geq$20% improvement in swollen joint count, and $\geq$20% improvement in three of the