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The durability of abatacept as a first and subsequent biologic and improvement in HAQ from a large multi-site real-world study

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A R T I C L E   I N F O

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A B S T R A C T

Objectives: Assessment of the effectiveness of newer biologics such as abatacept is essential in real-world practice.
Methods: RA patients administered infusions of abatacept via the Orencia Response Program network with at least one follow-up evaluation were included. The number needed to treat (NNT) to improve HAQ by at least the minimal clinically important difference (MID $\geq$ 0.22) and abatacept survival and differences between biologic-naïve and TNFi-experienced patients were assessed.
Results: Among 2929 patients enrolled, 1771 (60.5%) were eligible for analysis (mean age was 57.6 years, disease duration was 16.5 $\pm$ 11.0 (SD) years, 77.2% were female, and 79.2% had past TNFi), with mean follow-up of 13.8 $\pm$ 12.3 (SD) months. Half had comorbidities including hypertension (17%), diabetes (8.4%), asthma (6.0%), hypothyroidism (5.7%), and hyperlipidemia (4.0%). Mean (SE) durability of treatment was 26.8 (0.53) months, where 66% were receiving abatacept at 12 months and 53% at 24 months. Patient survival was longer where abatacept was the first biologic vs. post-TNFi ($P = 0.0001$). In the use of abatacept as a first biologic, 70% achieved MID in HAQ vs. 71% if post-TNFi ($P = 0.65$) with NNT to improve one patient with at least MID of HAQ was 1.4.
Conclusions: Abatacept is effective in improving HAQ in RA both pre and post first biologic in real-world patients with comorbidities. For those still on abatacept, HAQ continued to improve over the first 2 years. The durability of abatacept is better as a first biologic, but NNT to improve HAQ patients on treatment is the same post-DMARDs and post-TNFi. For treatment durability and HAQ MID achievement, abatacept use as a first biologic is better.

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Introduction

Randomized trials may or may not be generalizable to daily practice [1]. Real-world effectiveness for rheumatoid arthritis (RA)

medications may sometimes yield different results than efficacy data from randomized controlled trials (RCTs) due to the inclusion of different patients including those with more comorbidities, less adherence, different baseline previous drug exposures, concomitant interventions, and different disease activity [2,3]. It is important to be aware of the effectiveness of non-TNFi biologics in the real world with respect to treating patients with various comorbidities, including the benefit and durability of biologics such as abatacept. Patient registries represent a valuable supplement to randomized controlled trials enabling investigations beyond the highly controlled conditions of RCTs.

There are several RCTs with abatacept that estimate the treatment effect under conditions of strict inclusion and exclusion criteria including post-DMARD inadequate response, and post-TNFi use [4–8]. This is a retrospective analysis of the Canadian Orencia Response Program (ORP). The ORP is a database of patients enrolled by their physicians who prescribed abatacept under usual

care. Abatacept was administered IV and was infused in outpatient clinics or at home. Due to real-world access of abatacept over the years studied, many of the patients had tried multiple biologics previously, so we speculated there could be differences from results of previous trials as the patients would presumably be less responsive and have reduced retention as numerous registries have demonstrated that 2nd or more biologics have blunted rates of high response (remission and ACR50 responses) and less durability [9–12].

One can help determine effectiveness of drugs by studying the number needed to treat (NNT) for a measured improvement. The Health Assessment Questionnaire Disability Index (HAQ) reflects functional impairment in RA [13]. It can predict further disability, hospitalizations, and mortality [14–16]. Most RCTs in RA have shown large improvements in HAQ (0.5 at 6 months to 1 year) for TNFi [17,18], but the response has been less in observational studies [19,20]. It is widely reported that the minimal important change in HAQ is at least 0.22 [21]. The NNT for HAQ in RA with TNFi treatment has been reported as 1.94 in a single-site study of TNF treatment [22]. Genovese et al. [7] found in a RCT of abatacept that 47% of patients treated with abatacept for 6 months had at least a reduction (improvement) in HAQ of 0.3, post failure of TNFi. The NNT to improve HAQ by at least the minimal important change in real-world abatacept treatment, both as a first and subsequent biologic, has not been fully ascertained.

Data from routine clinical practice describing effectiveness as measured by treatment persistence and HAQ score are lacking. The data derived from the ORP database are uniquely suited to address the question of effectiveness of abatacept by changes in function over time and durability in real-world patients with various comorbidities. The objectives of this study were to (1) describe the real-world Canadian patients who received abatacept in the ORP including comorbidities and (2) determine the effectiveness of abatacept in Canadian RA patients by examining persistence of therapy and changes in HAQ overall and according to previous biologic use (none vs. one or more).

Methods

Data on patients administered abatacept in routine clinical practice via the ORP network between August 10, 2006, and February 2011 were obtained. ORP is a patient support program established to facilitate access to abatacept treatment and reimbursement among patients prescribed abatacept under usual care. Within this context, demographic, insurance, and medical information required for these purposes are collected. In the current analysis, all adult (≥18 years of age) administered abatacept with at least one follow-up evaluation where the HAQ was available were included. Patients who did not receive their abatacept via the network (i.e., where the ORP nurses did not collect the data) were excluded (as the data did not have IRB approval and may have not been systematically collected). ORP nurses collected a HAQ at every infusion. Demographic variables including age, gender, residence (province), baseline comorbidities, prior biologic treatment, HAQ at q6 monthly follow-up visits, and durability of abatacept were recorded. Comorbidities were collected at the baseline visit by the nurse from the ORP using standardized forms and patient self-report.

Durability of response was measured by the proportion of patients continuing abatacept over the variable length of time until dropout or last follow-up. An exploratory analysis was conducted to study the NNT to improve HAQ by at least the minimal important difference (MID) which is ≥0.22 [21]. Differences between biologic-naïve and TNFi-experienced patients

(previous use of one or more TNFis and other biologics) were compared.

Statistical analyses

Descriptive statistics including measures of central tendency (mean) and dispersion [standard deviation and 95% confidence intervals (CI) of the mean] for continuous variables and frequency distributions for categorical scale variables were produced. Between-group differences in patient characteristics were assessed for statistical significance using the independent-samples t-test for continuous variables and the Fisher's exact test or the chi-square for categorical variables, as appropriate. Durability of abatacept treatment was assessed with the Kaplan–Meier estimator of the survival function. Between-group (biologic naïve vs. biologic experienced) differences in HAQ improvement over time while adjusting for possible confounders were assessed using mixed models with repeated measures. Predictors of HAQ MID achievement were assessed using binary logistic regression. In addition, the impact of prior biologic exposure on HAQ MID achievement was also assessed using generalized estimating equations (GEE) and Cox regression. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC) and were based on available data. The physician and patient could choose where to be infused (within the network or elsewhere).

As this study is descriptive in nature, and no formal a priori sample size calculation was done.

Ethics approval

Data were collected at usual infusion visits for patients receiving abatacept using a central ethics review board approval, and patients signed a consent form. The analyses were also approved by the University of Western Ontario (Western) Ethics Review Board (review number, R-11-516, Health Sciences REB#18379E).

Results

Among the 2929 patients enrolled, 1771 (60.5%) were eligible for this analysis with a mean age of 57.6 years, long mean disease duration of 16.5 years (SD = 11.0), 77.2% were female, and most had past-TNFi exposure (79.2%). Patients included in the analysis were not significantly different with respect to demographics and geographic distribution from those not included (data not shown). The patients were from nine provinces, with Quebec enrolling 39%, Ontario 29%, and British Columbia 11% of the patients). The main lack of eligibility was due to patients not infusing in the ORP network (most of the patients who were not included) and some awaiting coverage. The mean (SD) follow-up in the database was 13.8 (12.3) months. Only 1/5 of the patients were biologic naïve; 28% had one previous biologic, 31% two, and 16% three previous biologics (Table 1). Comparisons between patients where abatacept was the first biologic vs. use as a subsequent biologic show that the latter were different (higher baseline HAQ and longer disease duration, but they were not older and they were more likely to discontinue abatacept and stop it earlier). Comorbidities were frequent. The most common included hypertension (17%), DM (8.4%), asthma (6.0%), hypothyroidism (5.7%), and elevated