Clinical Immunology 191 (2018) 67–74

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Comparison of efficacy of TNF inhibitors and abatacept in patients with rheumatoid arthritis; Adjusted with propensity score matching

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ARTICLE INFO

Keywords:
Rheumatoid artritis
Rheumatid factor
TNF inhibitors
Abatacept
Propensity score matching

ABSTRACT

The aim of this study was to compare the clinical outcome of patients with rheumatoid arthritis seen in routine clinical practice treated with either TNF inhibitors or abatacept. To overcome potential bias, both propensity score matching and Inverse Probability of Treatment Weighting were used for patient selection. The propensity score matching procedure selected 315 matched pairs of patients who were treated with TNF inhibitors or abatacept. At week 52, SDAI in TNF inhibitors was lower than abatacept. In contrast, analysis of biologics-naive patients using the propensity-score matching (n = 150; in each group) showed comparable clinical efficacy. Consistent results were obtained by the use of Inverse Probability of Treatment Weighting (581 patients treated with TNF inhibitors and 353 patients treated with abatacept). The predictors of response to each treatment were different; abatacept appeared to benefit patients with high baseline RF titers while TNF inhibitors appeared to benefit patients with low baseline HAQ-DI.

1. Introduction

With the development of TNF inhibitors, clinical remission has become the primary goal in the treatment of rheumatoid arthritis (RA) [1]. The other new drug introduced for the treatment of RA, abatacept, prevents T cell activation by inhibiting costimulatory signals, and its safety and effectiveness have been established in several clinical studies [2–6]. Moreover, the AMPLE (Abatacept Versus Adalimumab Comparison in Biologic-Naive RA Subjects with Background Methotrexate) clinical trial in RA patients with inadequate response to MTX, showed similar efficacy of abatacept and adalimumab [7,8]. Based on these data, the 2016 update on treatment does not recommend one over the other [9]. To our knowledge, however, there are no studies that have compared the efficacies of abatacept and adalimumab in routine clinical practice, and there is limited advice on drug selection [10].

Randomized control trial (RCT) is the gold standard clinical trial as it provides high quality evidence. However, there are limitations to RCTs [11]. In RCTs, the study subjects are selected using inclusion and exclusion criteria. Such exclusions may impair the generalizability of results [12]. On the other hand, observational studies typically involve patients who are commonly encountered in daily clinical practice; however, the study participants are subject to selection bias due to the uncontrolled differences. To overcome this issue, sophisticated statistical methods are often used to reduce the selection bias. The propensity score matching [13,14] and Inverse Probability of Treatment Weighting (IPTW) [15,16] are the most popular methods applied in clinical research to reduce selection bias by adjusting for potential confounding factors [17,18]. However, these methods also have some limitations. The propensity score matching requires certain number of subjects because matched patients have to be extracted from a primary study population. On the other hand, the IPTW carries the potential problem of emphasizing the importance of unusual cases in the study population. For this reason, it is important to use both methods in order to show consistent results.

The objective of this study was to compare the efficacy of TNF inhibitors and abatacept in routine practice using propensity score matching and IPTW, and to determine the predictive factors of the efficacy of the two drugs.

2. Material and methods

2.1. Patients and study design

All patients who started treatment with TNF inhibitors (which include etanercept, adalimumab, golimumab, and certolizumab pegol) or abatacept between November 2010 and January 2016 at our hospital

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https://doi.org/10.1016/j.clim.2018.03.018
Received 15 September 2017; Received in revised form 28 March 2018; Accepted 28 March 2018
Available online 31 March 2018
1521-6616/

Table 1
Baseline characteristics of the RA patients adjusted with the use of propensity score matching.

Characteristics	Total			Bio-naive patients		
	TNF inhibitors (n = 315)	Abatacept (n = 315)	P value	TNF inhibitors (n = 150)	Abatacept (n = 150)	P value
Age (years)	63.6 ± 13.1	64.0 ± 14.4	0.75	65.0 ± 12.6	64.4 ± 14.5	0.71
Gender (% female)	86.3	86.0	0.91	86.0	86.7	0.87
Disease duration (years)	9.3 ± 8.8	9.6 ± 10.0	0.73	8.1 ± 10.0	7.7 ± 9.5	0.72
Stage (I/II/III/IV %)	18/42/22/18	17/42/22/19	0.99	24/42/18/16	16/40/23/21	0.87
Prior use of biologics (%)	49.5	48.9	0.87	0.0	0.0	1.00
(Prior use of TNFi)	29.5	31.1	0.66	0.0	0.0	
(Prior use of Non-TNFi)	3.8	7.9	0.03	0.0	0.0	
(Prior use of both TNFi and non-TNFi)	15.6	10.5	0.06	0.0	0.0	
MTX use (%)	69.2	71.1	0.60	69.3	74.7	0.30
MTX dose (mg/week)	12.0 ± 3.7	11.9 ± 3.6	0.82	12.4 ± 3.5	11.7 ± 3.7	0.87
Glucocorticoid use (%)	25.7	25.4	0.93	26.0	23.3	0.59
Glucocorticoid dose (mg/day)	1.3 ± 3.1	1.6 ± 5.0	0.27	1.4 ± 3.3	1.4 ± 3.8	0.96
SJC, 0–28	6.4 ± 5.0	6.4 ± 4.8	0.95	6.3 ± 4.3	6.3 ± 4.4	0.89
TJC, 0–28	7.8 ± 6.0	7.8 ± 6.2	0.90	7.7 ± 5.3	7.7 ± 6.1	0.90
GH, VAS 0–100 mm	52.1 ± 25.5	52.6 ± 25.6	0.82	49.7 ± 24.8	51.3 ± 23.9	0.57
EGA, VAS 0–100 mm	42.8 ± 20.2	42.4 ± 21.9	0.79	41.9 ± 19.3	41.1 ± 19.2	0.71
DAS28-ESR	5.3 ± 1.3	5.3 ± 1.3	0.87	5.4 ± 1.1	5.3 ± 1.1	0.83
SDAI	25.2 ± 12.7	25.2 ± 12.7	0.96	24.6 ± 10.7	24.8 ± 11.1	0.88
HAQ-DI	1.4 ± 0.9	1.4 ± 0.8	0.94	1.3 ± 0.9	1.3 ± 0.8	0.79
CRP (mg/dL)	1.6 ± 2.6	1.5 ± 2.2	0.96	1.5 ± 1.9	1.4 ± 1.8	0.79
ESR (mm/h)	46.1 ± 30.6	47.2 ± 29.7	0.66	50.0 ± 29.2	48.5 ± 29.1	0.64
RF (U/ml)	162 ± 301	166 ± 310	0.87	180 ± 359	170 ± 327	0.81
MMP-3 (ng/mL)	179 ± 193	195 ± 205	0.30	200 ± 206	199 ± 199	0.96

Data are mean ± SD, or number (%) of patients.
TNFi TNF inhibitors, MTX methotrexate, SJC swollen joint count, TJC tender joint count, GH VAS patient's global assessment of disease activity visual analogue scale, EGA VAS evaluator global assessment of disease activity visual analogue scale, DAS disease activity score, SDAI Simplified Disease Activity Index, HAQ-DI health assessment questionnaire disability index, CRP C-reactive protein, ESR erythrocyte sedimentation rate, RF rheumatoid factor, MMP-3 matrix metalloproteinase 3.

were registered in the study (FIRST registry). The diagnosed of RA was based on the revised criteria of the American Rheumatism Association 1987 or the 2010 classification criteria of the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) [19–21]. The study was approved by the ethics review board of our university and was conducted as a non-blinded, retrospective observation study using anonymized data (approval number #H27-014). TNF inhibitors and abatacept were used within the health insurance coverage for RA in Japan. The observation period of the study was 52 weeks.

2.2. Treatment with abatacept and TNF inhibitors

TNF inhibitors and abatacept were prescribed for patients whose RA could not be controlled adequately by the standard doses of existing disease-modifying anti-rheumatic drugs (DMARDs). The list of biological DMARDs used by these patients appears in Supplementary Table 1.

2.3. Clinical efficacy and outcome

The primary outcome was disease activity at week 52, measured by the Simplified Disease Activity Index (SDAI) [22,23]. Additional secondary outcomes included retention rate and safety at week 52. Functional impairment was assessed using the health assessment questionnaire disability index (HAQ-DI) [24].

2.4. Propensity score matching and inverse probability of treatment weighting

Propensity score matching was conducted as described previously [25]. Briefly, the propensity score was estimated employing a multivariable logistic regression model to predict the use of abatacept, using the following key variables: age, sex, RA disease duration, prior use of biologics, methotrexate use, oral glucocorticoid use, SDAI, tender joint count, swollen joint count, patient's global assessment (PGA), physician's global assessment (EGA), DAS28-ESR, rheumatoid factor (RF), MMP-3, ESR, CRP and HAQ-DI. Patients were statistically extracted in each group based on the propensity score.

The IPTW is based on the propensity score and was also used as the primary tool to adjust for differences between the two treatment groups. By giving a weight of 1/(propensity score) to all subjects in the abatacept group, and 1/(1–propensity score) to TNF inhibitors group, the distribution of the baseline variables in each group became equal to the distribution in both groups combined. Patients with missing data at baseline were excluded since the propensity score could not be calculated (39 of 620 patients of the TNF group and 31 of 384 patients of the abatacept group). To include all patients in the analysis, the last observation carried forward (LOCF) method was used for patients who discontinued the medication before week 52.

2.5. Other statistical analyses

Patients characteristics were expressed as mean ± standard deviation or number (%) of patients. Kaplan–Meier method was used to assess the retention rates, and the differences between TNF inhibitors group and abatacept group were analyzed by the log-rank test. The paired *t*-test was used to detect differences in disease activity between baseline and week 52. Stepwise multiple regression analysis was performed to identify prognostic factors. The optimal cutoff value for the prognostic factor was calculated using receiver operator characteristic (ROC) curve analysis. All reported P values are two-sided and was not adjusted for multiple testing. The level of significance was $P < 0.05$. All analyses were conducted using JMP version 11.0 (SAS Institute Inc., Cary, NC) or SPSS software version 24.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Baseline characteristics by using propensity score matching

All patients who started treatment with TNF inhibitors (n = 620) and abatacept (n = 384) between 2010 and 2016 were enrolled in the