EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2019.19144

Original Article

Effects of biologic drugs on the prognosis of rheumatoid arthritis among patients with poor diabetes control

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Abstract

Objective: To investigate the effects of biological disease-modifying antirheumatic drugs (bDMARDs) on diabetes control among patients with rheumatoid arthritis (RA).

Methods: A total of 296 patients with RA were included in the study. The following background factors were investigated: age, gender, bDMARD type, methotrexate and prednisolone (PSL) dosages, glycated hemoglobin (HbA1c), C-reactive protein, and matrix metalloproteinase-3. We used the simplified disease activity index (SDAI) to evaluate the RA disease activity. Poor diabetes mellitus (DM) control was defined as a HbA1c of 6.0; accordingly, the patients were divided into good and poor DM control groups. SDAI and PSL dosage were the primary endpoints, respectively, 1 year later.

Results: HbA1c ranged from 6.6±0.68 to 6.5±0.82 and 5.1±0.29 to 5.4±0.34 in the poor and good DM control groups, respectively. Although the intergroup difference was significant (p=0.000), there was no significant intergroup difference during the treatment period (p=0.084). The SDAI ranged from 27.7±15.6 to 7.1±8.0 in the group with a poor DM control (n=83) and from 22.9±14.0 to 6.3±7.6 in the group with a good DM control (n=213).

Conclusion: The bDMARD therapy reduced the RA disease activity regardless of a good or poor DM control.

Keywords: Rheumatoid arthritis, HbA1c, biologic drugs

Introduction

Antirheumatic drugs such as methotrexate (MTX) and treatment with biological disease-modifying antirheumatic drugs (bDMARDs) have come to provide desired therapeutic effects in the treatment of rheumatoid arthritis (RA). However, RA is known to cause various complications, and the treatment and maintenance of complications are very important (1).

Diabetes mellitus (DM) is a common disease, and its complications such as neurological disorders, eye disorders, and renal disorders are well known. It also causes various complications in the cardiovascular system. As a result, it often leads to death. A good diabetes control is important for preventing complications. Since corticosteroids adversely affect glucose metabolism, it is a standard practice to avoid using these drugs as much as possible for RA treatment. However, they can be used in small amounts.

In this study, we investigated the effects of bDMARDs on diabetes control among patients with RA, as it has not been examined before.

Methods

The study used a cross-sectional design. It was conducted between January 1, 2013, and December 31, 2016. This multi-center study involved the Division of Rheumatology, Department of Medicine, Showa University Hospital; Showa University Koto-Toyosu Hospital; and Showa University Northern Yokohama Hospital. A total of 632 patients with RA from the All Showa University of RA database (ASHURA) were included in our study. The criteria used for the classification of RA complied with the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria (2). The following background factors were investigated: age; gender; body mass index (BMI); type of bDMARD; dosages of MTX and PSL; use of conventional synthetic disease-modifying antirheumatic drugs and nonsteroidal anti-inflammatory drugs; smoking history; glycated hemoglobin (HbA1c); presence or absence of hypertension and dyslipidemia; and the levels of serum creatinine, C-reactive protein, and matrix metalloproteinase-3 (MMP-3). We also used the simplified disease activity index (SDAI) (3) and health assessment question-

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Cite this article as: Miwa Y, Mitamura Y. Effects of biologic drugs on the prognosis of rheumatoid arthritis among patients with poor diabetes control. Eur J Rheumatol 2020; 7(2): 60-3.

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Submitted: September 5, 2019
Accepted: September 26, 2019
Available Online Date: January 2, 2020

naire disability index (HAQ-DI) to evaluate the RA disease activity and activities of daily living, respectively. Poor DM control was defined as a HbA1c of 6.0; accordingly, we divided the patients into groups with a good and poor DM control. The SDAI and PSL dosage were the primary and secondary endpoints, respectively.

The exclusion criteria were primary and secondary failures, adverse drug events, missing data, and patients who moved or had care withdrawn. There were no restrictions on the use of other DMARDs or nonsteroidal anti-inflammatory drugs. There were no limits on age or disease duration. Patients who requested that the examination be stopped and patients who were determined by a doctor to be inappropriate for inclusion in the study were excluded.

Statistical analysis

The following statistical analyses were performed: the Mann-Whitney U test, chi-squared test for independence, Student's t-test, and a repeated-measure analysis of variance (ANOVA). Repeated-measures ANOVA was used to evaluate the SDAI and PSL dosage, and HbA1c scores before the treatment and 1 year later.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version R commander designed to add statistical functions frequently used in biostatistics (4). All patients were not involved reporting patient and public involvement in research.

Main Points

- What is already known about this subject?

  Tocilizumab treatment decreased HbA1c levels in patients with rheumatoid arthritis (RA).

- What does this study add?

  Tumor necrosis factor inhibitor decreased the HbA1c levels in patients with RA.

- How might this impact clinical practice or future developments?

  The biological disease-modifying antirheumatic drugs (bDMARD) therapy reduced the RA disease activity and PSL dosage in both the groups with poor and good diabetes mellitus control. The bDMARD treatment for RA was recommended regardless of good or poor DM control.

Results

Of the 632 patients in the ASHURA Registry considered for the study, 336 were excluded due to primary failure, secondary failure, stopped because that led to remission, partial response, complications (infection, rash, cancer, pregnancy, infusion reaction, cytopenia, cardiopulmonary arrest, and others), transfer, discontinuation, withdrawal from the study, economic reasons, missing data, and use of conventional synthetic DMARDs (Figure 1).

Univariate analysis of the demographics and baseline characteristics of 296 patients with RA are presented in Table 1. Compared to the good DM control group, the poor DM control group had more elderly patients. Furthermore, BMI, the smoking rate, PSL dosage, and disease activity of RA were higher in the poor DM control group (Table 1).

The SDAI score ranged from 27.7±15.6 to 7.1±8.0 in the poor DM control group (n=83) and from 22.9±14.0 to 6.3±7.6 in the good DM control group (n=213). There was no interaction between the groups (Table 1). Repeated-measures ANOVA showed a significant difference between the groups (p=0.011) and during the treatment period (p=0.001). The PSL dosage ranged from 3.5±3.6 (mg/

Table 1. Unavailable analysis of the demographics and baseline characteristics of 296 patients with RA.

Factors		HbA1c > 6.0 group	HbA1c≦6.0 group	p
n		83	213	
Age (years)		60 (60-71)	57 (43-72)	0.000*
Sex (female), n (%)		65, (78)	181, (85)	0.056**
Body mass index (kg/m^2)		23.4 (20.8-26.9)	20.8 (18.9-22.9)	0.000*
Bio-naive (%)		64.1	59.5	0.370**
Smoking history, yes (%)		34 (41)	54 (26)	0.001**
Prednisolone dosage (mg/d) (pre)		3.5±3.6	2.3±3.0	0.002***
Prednisolone dosage (mg/d) (post)		2.2±3.0	1.6±3.6	0.141***
MTX dosage (mg/w)		8 (0.25-10)	8 (0-10)	0.030*
bDMARDs	Infliximab	16	33	0.329**
	Etanercept	12	30	
	Adalimumab	9	24	
	Golimumab	10	23	
	Certolizmab Pegol	6	22	
	Tocilizumab	14	46	
	Abatacept	16	35	
ESR (mm/H)		36 (14.25-53)	22 (12-43)	0.000*
CRP (mg/dL)		1.35 (0.40-3.96)	0.53 (0.09-2.42)	0.000*
MMP-3 (ng/mL)		223.7 (91.4-384.3)	127.5 (57.2-260.5)	0.000*
HbA1c (%) (pre)		6.4 (6.1-7.0)	5.5 (5.3-5.7)	0.000*
HbA1c (%) (post)		6.2 (5.9-6.95)	5.4 (5.2-5.675)	0.000*
SDAI (pre)		27.7±15.6	22.9±14.0	0.000***
SDAI (post)		7.1±8.0	6.3±7.6	0.425***
HAQ-DI		0.73±0.70	0.66±0.64	0.370***

MTX: methotrexate; bDMARDs: biological disease-modifying antirheumatic drugs; ESR: erythrocyte sedimentation rate; MMP-3: matrix metalloproteinase-3; SDAI: simplified disease activity index; HAQ-DI: Health Assessment Questionnaire Disability Index.
*analysis using a Mann-Whitney U test.
**analysis using a chi-squared test for independence.
***analysis using Student's t-test.

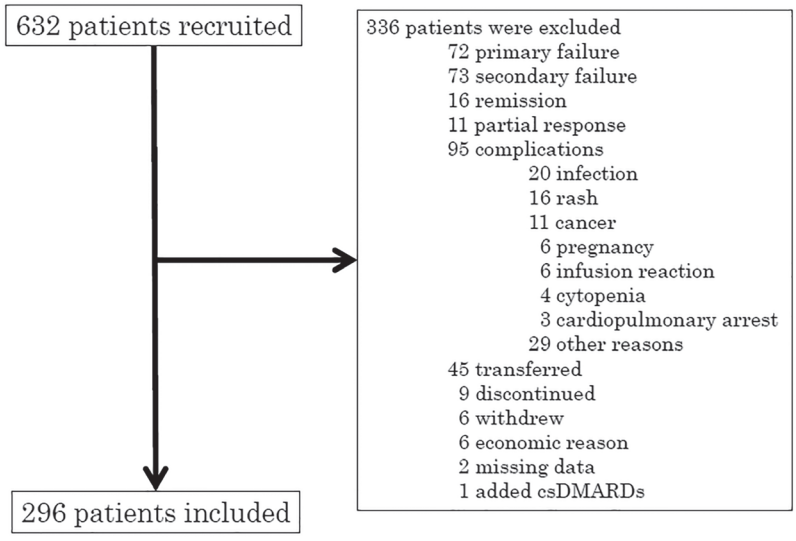

Figure 1. Study flow chart.

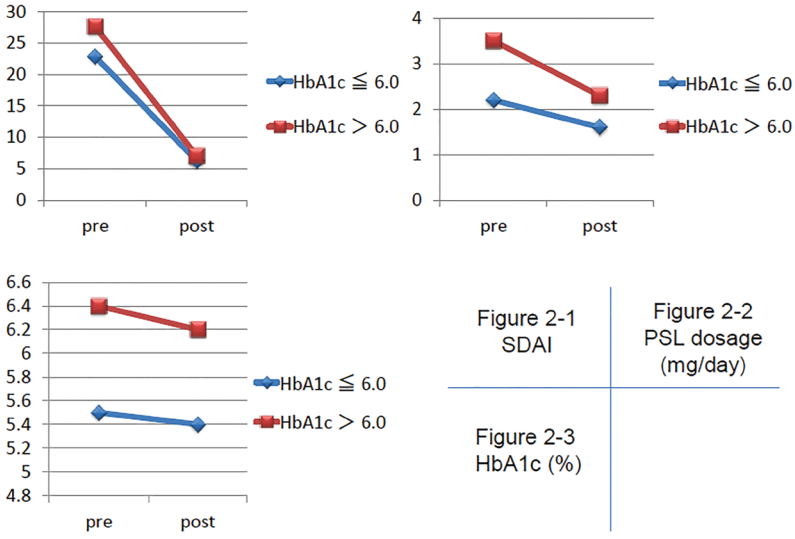

Figure 2. Changes in SDAI, PSL dosage, and HbA1c levels. Inter-individual variation of 0.011 and individual variation of 0.000 for SDAI; inter-individual variation of 0.008 and individual variation of 0.000 for PSL dosage (mg/day); and inter-individual variation of 0.000 and individual variation of 0.084 for HbA1c (%).

day) to 2.2±3.0 in the poor DM control group and from 2.3±3.0 to 1.6±3.6 in the good DM control group. A significant difference was observed between the groups (p=0.008) and during the treatment period (p=0.000). HbA1c ranged from 6.6±0.68 to 6.5±0.82 in the poor DM control group and from 5.1±0.29 to 5.4±0.34 in the good DM control group. Although a significant difference was observed between the groups (p=0.000), there was no significant difference during the treatment period (p=0.084).

Notably, there was no significant difference in the HAQ-DI. No patient reported HbA1c increasing by 1.0 or more during 1 year (Figure 2).

Discussion

In this study, there was no difference in the treatment response to bDMARDs depending on the value of HbA1c. In a previous study, tocilizumab (TCZ) treatment decreased the HbA1c levels in patients with RA to a greater extent than the tumor necrosis factor inhibitor (TNFi) (5). However, compared to the use of MTX alone, the use of TNFi with MTX was not associated with a significant change in HbA1c or fasting glucose levels (6). Because of comparing to the number of cases using TCZ, many numbers of cases using TNFi, there is no difference in the treatment response to bDMARDs depending on the HbA1c value. The HbA1c levels were not high prior to treatment.

The strength of this study was that regardless of the HbA1c value, the bDMARD use reduced the disease activity of RA, the PSL dosage, and the HbA1c level. Decreased HbA1c levels may lead to a reduction in the incidence of DM complications. Especially, the HbA1c odds ratio of cardiovascular risk was 6.1 compared to that at a regular rheumatology outpatient clinic (7). Finally, the mortality rate of patients with RA may be reduced. Thus, regardless of the HbA1c value, bDMARDs are important and are strongly recommended.

Our study has some limitations. First, we did not determine the patients' hemoglobin levels and homeostatic model assessment insulin resistance (HOMA-IR). Second, background factors were different between the two groups, and there was no adjustment for confounding factors. Third, the group with a poor DM control had fewer cases than the group with a good DM control. In the future, there is a need for further research of bDMARDs in this context.

Our results showed that the bDMARD therapy reduced the RA disease activity and PSL dosage in both groups with poor and good DM control. Therefore, we recommend the bDMARD treatment for RA regardless of a good or poor DM control.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the Department of Medicine, Showa University School of Medicine (No. 1435).

Informed Consent: Written informed consent was obtained from patients the parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Y.M., Y.M.; Design - Y.M., Y.M.; Supervision - Y.M., Y.M.; Resources - Y.M., Y.M.; Materials - Y.M., Y.M.; Data Collection and/or Processing - Y.M., Y.M.; Analysis and/or Interpretation - Y.M., Y.M.; Literature Search - Y.M., Y.M.; Writing Manuscript - Y.M., Y.M.; Critical Review - Y.M., Y.M.

Acknowledgements: Cooperation on data collection: all members of the Rheumatoid Arthritis Group of Showa University (ASHURA groups): Tsuyoshi Kasama, Nobuyuki Yajima. Takeo Isozaki, Kuninobu Wakabayashi, Sakiko Isojima, Ryo Yanai, Nao Oguro, Yoko Miura, Mayu Saito, Yuzo Ikari, Takahiro Tokunaga, Sho Ishii, Shinichiro Nishimi, Airi Nishimi, Mika Hatano, Kosuke Sakurai, Yoichi Toyoshima and Katsunori Inagaki.

Conflict of Interest: Yusuke Miwa has received research grants from Astellas Pharma Inc., Mitsubishi Tanabe Pharma Corporation, Pfizer Japan Inc.; Chugai Pharmaceutical Co., Ltd. Yuko Mitamura declare no conflicts of interest in association with the present study.

Financial Disclosure: The authors declared that this study has received no financial support.

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