



[Original Article]

The current situation of the treatment of rheumatoid arthritis in Chiba University Orthopaedic department

Michiaki Miura, Shigeo Hagiwara, Junichi Nakamura, Masahiko Suzuki

Taigen Lee, Tatsuya Kobayashi, Yasushi Wako, Yuya Kawai

Kento Nawata, Masahiko Sugano, Kensuke Yoshino, and Seiji Ohtori

Department of Orthopaedic Surgery, Graduate School of Medicine, Chiba University, Chiba 260-8677.

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Abstract

The introduction of new efficacious therapeutic agents and a treatment strategy aiming at early diagnosis and aggressive treatment intervention has drastically changed the treatment of rheumatoid arthritis (RA) over the past 20 years. Two large observational cohort studies, namely Institute of Rheumatology Rheumatoid Arthritis (IORRA), Tokyo Women's Medical University, and National database of rheumatic diseases by iR-net in Japan (NinJa), have shown the current treatment trends in patients with RA in Japan. The present study aimed to investigate the current situation of the treatment of patients with RA at Chiba University Orthopaedic department. A cross-sectional observational study including 195 patients with RA (45 males/150 females; mean age: 64.8 years; mean disease duration: 15.3 years) was conducted to address this question. Information on drug use, previous medical history, type of orthopedic surgeries related to RA, and laboratory data of the patients were examined. The rates of using methotrexate (mean dosage: 7.7 mg/week) and biologic agent were approximately 76% and 30%, respectively. Approximately 30% of patients had previously undergone orthopedic surgeries, and 16% underwent multiple surgeries. Total knee arthroplasty (TKA) was the most frequent surgery (22%), and bilateral procedure was performed in almost half of these patients with TKA. However, further studies corroborating the findings regarding the treatment of RA at our institution are required.

Key words: RA, database, methotrexate, biologic agents

I. Introduction

The treatment of rheumatoid arthritis (RA) has drastically changed over the past 20 years. The presence of anti-cyclic citrullinated peptide antibody and definite

criteria[1] allow early diagnosis. The introduction of methotrexate (MTX) and biologic agents and a combination of disease-modifying anti-rheumatic drugs is essential for the treatment of RA[2-4]. In addition, aggressive treatment intervention and well-defined treatment targets have contributed to this change[5-7].

The effectiveness and safety of these new therapeutic agents are supported by numerous randomized controlled trials (RCTs) [3,4,8]. However, the diversity between patients who meet the inclusion criteria of these

Address correspondence to Dr. Michiaki Miura.

Department of Orthopaedic Surgery, Graduate School of Medicine, Chiba University, 1-8-1, Inohana, Chuou-ku, Chiba 260-8677, Japan.

Phone: +81-43-226-2117. Fax: +81-43-226-2116.

E-mail: michi.m.55@gmail.com

RCTs and those who receive the real treatment, as well as the long-term results of the treatment must be taken into consideration[9]. The use of data from prospective observational cohort studies may permit investigators to overcome such challenges[10,11].

In Japan, the use of MTX (maximum dosage: 8 mg/week) for the treatment of patients with RA was approved in 1999. However, in 2011, this dosage was revised to 16 mg/week[12,13]. The use of tumor necrosis factor (TNF)- α inhibitor for the treatment of RA was approved in 2003 and that of other non-TNF biologic agents was approved in 2008. The Japan College of Rheumatology (JCR) recommended the use of MTX as first-line therapy and additional or alternative use of biologic agents in cases of insufficient treatment efficacy, according to the European League Against Rheumatism (EULAR) recommendations[14]. In 2000, a large observational cohort study involving patients with RA was conducted at the Institute of Rheumatology, Tokyo Women's Medical University (IORRA). In 2002, another multicenter observational cohort study (NinJa) was conducted[15,16]. Previously, other regional cohort studies have also been conducted[17,18]. However, to our knowledge, no observational cohort studies have been conducted in Chiba. Therefore, this study aimed to investigate the current situation of the treatment of patients with RA at Chiba University Orthopaedic department.

II. Patients and methods

A cross-sectional observational study involving patients with RA, diagnosed according to the American College of Rheumatology (ACR)/EULAR classification criteria, was conducted[1]. A total of 195 patients (45 males/150 females) treated at our institution in April 2016 were included in the study. The research protocol of this study was following the Helsinki Declaration, approved by the Institutional Review Boards. (Research Ethics Committees of Graduate School of Medicine, Chiba University; the reference number #849) All of the attending physicians were the board-certified rheumatologists, and the treatment plans were decided

by the conference. The mean age of the patients was 64.8 years (standard deviation [SD]: 11.8), and the mean duration of disease was 15.3 years (SD: 11.2). The information examined on drug use included the following: administration percentage and dosage of MTX and prednisolone (PSL), administration percentage of salazosulfapyridine, immunosuppressive drugs including ciclosporin and tacrolimus, bucillamine, and biologic agents. Moreover, previous medical history and the type of orthopedic surgeries related to RA including implant arthroplasty, hand surgery, and cervical spine surgery were investigated. Laboratory data including C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) were also examined.

III. Results

The administration rates of MTX (mean dosage: 7.7 mg/week), PSL (mean dosage: 4.8 mg/day), and biologic agents were approximately 77%, 51%, and 30%, respectively (Table 1, Fig. 1 and 2). Reasons for discontinuation of the previous MTX administration included respiratory disorder (5 patients), hepatopathy (2 patients), childbearing desire (2 patients), thrombocytopenia (1 patient), and fever induced by the drug (1 patient). Other serious problem didn't occur by the discontinuation and alteration of the drug. Previous accumulative orthopedic surgeries were

Table 1 drug information

All patients	n = 195
Patients using MTX, number (%)	148 (75.9)
Dosage of MTX, mg/week, mean \pm SD	7.7 \pm 3.4
Patients using PSL, number (%)	100 (51.3)
Dosage of PSL, mg/day, mean \pm SD	4.8 \pm 3.2
Patients using SASP, number (%)	68 (34.9)
Patients using ISD, number (%)	16 (8.2)
Patients using BUC, number (%)	11 (5.6)
Patients using biologic agents, number (%)	58 (29.7)
TNF- α inhibitor	44 (22.6)
IL-6 inhibitor	4 (2.1)
targeting T-cell	10 (5.1)

MTX, methotrexate; PSL, prednisolone; SASP, salazosulfapyridine; ISD, immune-suppressive drug; BUC, bucillamine; TNF, tumor necrosis factor; IL, interleukin; SD, standard deviation;

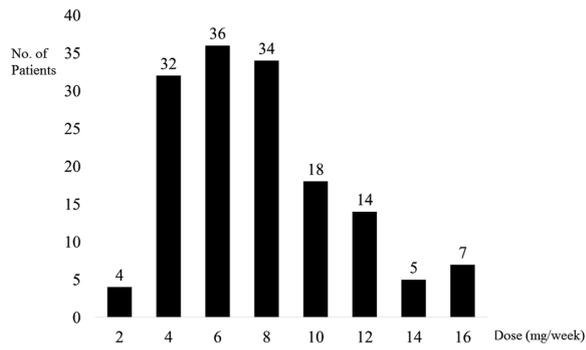


Fig. 1 Distribution of MTX dose (n = 150)

Mean dose: 7.7mg (Male 8.7mg, Female 7.4mg)

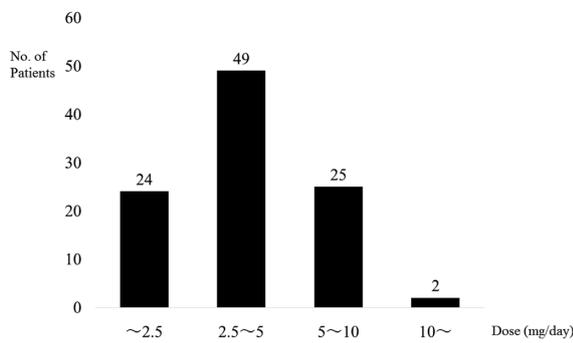


Fig. 2 Distribution of PSL dose (n = 100)

Mean dose: 4.8mg (Male 5.0mg, Female 4.7mg)

Table 2 previous RA related orthopedic surgery

All patients	n = 195
Patients with implant arthroplasty, number (%)	48 (24.6)
TKA, number (%)	42 (21.5)
Bilateral / contralateral, number (%)	19 (9.7) / 23 (11.8)
THA, number (%)	13 (6.7)
Bilateral / contralateral, number (%)	4 (2.1) / 9 (4.6)
TEA, number (%)	5 (2.6)
Bilateral / contralateral, number (%)	1 (0.5) / 4 (2.1)
Patients with hand surgery, number (%)	12 (6.2)
Patients with cervical spine surgery, number (%)	5 (2.6)
Patients with any surgery, number (%)	58 (29.7)
Patients with plural surgeries, number (%)	31 (16.4)

TKA, total knee arthroplasty; THA, total hip arthroplasty; TEA, total elbow arthroplasty;

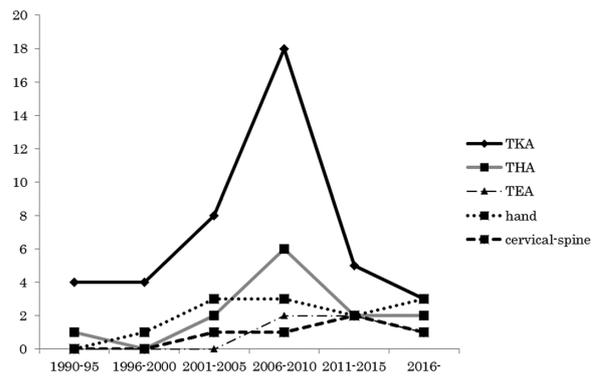


Fig. 3 Transition of RA related orthopedic surgery

The number of each surgeries conducted in each 5 years were shown.

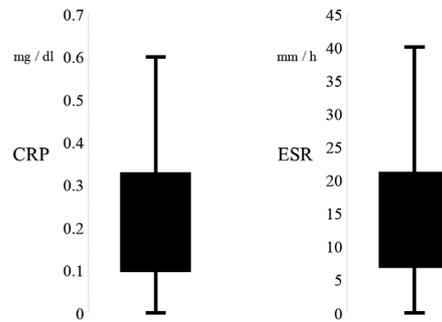


Fig. 4 Laboratory data

CRP (Median: 0.1 mg/dl, Mean: 0.41 mg/dl), ESR-60 (Median: 13 mm/h, Mean: 15.6mm/h)

reported in approximately 30% of patients, and total knee arthroplasty (TKA) was the most frequent surgery (22%) (Table 2), and the number of TKA and total hip arthroplasty (THA) decreased after 2011 (Fig. 3). Laboratory data showed that the mean CRP level and ESR were 0.41 and 15.6, respectively (Fig. 4).

IV. Discussion

Over the past 20 years, impressive improvements have been observed in the treatment of patients with RA. MTX has been reported to improve disease activity, function, and long-term outcomes including joint destruction and RA-associated mortality [19,20]. Currently, MTX is considered the anchor drug for the treatment of RA [14]. In the late 1990s and early 2000s, biologic agents were introduced for the treatment of RA. Currently, five TNF- α inhibitors, two interleukin-6 inhibitors, and one T-cell targeting agent have been

approved in Japan as second choice for the management of patients with RA. Clinical, radiographical, and patient-based outcome evaluations revealed drastic improvements in disease activity and progression with these agents[21,22]. Treatment using these efficacious agents and a new therapeutic strategy consisting of early diagnosis and aggressive intervention has led to marked improvement in long-term outcomes for patients with RA[6,7].

In recent years, the administration of MTX and biologic agents has significantly increased. The IORRA study corroborated these findings: the proportion of patients receiving MTX was approximately 40% in 2002 and approximately 75% in 2012. For biologic agents, the proportion of patients treated with these agents was 0% in 2002 and vs. approximately 20% in 2012[23]. The NinJa study showed that the proportion of patients receiving MTX increased from 39.6% in 2004 to 63.8% in 2014, and the mean weekly dose increased from 5.9 mg to 8.3 mg, respectively. Furthermore, it was reported that administration of biologic agents increased from 1.7% in 2004 to 27.4% in 2014[24]. The use of MTX is contraindicated during pregnancy and in those with hypersensitivity, serious infection, lymphatic disorder, hepatopathy, severe nephropathy, pleural and ascites fluid, and respiratory disorder[14]. Short-term and low-dose administration of glucocorticoids is also recommended by both the ACR and EULAR guidelines [14].

The NinJa study showed that TKA and THA were the most frequent surgeries related to RA; however, their frequency significantly decreased from 30.1 and 8.5 procedures per 1000 patients in 2004, respectively, to 11.5 and 6.1 procedures per 1000 patients in 2014, respectively. On the other hand, spine surgery showed a slow but significantly increasing trend due to operative indication, improved surgical technique, and use of developed instruments rather than RA severity[24]. The IORRA study showed that the number of implant arthroplasties gradually decreased since 2003 and stabilized around 2008. Surgeries involving fingers and wrists increased in number, and those procedures were mainly arthroplasties, which recently became available

in Japan. An explanation for this, which was supported by the clinical results of surgery, is that patients are well-controlled by MTX/biologic agents and require an improved quality of life[23]. The decrease of knee and hip joint arthroplasties occurred also in this study. Although the distribution of each surgery was almost same as other registry in this study[24], the percentage of the patient who underwent any surgery was higher than other registry. The reason might be that these patients were treated in Orthopaedic department.

The current situation of the treatment of patients with RA at our institution was investigated. The administration rates and dosage of MTX, PSL, and biologic agents were similar to those reported in recent studies. TKA was the most frequent orthopedic surgery related to RA, and bilateral procedure was performed in almost half of the patients who underwent TKA. Laboratory data suggested that disease activity was nearly controlled with our treatment.

A limitation of this study was the lack of data on patient visual analog scale (VAS) and the number of swollen/tender joints; thus, the disease activity could not be sufficiently evaluated. Another limitation is that this was the first observational study to investigate the situation of the treatment of patients with RA at our institution and no previous data are available to compare the findings of this study, so the changes of the trend of drug information or orthopedic surgeries were not proven.

In conclusion, the current situation of the treatment of patients with RA at our institution was similar to that demonstrated by other Japanese studies investigating RA. Further longitudinal studies are warranted to assess this approach in detail and corroborate current findings.

Author contributions

guarantor of integrity of the entire study: NJ, OS. study concepts and design: All authors. literature research: MM, HS, NJ. clinical studies: MM, HS. experimental studies / data analysis: All authors. statistical analysis: MM. manuscript preparation: MM, HS. manuscript editing: All authors.

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Conflict of interest

The other authors do not receive any financial support or other benefits from commercial sources for the work.

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