









Biological Agent and Total Hip Arthroplasty in Rheumatoid Arthritis

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Purpose: Therapies for treatment of rheumatoid arthritis (RA) have shown significant improvement since the introduction of biological agents (BIO) in 2003 and Janus kinase inhibitors (JAKi) in 2013 in Japan. The rate of orthopedic surgery, including total hip arthroplasties (THA), may reflect trends in disease severity, management, and health outcomes.

Materials and Methods: An analysis of data on THAs performed at our institutes for treatment of RA with BIO or non-BIO therapy from 2004 to 2021 was conducted.

Results: A total of 40,328 orthopedic surgeries, including 5,938 primary THAs and 204 RA-THAs, were performed between 2004 and 2021. An increase in the annual rate of THA performed for patients undergoing orthopedic surgery was observed. The rates of THA decreased annually for patients with RA when compared to the total number of orthopedic surgeries and primary THAs performed.

Conclusion: The number of THAs performed for patients with RA may show an annual decrease resulting from early and aggressive drug therapy for management of RA in the era of BIO and JAKi. However, patients with RA undergoing THA have several unmet needs, including secondary osteoarthritis, dislocation, periprosthetic joint infection, and periprosthetic fracture with osteoporosis.

Keywords: Total hip arthroplasties, Rheumatoid arthritis, Biological agents, Janus kinase inhibitors

INTRODUCTION

Rheumatoid arthritis (RA), an inflammatory disease, is associated with joint destruction. Joint destruction has been reported in small joints including the hand or foot, as well as in large joints, including the hip and knee^{1,2)}. In cases of hip joint damage caused by RA-associated inflammation, the ability to stand and walk is diminished, thus, activities of daily living and quality of life tend to show a rapid decrease in patients with RA^{2,5)}. Before the era of the biological agents (BIO) and Janus kinase inhibitors (JAKi), joint arthroplasty

performed within 10 years after the onset of RA was associated with a high level of disease activity and mortality^{6,7)}. In addition, an Otto pelvis or protrusio acetabuli with a Dorr type C⁸⁾ femoral canal, indicating the elongation of the femoral medullary cavity, was observed as part of the typical hip destruction observed in patients with severe RA^{9,10)} (Fig. 1A, B). In many patients with severe RA, examination of the entire leg showed valgus deformity of the lower legs with flexion contracture of the knee (Fig. 1C) before the era of BIO and JAKi.

Since 2000, knowledge regarding treatment strategies

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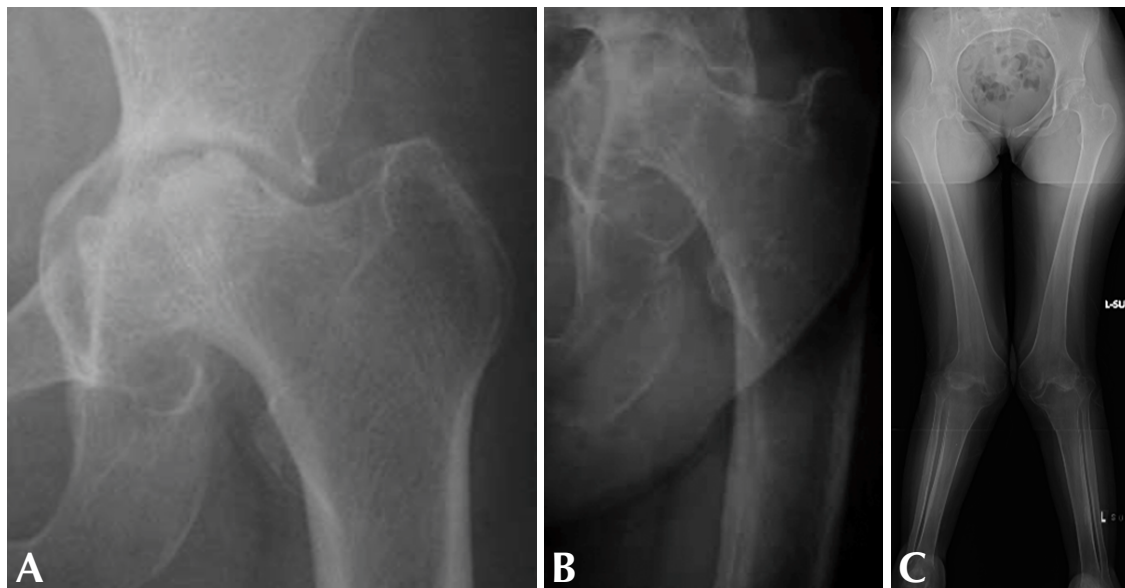


Fig. 1. A typical X-ray of hip destruction in patients with rheumatoid arthritis shows Otto pelvis, protrusio acetabuli (A), and a Dorr type C femoral canal (elongation of the medullary cavity) (B) before the era of BIO and JAKi. (C) Valgus deformity of the lower legs with flexion contracture of the knee. BIO: biological agents, JAKi: Janus kinase inhibitors.

that can be applied in clinical practice along with the availability of newer disease-modifying anti-rheumatic drugs, including BIO and JAKi, has led to a paradigm shift in the treatment of RA.

In Japan, methotrexate (MTX) up to 8 mg per week was approved as an RA drug in 1999, and the first BIO was approved in 2003. The allowable dose of MTX was then increased to 16 mg/week in 2011. The first JAKi was approved in 2013¹⁰⁻¹². The rate of orthopedic surgery and total hip arthroplasty (THA) may reflect trends in disease severity, management, and health outcomes in the era of BIO and JAKi, based on the rapid advancement of RA treatment since 2003^{9,13,14}.

The objective of this study is to determine the number and rate of orthopedic surgeries and THAs performed between 2004 and 2021 among patients with RA from our orthopedic surgery and total joint arthroplasty registry.

MATERIALS AND METHODS

1. Study Design

The number and rate of orthopedic surgeries and THAs performed between 2004 and 2021 on patients with RA who were admitted to our institutes (Yamagata University Hospital and Yamagata Saisei Hospital) was determined using our orthopedic surgery and total joint arthroplasty registry¹⁰. Cemented THAs

were performed in all cases from 2004 to 2016. Hybrid THAs (cementless cup and cemented stem) have also been performed since 2017. In 2021, hybrid THAs were performed in 72% of primary THAs, including patients with RA. Composite beam stems (YU stem; Kyocera) were used from 2004 to 2014. However, we began use of loaded taper stems in 2015 (Exeter [Stryker], CPT stem [Zimmer], C-stem [Depuy], or DTP stem [Kyocera]).

Data on patients who underwent THA including the use of diagnostic procedure combination systems and complications of THA were collected from medical records, surgical records, and shipment documents for orthopedic implants. All THAs were performed using the posterior approach from 2004 to 2021. Patients who presented with many dislocations were counted as one case in this study.

The study protocol, which adheres to the principles of the 2013 Declaration of Helsinki, was approved by the Ethics Committee of Yamagata University (No. 2008-102, H27-163). The written informed consent was waived by the Ethics Committee due to the retrospective nature of the study.

2. Statistical Analysis

Univariable regression analyses were performed using the Mann–Whitney U test and Spearman's correlation analysis was performed using IBM SPSS Statistics software (ver. 25; IBM Corp.) for comparison of data.

Values of $P < 0.05$ were considered statistically significant.

RESULTS

A total of 40,328 orthopedic surgeries were performed from 2004 to 2021 in our institutes. A total of 5,938 primary THAs and 204 RA-THAs were performed or supervised by 12 senior hip surgeons over 18 years. Of 40,328 orthopedic surgeries, 5,938 primary

THAs were performed from 2004 to 2021 in our institutes (Fig. 2). The rate of primary THA showed a direct increase along with orthopedic surgeries ($r = 0.9$, $P < 0.05$). Of these, 204 RA-THAs were performed from 2004 to 2021. The rate of RA-THA showed a slight negative correlation with the rate of primary THA ($r = -0.6$, $P < 0.05$; Fig. 3)¹⁰. The rate of THA performed on patients with RA per annual primary THA showed a decline, in particular, by 4.0% (13/329) in 2020 and by 1.4% (5/352) in 2021, which may have been related to

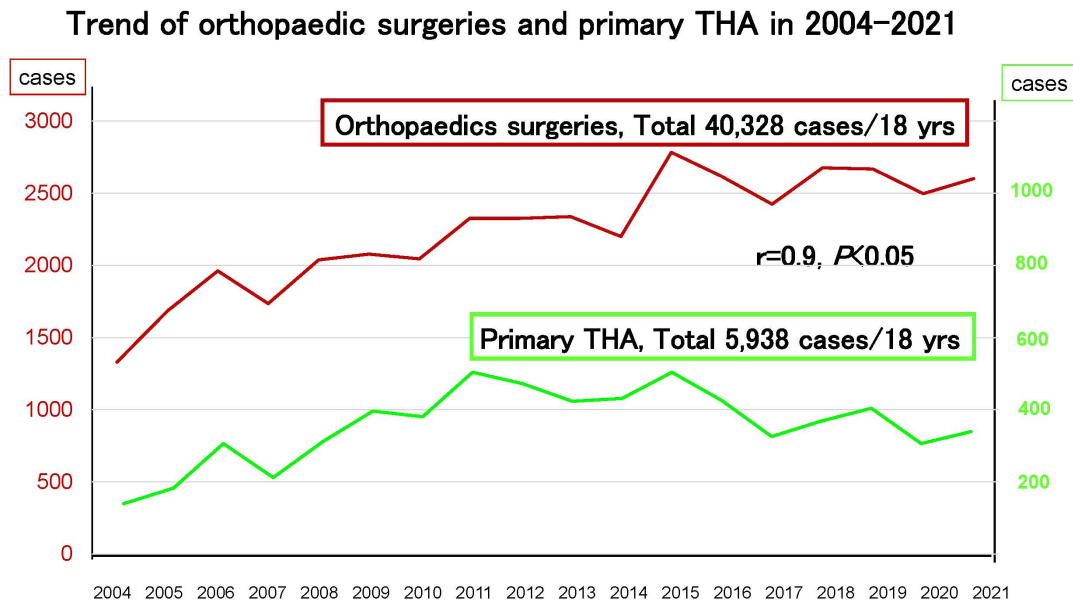


Fig. 2. Trend of orthopedic surgeries with primary THA in our institutes. A total of 40,328 orthopedic surgeries, including 5,938 primary THA, were performed from 2004 to 2021. THA: total hip arthroplasty.

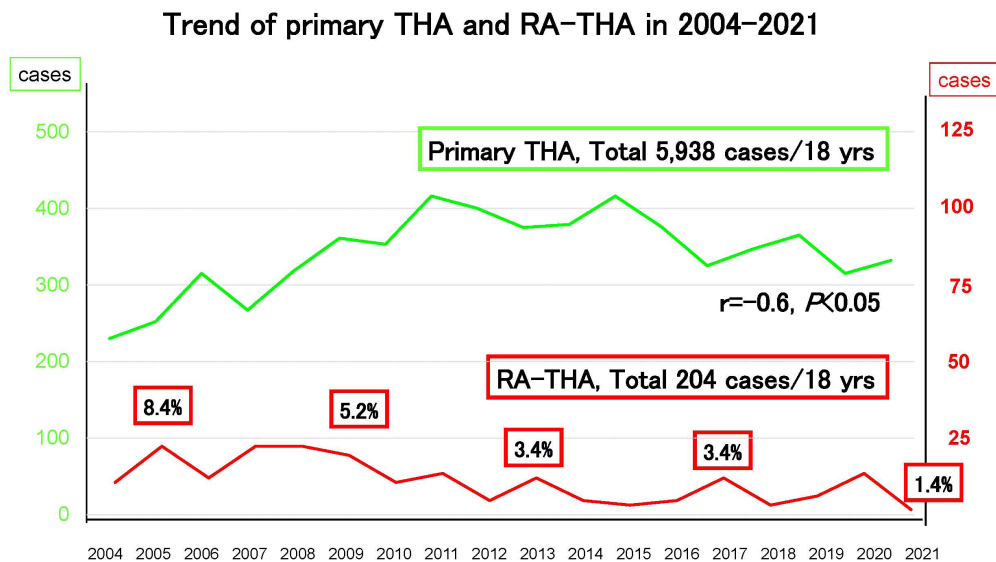


Fig. 3. Trend of orthopedic surgeries with primary THA with RA-THA in our institutes. A total of 204 RA-THAs were performed from 2004 to 2021. The rate of RA-THA showed a slight negative correlation with primary THA. THA: total hip arthroplasty, RA: rheumatoid arthritis.

Table 1. Trends of Orthopedic Surgeries and RA-THA

	2004-2012	2013-2021	2013-2021/2004-2012	Total (2004-2021)
Orthopedic surgeries	17,524	22,804	(1.3 times)	40,328
Primary THA	2,673	3,265	(1.2 times)	5,938
RA-THA	128	76	(0.6 times)	204

Values are presented as number only or times only.
RA: rheumatoid arthritis, THA: total hip arthroplasty.

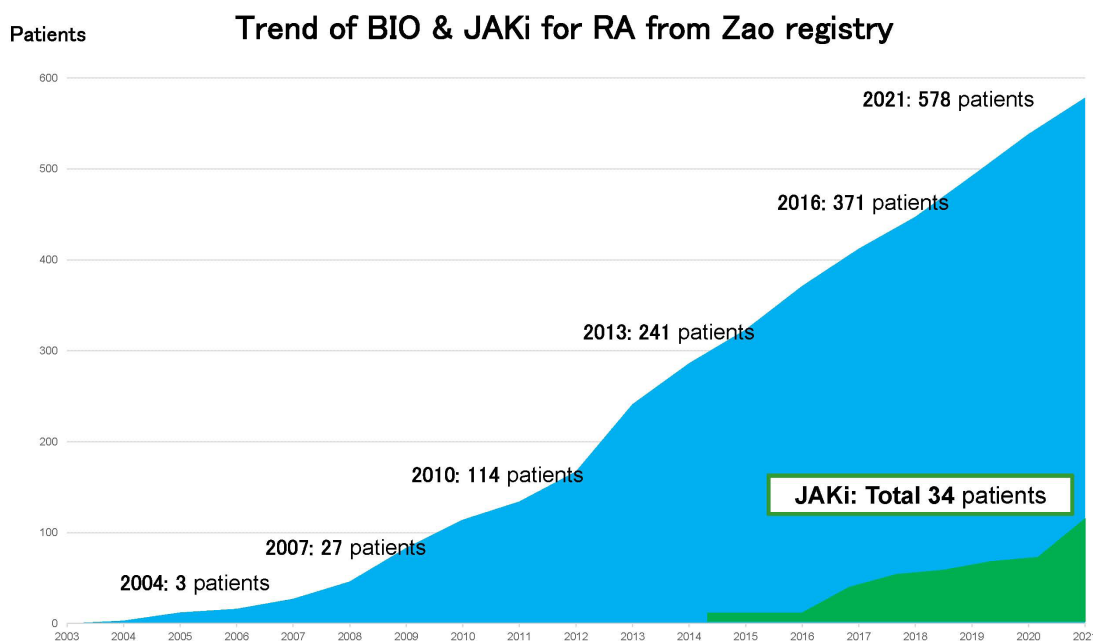


Fig. 4. The trend of BIO and JAKi for RA from our Zao registry¹⁰. The usage of BIO and JAKi has increased year by year. BIO: biological agents, JAKi: Janus kinase inhibitors, RA: rheumatoid arthritis.

Table 2. Dislocation and Periprosthetic Fracture Rate in Non-RA-THA and RA-THA in 2004-2021

	Non-RA-THA (n=5,734)	RA-THA (n=204)	Total (n=5,938)
Dislocation	59 (1.0)*	6 (2.9)*	65 (1.1)*
Periprosthetic fracture	13 (0.2)	2 (1.0)	15 (0.3)

Values are presented as number (%).
RA: rheumatoid arthritis, THA: total hip arthroplasty.
* $P < 0.05$.

the impact of the coronavirus disease 2019 (COVID-19) pandemic in 2020 and 2021. The total number of orthopedic surgeries and primary THAs performed during 2013-2021 increased and was higher than during 2004-2012; however, the number of RA-THAs decreased by half (Table 1). According to our Zao registry, usage of BIO and JAKi has shown an annual increase (Fig. 4)¹⁰.

The occurrence rate for dislocations of primary THA

Table 3. Cause of Revision THA in Patients with Non-RA or RA in 2004-2021

Cause of revision THA	Non-RA-revision THA	RA-revision THA	Total
Aseptic loosening	376 (69.0)	13 (81.3)	389 (69.3)
Infection	77 (14.1)	2 (12.5)	79 (14.1)
Frequent dislocation	69 (12.7)	1 (6.3)	70 (12.5)
Periprosthetic fracture	18 (3.3)	0	18 (3.2)
Breakage	5 (0.9)	0	5 (0.9)
Total	545/561 (97.1)	16/561 (2.9)	561

Values are presented as number (%).
THA: total hip arthroplasty, RA: rheumatoid arthritis.

was 1.1% (65/5,938), including 2.9% (6/204) for patients with RA. The rate of dislocation for patients who underwent RA-THA was higher than that for all patients who underwent THA ($P < 0.05$). The occurrence rate for periprosthetic fracture (PPF) was 0.3% (15/5,938) for



Fig. 5. The characteristic feature of hip destruction in patients undergoing RA-THA appears to be a result of RA synovitis and OA change with mild acetabular dysplasia in the era of BIO and JAKi in Japan. RA: rheumatoid arthritis, THA: total hip arthroplasty, OA: osteoarthritis, BIO: biological agents, JAKi: Janus kinase inhibitors.

primary THA, including 1.0% (2/204) for patients with RA (Table 2).

Revisions of THA were performed in 561 cases including 16 cases with RA from 2004 to 2021. Of these, aseptic loosening in 13 cases (81.3%), infection in two cases (12.5%), and frequent dislocation of the THA in one case were the reasons for THA revision in patients with RA (6.3%) (Table 3).

DISCUSSION

1. Trend of Hip Joint Destruction in Patients with RA in the BIO and JAKi Era

THA is regarded as an effective procedure for treating hip joint destruction in patients with musculoskeletal diseases including RA. However, the rate of orthopedic surgery including THA, decreased for patients with RA, reflecting trends in disease severity in the era of BIO and JAKi^{5,6,9,15-18}.

According to data from the Finnish Coxa Hospital registry, total joint arthroplasties have decreased since 1990 compared to the period before approval of MTX and BIO¹⁵. According to the UK and Canada registry of THA, the frequency of RA-THAs performed in patients with RA has decreased in the BIO era in the United Kingdom of Great Britain and Northern Ireland (UK) and Canada¹⁹. In addition, according to the Japanese registry of RA surgeries, the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) cohort, RA sur-

geries and RA-THAs have shown an annual decrease. However, the number of hand and foot surgeries for treatment of RA has increased in the IORRA cohort¹².

2. Current Hip Joint Changes in Patients with RA in the BIO and JAKi Era

Several surgeons have reported that progression of joint destruction due to RA and osteoarthritis (OA) with osteoporosis continues, particularly in large joints with a Larsen grade II or higher severity, despite the potential for remission of RA^{20,21}. In Japan, destruction due to RA-associated synovitis and OA change with mild acetabular dysplasia appears to be the characteristic feature of hip destruction in patients undergoing RA-THA (Fig. 5).

Tsushima et al.²² reported a decrease in performance of RA-THA in 2013-2019 compared to 1998-2003. The current changes in the hip joint observed in RA patients are similar to the primary changes in OA that were characterized radiographically by the development of capital drop and decreased central migration.

Regarding RA-knee, a deep learning model for classifying anteroposterior knee radiographs according to “RA” and “OA-like RA” groups was developed by Takeda et al.²³. They reported that the percentage of “OA-like RA” showed a significant increase from 20.9% in 2006 to 67.7% in 2020. However, it appears that RA-knee is not the same as OA-knee. Nejima et al.²⁴ reported that the entire lower limb alignment was more

valgus in patients with RA-knee compared to those with OA-knee. In addition, Jensen et al.²⁵⁾ reported that the histological findings of the femoral head in RA, which they termed secondary OA, differed from those of the femoral head in OA.

The complications affecting patients who had undergone RA-THA differed from those of patients who underwent OA-THA. According to a single large center study conducted in Australia, increasing rates of dislocation were reported, similar rates of infection and aseptic loosening were observed, and decreasing rates of revision and PPF were observed for RA-THA compared to OA-THA²⁶⁾. Although higher rates of dislocation were observed, a higher prevalence of PPF was not observed in this study. These results might be explained by the primary use of composite beam stems in performance of RA-THA^{27,28)}. In addition, although aseptic loosening was the most common reason for THA revision, it may not detect the sources of infection in cases of THA revision³⁰⁾. In fact, use of antibiotic bone cement during performance of primary THA was reported to decrease the rate of THA revision^{31,32)}.

3. Elderly Patients with RA and Late-onset of RA

The global prevalence of elderly patients with RA and late-onset RA is increasing³³⁾. The population of Japan is increasing faster than that of any other country³⁴⁾. Fractures caused by osteoporosis are a significant problem for the elderly. In the IORRA study, it was reported as a significant risk factor for fractures in Japanese patients with RA³⁵⁾. In Cox regression models, risk factors for fracture in patients with RA included a health assessment questionnaire (HAQ), age, history of fractures, and orthopedic surgeries. The reported rate of PPF in patients with RA ranged from 0.3% to 2.5%^{26,35)}. According to the general practitioner database, the risks of pelvic and vertebral fractures tend to be higher for patients with RA compared with control subjects in the UK³⁶⁾. Ravi et al.³⁷⁾ reported that the surgeon's experience in performance of total joint arthroplasties for treatment of patients with RA influenced a direct decline in surgical complications. In addition, efforts to improve our surgical strategies and techniques for management of patients with RA should continue.

4. Limitations

This study has several limitations. First, some patients living outside our local area visited our institutes to undergo THA. Any complications of THA occurring in a patient who lives outside our local area might be treated at secondary and tertiary care facilities located in their area. Therefore, some cases are not included in our registry. Second, we collected information on cases of infection following THA on patients who underwent THA revision, but not all cases. We were not able to investigate cases involving patients who chose conservative therapy or debridement of infectious THA. Last, we were not able to obtain clinical data on RA, including disease activity score and history of medication. Considering the limitations of this study, conduct of additional research will be required to confirm our findings.

CONCLUSION

Prior to the era of BIO and JAKi, joint arthroplasty performed within 10 years after the onset of RA was associated with a high level of disease activity and mortality. Significant advancements in RA therapy were reported around 2003, and disease activity showed improvement over the long term in Japan.

Due to early and aggressive drug therapy for treatment of RA in the era of BIO and JAKi, a decrease in the annual number of THAs performed on patients with RA may occur. Even in the era of BIO and JAKi, patients with RA undergoing THA have several unmet needs, including secondary OA, dislocation, PPF with osteoporosis, and periprosthetic joint infection.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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