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Original Article

Assessment on Treatments With Conventional Synthetic Disease-modifying Drugs Before Initiating Biologics in Patients With Rheumatoid Arthritis in Korea: A Population-based Study

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Objective: To assess pre-biologic treatments with conventional synthetic disease-modifying drugs (csDMARDs) prior to biologics initiation among patients with rheumatoid arthritis (RA).

Methods: Using Korea National Health Insurance database, we examined pre-biologic treatments of RA patients on the following four items: whether 1) initial methotrexate (MTX) therapy was given, 2) MTX dose was escalated up to ≥15 mg/week within 1-year post-diagnosis, 3) prednisone-equivalent glucocorticoid was used at a dose of ≤7.5 mg/day, and 4) glucocorticoid was discontinued within 6 months of treatment. Multivariable logistic regressions identified predictors of items 2) and 4) fulfillment.

Results: Among 6,986 biologics initiators with RA, 54.9% used MTX as the 1st csDMARD. Within 1-year post-diagnosis, 85.2% used MTX with half of them achieving a dose of ≥15 mg/week. The majority (75.2%) of patients used glucocorticoids initially and 64.5% were still on glucocorticoids at 6 months, mostly at a dose of ≤7.5 mg/day. csDMARD combination was observed in 85.7%. Item 2) fulfillment was associated with males, younger age, glucocorticoid, combination therapy, cyclo-oxygenase-2 inhibitors, and viral hepatitis. Item 4) fulfillment was associated with males, MTX dose of ≥15 mg/week, combination therapy, viral hepatitis, and hospitalizations.

Conclusion: RA patients in Korea were predominantly treated with MTX-based csDMARD combination plus glucocorticoids before initiating biologics, without sufficient MTX dose escalation or glucocorticoid discontinuation. Items 2) and 4) fulfillments were associated with patient age and gender, concomitant treatments, and comorbidities.

Keywords: Rheumatoid arthritis, Disease-modifying anti-rheumatic drugs, Methotrexate, Glucocorticoids, Combination therapy

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INTRODUCTION

Treatment of rheumatoid arthritis (RA) has dramatically changed with introduction of biologic disease modifying antirheumatic drugs (bDMARDs). However, despite their high efficacy, immediate use of bDMARDs does not necessarily confer significant benefits to RA activity control compared to step-up use, particularly under the treat-to-target strategy [1]. Therefore, both the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) guidelines recommend methotrexate (MTX) as the first treatment agent to induce remission or low disease activity [2-4]. Of note, rapid dose escalation and parenteral use of MTX are also recommended before initiating a bDMARD, based on better efficacies associated with such measures [3-8]. Considering dramatic increase of healthcare cost associated with bDMARD use, it is highly relevant in terms of cost-effectiveness to examine whether patients are treated with conventional synthetic DMARDs (csDMARDs) as recommended by treatment guidelines before they initiate bDMARDs [2-4]. Moreover, information on this issue is particularly essential in countries that take a universal healthcare coverage policy with national regulations on csDMARD treatments before initiating bDMARDs. However, data on this issue are scarcely available from the literature.

To meet this end, we used Korea National Health Insurance Service (KNHIS) database to assess pre-biologic treatments with csDMARDs prior to bDMARD initiation among patients with RA.

MATERIALS AND METHODS

Data source

We used the 2003~2016 KNHIS database. The KNHIS database contains longitudinal patient data including demographics, International Classification of Diseases Tenth Revision (ICD10) diagnosis codes, procedures, prescription records (drug names, prescription and dispensing dates, days' supply, dose, and route of administration), and type of medical utilization (outpatient, inpatient, or emergency department) of all Korean citizens. The Institutional Review Board of the Seoul National University Bundang Hospital approved the study protocol (X-1704-393-903) and waived the need for patient consent based on deidentified database. This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines.

Study population

We identified patients aged ≥18 years with an ICD10 code of seropositive RA (M05.x) who initiated bDMARDs (infliximab, adalimumab, golimumab, etanercept, abatacept, rituximab, or tocilizumab) (Figure 1) [9]. This RA identification algorithm has been validated to have a predictive positive value of more than 85%. Then, we applied a V-code for seropositive RA, which ensures that the patient is a beneficiary of 90% reimbursement of the drug cost from the Korean government. Requirement of seropositivity is relevant in that the use of bDMARDs among

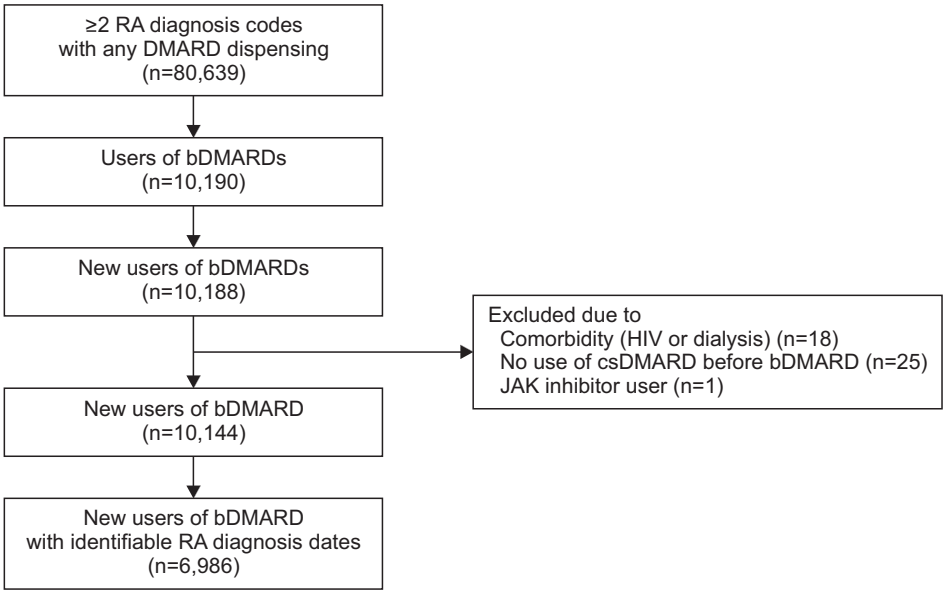

Figure 1. Patient selection process. DMARDs: disease modifying antirheumatic drugs, bDMARDs: biologic DMARDs, csDMARDs: conventional synthetic DMARD, HIV: human immunodeficiency virus, JAK: Janus kinase, RA: rheumatoid arthritis.

RA patients is largely limited to seropositive cases in Korea due to reimbursement criteria. Patients who had dialysis services or human immunodeficiency virus infection were excluded since their DMARD use is expected to substantially differ from that of RA population in general.

To define initiators of bDMARDs, patients were required to be free of any bDMARDs for at least 12 months prior to the first dispensing date (=index date) of a bDMARD they initiated. Among patients who satisfied the above RA identification algorithm [9], the RA diagnosis date was defined as the earliest date among DMARD dispensing dates, free of any DMARD use for ≥365 days before the RA diagnosis date.

Outcomes

We defined the following four items of optimal treatment [3,4]: 1) use of MTX as part of the initial treatment, 2) MTX dose escalation of ≥15 mg/week within 1-year post-diagnosis, 3) low dose glucocorticoid use (≤7.5 mg/day of prednisone-equivalent dose), and 4) glucocorticoid discontinuation within 6 months of treatment. Glucocorticoids were considered discontinued at 6 months if the last available dates of glucocorticoids did not exceed 180-days from RA diagnoses, namely, the first csDMARD dispensing dates, and free of further dispensing for at least 90 days.

While the international guideline such as EULAR recommendations do not recommend a step-up from MTX monotherapy to csDMARD combination before bDMARD initiation [3,4], the Health Insurance Review and Assessment Service (HIRA) of Korea require as reimbursement conditions to use MTX plus other csDMARD before initiating bDMARDs, based on previous studies showing non-inferiority of such combination therapy compared to bDMARD use [10-13]. Since the HIRA reimbursement criteria are expected to impact treatment patterns of pre-index period, we looked at csDMARD combination patterns in addition to the four proxies listed above. The csDMARDs examined regarding combination were MTX, sulfasalazine, hydroxychloroquine, leflunomide, tacrolimus, azathioprine, cyclophosphamide, cyclosporine, bucillamine, and D-penicillamine.

Patient comorbidities

We obtained information on comorbidities including cardiovascular, metabolic, pulmonary, gastrointestinal, renal, infectious, and malignancies, together with Charlson-Deyo comor-

Table 1. Baseline characteristics of bDMARD initiators

Covariates	bDMARD initiators with identifiable RA diagnosis dates (n=6,986)
Age at index date (yr)	56.5±10.6
Female sex	5,466 (78.2)
Index bDMARDs	
TNF inhibitors	5,887 (84.3)
Abatacept	524 (7.5)
Tocilizumab	536 (7.7)
Rituximab	39 (0.6)
Index year	
2004	25 (0.4)
2005	75 (1.1)
2006	106 (1.5)
2007	156 (2.2)
2008	251 (3.6)
2009	496 (7.1)
2010	496 (7.1)
2011	640 (9.2)
2012	895 (12.8)
2013	856 (12.3)
2014	1,237 (17.7)
2015	1,008 (14.4)
2016	745 (10.7)
Pre-RA comorbidities*	
Stroke or TIA	269 (3.9)
Myocardial infarction	34 (0.5)
Angina pectoris	304 (4.4)
Coronary revascularization	11 (0.2)
Heart failure	103 (1.5)
Atrial fibrillation	44 (0.6)
Venous thromboembolism	79 (1.1)
Hypertension	2,179 (31.2)
Hyperlipidemia	1,665 (23.8)
Obesity	18 (0.3)
Diabetes	1,095 (15.7)
Chronic hepatitis B or C	280 (4.0)
COPD	1,275 (18.3)
Bronchiectasis	160 (2.3)
Asthma	876 (12.5)
IBD	39 (0.6)
Chronic kidney disease	94 (1.4)
Hypothyroidism	537 (7.7)
Cancer	249 (3.6)
Hospitalizations	2,234 (32.0)
Comorbidity index	1.9±1.3

Values are presented as mean±standard deviation or number (%). bDMARDs: biologic disease modifying anti-rheumatic drugs, COPD: chronic obstructive pulmonary disease, IBD: inflammatory bowel disease, NA: not applicable, RA: rheumatoid arthritis, TNF: tumor necrosis factor, TIA: transient ischemic attack. *Pre-RA omorbidities ascertained from the 1-year period prior to RA diagnosis.

bidity score (Table 1) [14].

Statistical analysis

Variables were expressed as mean±standard deviation (SD) or numbers (%). To assess longitudinal trends, we used the Cochran-Armitage test for categorical variables and general linear models for continuous variables [15,16].

To identify predictors associated with MTX dose of ≥15 mg/week within 1-year post-diagnosis and glucocorticoid-free status within 6 months of treatment, we conducted a multivariable logistic regression analysis, providing odds ratios (ORs) and 95% confidence intervals (CIs). Regression models included age at diagnosis, gender, index year, csDMARD treatments during 1-year after diagnosis, and 1-year pre-RA comorbidities. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). $p<0.05$ was considered statistically significant.

RESULTS

Characteristics of the study population

Figure 1 shows our study population selection process. Among 10,144 bDMARD initiators, 6,986 with identifiable RA diagnosis dates were included in the study. Demographics, distribution of index years, and pre-RA comorbidities of study participants are summarized in Table 1. The mean±SD age at the index date was 56.5±10.6 years. The majority (78.2%) of subjects were females. The mean±SD interval from RA diagnosis to bDMARD initiation was 3.9±3.2 years.

Treatment patterns and proxy fulfillments within 1-year post-diagnosis

Since the international recommendations primarily focus on initial treatment strategies after RA diagnosis [3,4], items were examined for the 1-year period after RA diagnosis or prior to bDMARD initiation, whichever came first (Table 2).

MTX was used as part of an initial treatment strategy among 54.9% of RA patients. The mean±SD initial dose of MTX was

Table 2. Treatment patterns during the 1-year post-diagnosis and 1-year pre-index period

	bDMARD initiators with RA diagnosis dates (n=6,986)		
	At RA diagnosis	1-year post-diagnosis period	1-year pre-index period
csDMARD used			
MTX	3,834 (54.9)	5,953 (85.2)	6,339 (90.7)
leflunomide	240 (3.4)	2,263 (32.4)	3,699 (53.0)
Sulfasalazine	2,006 (28.7)	3,668 (52.5)	2,875 (41.2)
Tacrolimus	14 (0.2)	489 (7.0)	1,474 (21.1)
Hydroxychloroquine	4,417 (63.2)	5,545 (79.4)	4,226 (60.5)
Dose regimen of MTX			
Mean maximal dose (mg/week)	9.2±10.1*	14.1±13.1†	14.8±17.3‡
Maximal MTX dose ever used			
<10 mg/week	2,108 (55.0)*	773 (13.0)†	563 (8.9)‡
10~<15 mg/week	1,435 (37.4)*	2,271 (38.2)†	2,442 (38.5)‡
15~<20 mg/week	237 (6.2)*	2,357 (39.6)†	2,700 (42.6)‡
≥20 mg/week	54 (1.4)*	552 (9.3)†	634 (10.0)
Subcutaneous MTX users	29 (0.4)	196 (2.8)	313 (4.5)
csDMARD combination	3,300 (47.2)	5,987 (85.7)	6,898 (98.7)
MTX-based combination	2,738 (39.2)	5,526 (79.1)	5,956 (85.3)
Ever-users of glucocorticoid	5,253 (75.2)	6,727 (96.3)	6,845 (98.0)
Mean daily dose of glucocorticoid (mg)§	-	4.4±4.2	5.5±3.7

Values are presented as number (%) or mean±standard deviation. bDMARD: biologic disease modifying anti-rheumatic disease, csDMARD: conventional synthetic disease modifying anti-rheumatic drug, MTX: methotrexate, RA: rheumatoid arthritis. *% among 3,834 MTX users; †% among 5,953 MTX users; ‡% among 6,339 MTX users; §prednisone-equivalent dose.

9.2±10.1 mg/week. Within 1-year after RA diagnosis, 85.2% of patients eventually used MTX. Among them, 48.9% ever tried a dose beyond 15 mg/week. The mean±SD maximal dose of MTX was 14.1±13.1 mg/week (folate supplementation in more than 99% of MTX users). Parenteral MTX use was seen in 2.8% over this period.

Glucocorticoids were used in 75.2% of RA patients as part of an initial treatment. Only a minority of glucocorticoid users tapered off the drug, with 64.5% and 61.9% of RA patients being still on glucocorticoids at 6 months and 12 months, respectively. 79.5% of all glucocorticoid users received prednisone-equivalent doses of ≤7.5 mg/day during the 1-year post-diagnosis period. The mean daily dose of glucocorticoids was 5.5±4.2 mg.

csDMARD combination as an initial treatment strategy was seen in 47.2% of patients, with 83.0% of them using MTX. Eventually, 85.7% of RA patients used csDMARD combination. The mean±SD time from RA diagnosis to csDMARD combination was 188±479 days.

Treatment patterns and MTX dose escalation fulfillment during the 1-year pre-index period

We looked for treatment patterns including MTX dose escalation during the 1-year pre-index period before initiating bDMARDs, when RA activity would have been highly active (Table 2).

Compliant with the HIRA requirements of Korea, 90.7% of patients used MTX (folate supplementation in more than 98% of MTX users) during this period. However, only 52.6% of them ever reached a maximal dose of ≥15 mg/week. Less than 5% used parenteral MTX. We observed a high rate of glucocorticoid use (98.0%), and csDMARD combination (98.7%), and use of potent csDMARDs (leflunomide in 53.0%, and tacrolimus in 21.1%) [17,18], reflecting high disease activity before initiating bDMARDs during this period. The mean daily prednisone-equivalent dose of glucocorticoids was 5.5±3.7 mg.

Longitudinal trends in treatment patterns of csDMARDs

We looked for longitudinal changes in annual csDMARD use for 1-year post-diagnosis (Table 3), and 1-year pre-index periods (Supplementary Table 1). Highly prevalent use (82.5%~91.2%) of MTX within 1-year after RA diagnosis was observed across all calendar years. However, the proportion of MTX users with an initial or maximal dose of ≥15 mg/week had significantly decreased over the years (p for trend <0.001). Unlike such a declining trend of MTX dose, the use of tacrolimus gradually has increased (p for trend <0.001). The csDMARD combination rate within 1-year of diagnosis was consistently high (>85%) over time despite a trend of decrease (p=0.003).

During the pre-index period, MTX use (at least 85% of RA patients) and csDMARD combination (at least 97.9% of RA patients) were consistently high (Supplementary Table 1). Similar

Table 3. Longitudinal trends in csDMARD use during 1-year after diagnosis

	~2007 (n=362)	2008 (n=251)	2009 (n=496)	2010 (n=496)	2011 (n=640)	2012 (n=895)	2013 (n=856)	2014 (n=1,237)	2015 (n=1,008)	2016 (n=745)	p for trend
MTX as a first csDMARD	56.1	49.0	52.0	52.2	50.6	54.2	54.6	57.6	56.7	57.7	
Initial MTX dose											
≥15 mg/week	15.8	11.4	9.7	6.2	8.1	6.6	8.3	7.4	5.5	5.1	<0.001
Maximal MTX dose ever used*											
≥15 mg/week	61.6	50.2	54.2	52.2	50.6	48.2	50.0	47.7	44.0	42.5	<0.001
csDMARDs ever used											
MTX	91.2	82.5	86.7	85.7	84.5	84.4	84.0	86.1	84.5	84.4	0.073
Leflunomide	32.6	31.5	37.5	32.9	33.6	30.2	29.8	34.4	32.4	30.6	
Sulfasalazine	59.7	57.4	58.3	53.8	53.0	51.6	52.8	48.5	52.3	49.7	<0.001
Tacrolimus	0.0	0.0	2.4	7.3	7.7	6.3	8.3	6.7	10.4	10.6	<0.001
Hydroxychloroquine	80.4	82.9	81.7	82.7	81.4	77.7	76.4	79.2	78.9	78.5	0.019
csDMARD combination	90.1	85.7	90.1	86.7	86.9	84.7	82.6	85.4	84.6	85.9	0.003

Values are presented as percent. csDMARD: conventional synthetic disease modifying anti-rheumatic disease, MTX: methotrexate, RA: rheumatoid arthritis. *% among annual MTX users (n=330 in ~2007, 207 in 2008, 430 in 2009, 425 in 2010, 541 in 2011, 755 in 2012, 719 in 2013, 1,065 in 2014, 852 in 2015, 629 in 2016).

to the patterns of the 1-year post-diagnosis period, the proportion of MTX users with a maximal dose of ≥15 mg/week had significantly decreased over time (p for trend<0.001) while the use of leflunomide (p for trend=0.021) and tacrolimus has increased (p for trend<0.001).

Predictors associated with proxy fulfillments

The use of pre-biologic MTX ≥15 mg/week within 1-year post-diagnosis was associated with younger age at RA diagnosis (OR 1.02 per 1-year decrease, 95% CI 1.01~1.02), male gender (OR 1.27, 95% CI 1.12~1.45), combination therapy (OR 3.74, 95% CI 3.02~4.62), glucocorticoid use (OR 2.50, 95% CI 1.74~3.59), and cyclooxygenase-2 inhibitor (OR 1.27, 95% CI 1.14~1.41) during this period (Table 4). Glucocorticoid discontinuation within 6 months from treatment was associated with male gender (OR 1.34, 95% CI 1.12~1.60), maximal MTX dose ≥15 mg/week (OR 1.63, 95% 1.40~1.89), combination therapy (OR 1.34, 95% CI 1.01~1.79), and pre-RA hospitalization (OR 1.30, 95% CI 1.11~1.53) (Table 4). Among comorbidities from the 1-year post-diagnosis period, chronic viral hepatitis B or C was associated with both MTX use of ≥15 mg/week and glucocorticoid discontinuation. The Charlson-Deyo comorbidity score was not associated with these proxies.

DISCUSSION

In this population-based nationwide study, we found that approximately 13% of RA population ever used bDMARD with a mean interval of 3.9 years from RA diagnosis to bDMARD initiation. We observed that the DMARD combination and glucocorticoids were the main treatment strategy before using bDMARD in most of the RA cases. However, MTX was chosen as the 1st csDMARD in only half of newly diagnosed RA patients and MTX dose escalation (≥15 mg/week) was observed among only half of its users. The underuse of MTX as the 1st starting DMARD among RA patients is in line with prescription patterns of other countries where 40%~50% of newly RA patients initiate MTX as the 1st agent [7,19]. Glucocorticoid discontinuation was achieved in a minority (less than 10% of glucocorticoid users) of the patients, within a dose of ≤7.5 mg/day. These treatment patterns were different from the international guidelines [3,4]. Instead, we observed a high compliance to HIRA reimbursement criteria, showing MTX-based csDMARD combination before bDMARD initiation. Trend analyses showed annual decrease of initial and maximal doses of MTX with increased use of alternative drugs such as tacrolimus and leflunomide. Patient age and gender, concomitant treatments, and comorbidity status were associated with MTX dose of ≥15 mg/week within the 1-year post-diagnosis period and glucocorticoid discontinu-

Table 4. Predictors of MTX use of ≥15 mg/week within the 1st year of diagnosis and glucocorticoid discontinuation within 6 months

Predictors	MTX ≥15 mg/week*	Glucocorticoid discontinuation†
Age at diagnosis (per 1-year decrease)	1.02 (1.01~1.02)	
Male	1.27 (1.12~1.45)	1.34 (1.12~1.60)
Medications		
Maximal MTX ≥15 mg/week	NA	1.63 (1.40~1.89)
csDMARD combination	3.74 (3.02~4.62)	1.34 (1.01~1.79)
Glucocorticoid use	2.50 (1.74~3.59)	NA
Cox-2 inhibitor use	1.27 (1.14~1.41)	
Comorbidities		
Chronic hepatitis B or C	1.33 (1.03~1.73)	1.93 (1.25~2.96)
Hospitalization		1.30 (1.11~1.53)

Values are presented as odds ratio (95% confidence interval). Cox: cyclooxygenase, csDMARD: conventional synthetic disease modifying antirheumatic drug, MTX: methotrexate, NA: not applicable, RA: rheumatoid arthritis. *The model included age, sex, index year, csDMARDs (leflunomide, tacrolimus, hydroxychloroquine, sulfasalazine), combination therapy, glucocorticoids, analgesics, and comorbidity list in Table 1. Comorbidities included in the model were ascertained from the 1st year after RA diagnosis. †The model included age, gender, index year, csDMARDs (MTX, leflunomide, tacrolimus, hydroxychloroquine, sulfasalazine), MTX dose, combination therapy, analgesics, and comorbidity list in Table 1. Comorbidities included in the model were ascertained from the 1st year after RA diagnosis.

ation within 6 months.

The proportion of patients who used bDMARD in Korea (12.6%, Figure 1) was relatively low compared to that in other countries having no prescription regulations or more generous reimbursement criteria such as USA (48.6%), France (60.2%), and Japan (50.5%) [20]. The proportion however was similar to that in the UK where a similar reimbursement threshold of Disease Activity Score 28-erythrocyte sedimentation rate of ≥5.1 despite csDMARD treatment has been implemented. In addition, the interval from RA diagnosis to bDMARD initiation of 3.9 years was much longer than recommended by the guidelines in case of not achieving low disease activity or remission within 3~6 months of treatment [3,4]. Such delayed bDMARD use may lead to loss of optimal treatment window for remission induction.

Previous studies described an optimal MTX use involves MTX use as the 1st csDMARD, rapid dose escalation, and parenteral route of administration in case of insufficient response to oral MTX [6,7]. In our study, 54.7% of RA patients in Korea received MTX as an initial therapy, and only half of the users achieved the maximal dose of ≥15 mg/week within 1-year after RA diagnosis. A limited proportion of patients tried parenteral MTX. Considering persistent glucocorticoid use during this period, RA activity was likely to be high enough to require MTX dose escalation. The proportion of MTX users (<10%) who ever tried a dose of ≥20 mg/week in our study was in contrast with that (26.4%~50%) in the European or USA cohorts [7,21]. One of the reasons for this finding might be due to concerns about potential toxicity with a higher MTX dose [22-24]. It has been noted that a lower maximal dose might be more appropriate for Asians due to possible toxicities [8,25,26]. In Japan, the MTX dose is allowed up-to 16mg/week due to potential toxicities [26]. Although studies are limited on dose-dependent adverse events in Korean population, future studies are essential to generate both biological and clinical evidence for optimal MTX dose among Koreans in terms of safety.

According to 2013 EULAR recommendations, only short-term use of low dose (≤7.5 mg/day) glucocorticoids is recommended in combination with a csDMARD for up to 6 months with rapid tapering [4]. Although glucocorticoids were mostly used at a low dose, discontinuation occurred in only a minority of patients in our cohort. The persistent use of glucocorticoids might in part be due to unremitting RA activity associated with suboptimal MTX use and beliefs in benefits of glucocorticoids outweighing risks [27,28].

Compared to the French cohort showing 10%~25% of csDMARD combination during the first year after RA diagnosis [7], more than 85% of csDMARD combination during the same period in our study was striking. Besides, almost all patients (>95%) in our study ever used csDMARD combination before bDMARD initiation probably due to HIRA requirements. It is still debatable whether to use csDMARD combination following failure of csDMARD monotherapy. Unlike 2008/2012 ACR guidelines that still offered an option of combining csDMARDs following MTX monotherapy failure [2], 2010/2013 EULAR recommendations did not support a step-up from MTX monotherapy to csDMARD combination in patients with poor prognostic factors (e.g., seropositivity as in our patients) [3,4]. However, comparable efficacy of csDMARD combination compared to bDMARD use has been claimed for patients with early arthritis and for MTX refractory patients in previous studies [10-13]. Therefore, csDMARD combination could be a viable option before bDMARD use among patients who cannot afford high costs of bDMARDs [29].

The longitudinal trend analysis showed that the average MTX dose has continually decreased over time. But use of leflunomide or tacrolimus has gradually increased particularly before initiating bDMARDs. Both leflunomide and tacrolimus have shown comparable efficacy to MTX in RA patients [17,18,30,31]. Since the HIRA reinforces csDMARD combination before initiating bDMARDs, physicians might prefer using lower dose MTX plus other potent csDMARDs rather than optimizing MTX dose in an attempt to obtain early achievement of HIRA requirements or to avoid toxicities at higher doses.

The real-world treatment patterns in our study could be explained by multiple reasons. It is inevitable that HIRA criteria altered treatment patterns during the pre-index period. However, the initial treatment strategy may be minimally affected by the HIRA requirements. Thus, a low proportion of MTX use as the 1st DMARD, lack of MTX dose escalation, or continuous glucocorticoid use could be associated with other reasons than HIRA requirements, such as preference to potent non-MTX drugs [17,18], concerns for toxicities of high dose MTX [22-26], and beliefs in benefits of glucocorticoids [27,28].

In our multivariable regression analysis, significant predictors of higher MTX dose and glucocorticoid discontinuation included demographics (younger age and/or male), concomitant treatments, and comorbidity status. Younger age was associated

with MTX use of ≥15 mg/week probably due to less concerns for toxicities. Concomitant treatments (combination therapy, glucocorticoids use, and cox-2 inhibitors) associated with higher MTX dose also reflect high RA activity of the given patients. On the other hand, glucocorticoid discontinuation was associated with aggressive treatment strategies (combination therapy and MTX use of ≥15 mg/week). This is consistent with our previous findings [32]. Thus, there is a possibility that bDMARD was unnecessarily used in a subgroup of patients whose disease activity might have been controlled with elevated doses of MTX. We found significant associations of higher dose of MTX and glucocorticoid withdrawal with previous hospitalizations and chronic viral hepatitis, but not comorbidities. A higher rate of chronic hepatitis B or C might be explained by more vigilant surveillance following higher MTX dose or glucocorticoid treatment because high dose users or glucocorticoid users were likely to visit the clinic more frequently due to high disease activity.

Several strengths are worth to mention in this study. First, few previous studies have evaluated treatment patterns of csDMARDs before bDMARD initiation, particularly in relation to early (≤1-year from diagnosis) treatment strategies. Second, analyses were relevantly comprehensive, comparing real-world treatment patterns and evaluating annual trends. Third, this nationally representative database can ensure generalizability of the study findings to those countries where they require csDMARD failure to qualify for reimbursement of bDMARD therapy [33]. Fourth, we could also determine the effect not only of clinical treatment guidelines but also of national health regulations on prevalent treatment patterns.

Our study has some limitations. First, using claims database, we did not have information on RA severity/activity and specific reasons for suboptimal MTX use, e.g., toxicities. Second, only bDMARD initiators were included in this study. Therefore, we did not compare them with never- bDMARD users who may have had different treatment patterns. Nevertheless, our findings are still relevant in terms of active RA patients because bDMARD users show in general high RA activity and need more rigorous treatment. Third, we used the 2004~2016 database, and the pre-biologic treatment patterns would be different at present. However, our data on longitudinal treatment patterns provide useful information to infer trajectories on current treatment patterns.

CONCLUSION

In conclusion, we observed a real-world practice on csDMARD before bDMARD therapy in Korea. MTX-based csDMARD combination and low dose glucocorticoid was prevalently used from diagnosis until bDMARD initiation, but MTX dose escalation and glucocorticoid discontinuation was suboptimal. It requires future studies on the specific reasons why they concern the high dose MTX (≥15 mg/week) and glucocorticoid discontinuation.

SUPPLEMENTARY DATA

Supplementary data can be found with this article online at https://doi.org/10.4078/jrd.2022.29.2.79

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CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

E.H.K. conceived and designed the study. A.S. conducted the programing, acquired the data, and did statistical analysis. M.J.K., E.H.P., and E.H.K. drafted the manuscript. M.J.K., E.H.P., A.S., Y.J.H., Y.J.L., E.B.L., H.J.B., and E.H.K. interpreted the data, critically revised the manuscript for important intellectual content, and approved the final version of the manuscript.

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REFERENCES

1. Bortoluzzi A, Valesini G, D'Angelo S, Frediani B, Bazzichi L, Afeltra A, et al. Immediate treatment with tumour necrosis factor inhibitors in synthetic disease-modifying anti-rheumatic drugs-naïve patients with rheumatoid arthritis: results of a modified Italian Expert Consensus. Rheumatology (Oxford) 2018;57(57 Suppl 7):vii32-41.
2. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2012;64:625-39.
3. Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964-75.
4. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492-509.
5. Verstappen SM, Jacobs JW, van der Veen MJ, Heurkens AH, Schenk Y, ter Borg EJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis 2007;66:1443-9.
6. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. Ann Rheum Dis 2009;68:1094-9.
7. Gaujoux-Viala C, Rincheval N, Dougados M, Combe B, Fautrel B. Optimal methotrexate dose is associated with better clinical outcomes than non-optimal dose in daily practice: results from the ESPOIR early arthritis cohort. Ann Rheum Dis 2017;76:2054-60.
8. Visser K, Katchamart W, Loza E, Martinez-Lopez JA, Salliot C, Trudeau J, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis 2009;68:1086-93.
9. Kim SY, Servi A, Polinski JM, Mogun H, Weinblatt ME, Katz JN, et al. Validation of rheumatoid arthritis diagnoses in health care utilization data. Arthritis Res Ther 2011;13:R32.
10. van Vollenhoven RF, Geborek P, Forslind K, Albertsson K, Ernestam S, Petersson IF, et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet 2012;379:1712-20.
11. de Jong PH, Hazes JM, Barendregt PJ, Huisman M, van Zeben D, van der Lubbe PA, et al. Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: first results of the tREACH trial. Ann Rheum Dis 2013;72:72-8.
12. Moreland LW, O'Dell JR, Paulus HE, Curtis JR, Bathon JM, St Clair EW, et al. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of Early Aggressive Rheumatoid Arthritis Trial. Arthritis Rheum 2012;64:2824-35.
13. O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med 2013;369:307-18.
14. Needham DM, Scales DC, Laupacis A, Pronovost PJ. A systematic review of the Charlson comorbidity index using Canadian administrative databases: a perspective on risk adjustment in critical care research. J Crit Care 2005;20:12-9.
15. Cochran WG. Some methods for strengthening the common χ^2 tests. Biometrics 1954;10:417-51.
16. Armitage P. Tests for linear trends in proportions and frequencies. Biometrics 1955;11:375-86.
17. Cohen S, Cannon GW, Schiff M, Weaver A, Fox R, Olsen N, et al. Two-year, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. Utilization of Leflunomide in the Treatment of Rheumatoid Arthritis Trial Investigator Group. Arthritis Rheum 2001;44:1984-92.
18. Furst DE, Saag K, Fleischmann MR, Sherrer Y, Block JA, Schnitzer T, et al. Efficacy of tacrolimus in rheumatoid arthritis patients who have been treated unsuccessfully with methotrexate: a six-month, double-blind, randomized, dose-ranging study. Arthritis Rheum 2002;46:2020-8.
19. Desai RJ, Solomon DH, Liu J, Kim SC. Secular trends in use of disease modifying anti-rheumatic drugs for the treatment of rheumatoid arthritis in the United States. Arthritis Rheumatol 2015;67(Suppl 10):2725. Available from: https://onlinelibrary.wiley.com/doi/10.1002/art.39448.
20. Kaló Z, Vokó Z, Östör A, Clifton-Brown E, Vasilescu R, Battersby A, et al. Patient access to reimbursed biological disease-modifying anti-rheumatic drugs in the European region. J Mark Access Health Policy 2017;5:1345580.
21. Curtis JR, Zhang J, Xie F, Beukelman T, Chen L, Fernandes J, et al. Use of oral and subcutaneous methotrexate in rheumatoid arthritis patients in the United States. Arthritis Care Res (Hoboken) 2014;66:1604-11.
22. Schnabel A, Reinhold-Keller E, Willmann V, Gross WL. Tolerability of methotrexate starting with 15 or 25 mg/week for rheumatoid arthritis. Rheumatol Int 1994;14:33-8.
23. Curtis JR, Beukelman T, Onofrei A, Cassell S, Greenberg JD, Kavanaugh A, et al. Elevated liver enzyme tests among patients with rheumatoid arthritis or psoriatic arthritis treated with methotrexate and/or leflunomide. Ann Rheum Dis 2010;69:43-7.
24. Solomon DH, Glynn RJ, Karlson EW, Lu F, Corrigan C, Colls J, et al. Adverse effects of low-dose methotrexate: a randomized trial. Ann Intern Med 2020;172:369-80.
25. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960-77.

26. Kameda H, Fujii T, Nakajima A, Koike R, Sagawa A, Kanbe K, et al. Japan College of Rheumatology guideline for the use of methotrexate in patients with rheumatoid arthritis. Mod Rheumatol 2019;29:31-40.
27. Svensson B, Boonen A, Albertsson K, van der Heijde D, Keller C, Hafström I. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. Arthritis Rheum 2005;52:3360-70.
28. Tengstrand B, Larsson E, Klareskog L, Hafström I. Randomized withdrawal of long-term prednisolone treatment in rheumatoid arthritis: effects on inflammation and bone mineral density. Scand J Rheumatol 2007;36:351-8.
29. Smolen JS, Landewé RBM, van der Heijde D. Response to: '2016 update of the EULAR recommendations for the management of rheumatoid arthritis: no utopia for patients in low/middle-income countries?' by Misra et al. Ann Rheum Dis 2017;76:e48.
30. Singer O, Gibofsky A. Methotrexate versus leflunomide in rheumatoid arthritis: what is new in 2011? Curr Opin Rheumatol 2011;23:288-92.
31. Nakajima A, Inoue E, Taniguchi A, Momohara S, Yamanaka H. Effectiveness of tacrolimus in comparison with methotrexate or biologics in propensity score-matched patients with rheumatoid arthritis. Mod Rheumatol 2016;26: 836-43.
32. Park EH, Shin A, Ha YJ, Lee YJ, Lee EB, Song YW, et al. Risk factors associated with initiation of a biologic disease modifying anti-rheumatic drug in patients with rheumatoid arthritis: a nested case-control study on 34,925 patients. Joint Bone Spine 2021;88:105057.
33. Putrik P, Ramiro S, Kvien TK, Sokka T, Uhlig T, Boonen A; Equity in Clinical Eligibility Criteria for RA treatment Working Group. Variations in criteria regulating treatment with reimbursed biologic DMARDs across European countries. Are differences related to country's wealth? Ann Rheum Dis 2014;73:2010-21.