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Original Article

Use of Disease-modifying Antirheumatic Drugs After Cancer Diagnosis in Rheumatoid Arthritis Patients

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Objective: There is no recommendation for the use of disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis (RA) who developed cancer. We examined changes in the DMARDs prescription patterns associated with cancer diagnosis in RA patients.

Methods: We reviewed the medical records of 2,161 RA patients who visited rheumatology clinic between January 2008 and February 2017 and found 40 patients who developed cancer during RA treatment. In these patients, we examined DMARDs prescription patterns before and right after cancer diagnosis and at recent outpatient clinic visits.

Results: Before cancer diagnosis, methotrexate (MTX)-combined conventional synthetic DMARDs (csDMARDs) were most commonly prescribed (22, 55.0%) and biological DMARDs (biologics) in nine patients (22.5%). For cancer treatment, 19 patients received chemotherapy (including adjuvant chemotherapy) and 21 patients had surgery only. Right after cancer diagnosis, changes in the DMARDs prescription patterns were similar in discontinuation (13, 32.5%), switching (14, 35.0%), and maintenance (13, 32.5%). DMARDs were discontinued more frequently in the chemotherapy group (9/19, 47.4%) than the surgery only group (4/2, 19.0%) ($p<0.05$). Among the 13 patients who discontinued DMARDs, nine (69.2%) resumed DMARDs after a median of 5.5 months (interquartile range [IQR] 2.9, 18.3) due to arthritis flare. At a median of 4.6 years (IQR 3.3, 6.7) after cancer diagnosis, 25 patients were evaluated at recent outpatient clinic visits. Four patients received no DMARD, three MTX monotherapies, 11 csDMARDs combination therapies, and seven biologics.

Conclusion: A significant number of RA patients who developed cancer during RA treatment were still receiving DMARDs including biologics after cancer diagnosis.

Keywords: Biologics, Cancer, Disease-modifying antirheumatic drugs, Methotrexate, Rheumatoid arthritis

INTRODUCTION

Patients with rheumatoid arthritis (RA) are more susceptible to malignancies such as lung cancer and lymphoma than the general population [1-3]. However, it is not clear how to treat RA patients who developed cancer during RA treatment. There is no established recommendation for the use of disease-modifying antirheumatic drugs (DMARDs) in these patients [4-7].

Several conventional synthetic DMARDs (csDMARDs) and biological DMARDs (biologics) used for RA treatment have immunosuppressive activity and the potential of suppressing antitumor immunity and increasing the risk of infection. Therefore,

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once cancer is diagnosed, strong csDMARDs with significant immunosuppressive activities such as methotrexate (MTX), leflunomide (LEF), and tacrolimus (TC) and biologics are usually discontinued. However, if RA disease activity increases after the discontinuation of DMARDs, it is likely to adversely affect the prognosis of not only arthritis but also cancer [8,9].

Many reports have shown that biologics such as tumor necrosis factor (TNF) inhibitors did not increase the risk of cancer recurrence in RA patients with prior cancer history [5-7,10-13]. This means that if arthritis worsens, the same DMARDs therapy strategy could be considered in RA patients with prior cancer history as those without. However, it is not yet clear when DMARDs can be resumed in RA patients with cancer history [4]. Furthermore, little is known about DMARDs treatment right after cancer diagnosis.

We investigated DMARDs prescription patterns at three time points (before and right after cancer diagnosis and recent outpatient clinic visits) in RA patients who were diagnosed with cancer while being treated for RA.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the medical records of 2,161 patients with RA who visited the rheumatology clinic of the Saint Vincent's Hospital in Suwon, Korea between January 2008 and February 2017. All the patients satisfied the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA. We found 118 RA patients with combined cancer. Patients who developed cancer prior to RA were excluded and the remaining 40 patients who developed cancer while being treated for RA were included in our study. This study was approved by the Institutional Review Board of Saint Vincent's Hospital (VC18RESI0035) and conducted in accordance with the provisions of the Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects.

DMARDs prescription pattern and cancer treatment modality

We examined age, sex, RA-related data (disease duration, seropositivity, DMARDs prescription pattern) and cancer-related data (cancer type, cancer stage, and cancer treatment modality). DMARDs prescription patterns were examined at three time points: before and right after cancer diagnosis and at recent outpatient clinic visits (latest visit at the time of data collection). In patients who underwent surgery, DMADRDs prescription pattern right after cancer diagnosis was examined one month after surgery considering that DMARDs may be temporarily stopped before and right after surgery. DMARDs prescription patterns were divided into csDMARDs monotherapy, csDMARDs combination therapy, and biologics. Changes in DMARDs prescription patterns were classified into discontinuation, switching, and maintenance. Cancer treatment modalities were divided into surgery only and chemotherapy. Patients who received adjuvant chemotherapy along with surgery were classified as the chemotherapy group.

Statistical analysis

Descriptive statistics were expressed as median and interquartile range (IQR). Differences between the two groups were compared using Chi-square test. All statistical analyses were performed using SPSS 17 software (SPSS Inc., Chicago, IL, USA) and p-value < 0.05 was considered statistically significant.

RESULTS

Characteristics of enrolled patients and DMARDs prescription before cancer diagnosis

Forty patients were diagnosed with cancer while being treated for RA (Table 1). Thirty-one patients had been treated with csDMARDs (four with monotherapy, 27 with combination therapy) and nine (22.5%) with biologics (Table 2). MTX was used in 30 patients (75.0%) (MTX monotherapy in three, combination

Table 1. Clinical characteristics of rheumatoid arthritis patients with cancer

	Total (n=40)	Surgery only (n=21)	Chemotherapy (n=19)*
Age at cancer diagnosis (yr)	67 (55, 73)	70 (52, 77)	66 (57, 71)
Female	28 (70.0)	16 (76.2)	12 (63.2)
Disease duration (yr)	4.5 (2.7, 4.5)	3.4 (1.5, 11.4)	4.2 (2,0, 10.0)
Seropositivity†	36 (90.0)	19 (90.5)	17 (89.5)

Values are presented as median (interquartile range) or number (%). *Chemotherapy only=nine, Adjuvant chemotherapy=ten. †Seropositivity=positive for rheumatoid factor or anti-citrullinated protein antibody.

Table 2. DMARDs at the time of cancer diagnosis in rheumatoid arthritis patient

DMARDs prescription patterns		Total (n=40)	Surgery only (n=21)	Chemo-therapy (n=19)*
csDMARDs (n=31)				
Monotherapy (n=4)	MTX	3	3	0
	SSZ	1	1	0
Combination (n=27)	MTX (+)	22	8	14
	MTX (–)	5	2	3
Biologics (n=9)	MTX (+)	5	4	1
	MTX (–)	4	3	1

DMARDs: disease modifying anti-rheumatic drugs, csDMARDs: conventional synthetic DMARDs, MTX: methotrexate, SSZ: sulfasalazine, MTX (+): methotrexate used, MTX (–): methotrexate not used. *Chemotherapy only=nine, Adjuvant chemotherapy=ten.

with other csDMARDs in 22, combination with biologics in five).

Lung cancer was the most common, with 10 patients. There were six patients with stomach cancer, four with thyroid cancer, three with colon cancer, two each with cervical cancer, bladder cancer, breast cancer, renal cancer, and one each with pancreas cancer, skin cancer, common biliary duct (CBD) cancer, vaginal cancer, ovary cancer, palate cancer, malignant schwannoma, chronic myelogenous leukemia, myelodysplastic syndrome. When it comes to tumor stages in 38 patients with solid cancers, stage 1 was the most common with 19 patients (50.0%), stage 2 with four (10.5%), stage 3 with seven (18.4%), and stage 4 with eight (21.1%).

Twenty-one patients (52.5%) received surgery only and 19 (47.5%) received chemotherapy (chemotherapy only in nine and adjuvant chemotherapy with surgery in 10). MTX-combined csDMARDs were most commonly used before cancer diagnosis both in the surgery only group and the chemotherapy group (Table 2).

DMARDs prescription patterns right after cancer diagnosis

Thirteen patients (32.5%) stopped DMARDs right after cancer diagnosis: four in the surgery only group (4/21, 19.0%) and nine in the chemotherapy group (9/19, 47.4%) ($p<0.05$) (Table 3). DMARDs were switched in 14 patients (35.0%). Of these 14 patients, eight received csDMARDs monotherapy (MTX in three, hydroxychloroquine [HCQ] in four, and sulfasalazine [SSZ] in one) and six received csDMARDs combination therapy (MTX+HCQ in one, SSZ+HCQ in four, and LEF+TC+HCQ in one). Thirteen patients (32.5%) maintained the same DMARDs as before cancer diagnosis. Among csDMARDs, HCQ was used the most (16 patients) and the number of patients receiving MTX was decreased from 30 to 14 (MTX monotherapy in six, combination with other csDMARDs in eight). Biologics were maintained in two out of nine patients. One was a 72-year-old patient with stage II colon cancer who received etanercept and the other was an 80-year-old patient with stage I bladder cancer who received tocilizumab.

Table 3. DMARDs right after cancer diagnosis in rheumatoid arthritis patients

Changes in DMARDs prescription patterns		Prescribed DMARDs
Discontinuation (n=13)*		-
Switching (n=14)	Monotherapy (n=8)	MTX (n=3), HCQ (n=4), SSZ (n=1)
	Combination (n=6)	MTX+HCQ (n=1)
		SSZ+HCQ (n=4)
		LEF+TC+HCQ (n=1)
Maintenance (n=13)	Monotherapy (n=4)	MTX (n=3), SSZ (n=1)
	Combination (n=7)	MTX+SSZ+HCQ (n=1)
		MTX+LEF+HCQ (n=3)
		MTX+BL+MR (n=1)
		SSZ+HCQ (n=1)
		LEF+BL+HCQ (n=1)
	Biologics (n=2)	ETA (n=1)†, TCZ (n=1)‡

DMARDs: disease modifying anti-rheumatic drugs, MTX: methotrexate, HCQ: hydroxychloroquine, SSZ: sulfasalazine, TC: tacrolimus, LEF: leflunomide, BL: bucillamine, MR: mizoribine, ETA: etanercept, TCZ: tocilizumab. *Four in the surgery only group (4/21, 19.0%), nine in the chemotherapy group (9/19, 47.4%) ($p<0.05$). †Patient with stage II colon cancer. ‡Patient with stage I bladder cancer.

Resumption of DMARDs in the discontinuation group

Among the 13 patients who stopped DMARDs right after cancer diagnosis (four in the surgery only group, nine in the chemotherapy group), nine (69.2%) (three in the surgery only group, six in the chemotherapy group) resumed DMARDs due to the aggravation of arthritis after a median of 5.5 months (IQR 2.9, 18.3) (Table 4). Among the three patients in the surgery only group, two had received MTX-combined csDMARDs be-

Table 4. Resumption of DMARDs (n=9)* in the discontinuation group (n=13)

Cancer treatment	Surgery only (n=3)	Chemotherapy (n=6)
DMARDs (before cancer diagnosis → resumption)	MTX+LEF → MTX	MTX+SSZ+HCQ → MTX
	MTX+SSZ → ETA	MTX+LEF+HCQ → LEF+HCQ
	MTX+ADA → same	MTX+LEF+SSZ → LEF+HCQ
		MTX+SSZ+TC → MTX
		MTX+HCQ → same
		MTX+HCQ → LEF+HCQ

DMARDs: disease modifying anti-rheumatic drugs, MTX: methotrexate, LEF: leflunomide, SSZ: sulfasalazine, HCQ: hydroxychloroquine, TC: tacrolimus, ETA: etanercept, ADA: adalimumab, IQR: interquartile range. *Time interval between discontinuation and resumption of DMARDs was median of 5.5 months (IQR 2.9, 18.3).

Table 5. DMARDs at recent outpatient clinic visits (n=25)*

DMARDs prescription patterns			Prescribed DMARDs
No DMARD (n=4)†			
csDMARDs (n=14)			
Monotherapy (n=3)			MTX (n=3)
Combination (n=11)	MTX (+)	(n=8)	MTX+HCQ (n=1), MTX+HCQ+SSZ (n=1), MTX+TC (n=1), MTX+LEF (n=5)
	MTX (–)	(n=3)	LEF+HCQ (n=1), SSZ+TC (n=1), SSZ+HCQ (n=1)
Biologics (n=7)	MTX (+)	(n=3)	ADA (n=1), TCZ (n=1), ABA (n=1)
	MTX (–)	(n=4)	ETA (n=2), TCZ (n=2)

DMARDs: disease modifying anti-rheumatic drugs, csDMARDs: conventional synthetic DMARDs, MTX: methotrexate, SSZ: sulfasalazine, HCQ: hydroxychloroquine, TC: tacrolimus, LEF: leflunomide, ADA: adalimumab, TCZ: tocilizumab, ABA: abatacept, ETA: etanercept, IQR: interquartile range. *At a median of 4.6 years (IQR 3.3, 6.7) after cancer diagnosis, five patients died (four out of 13 in the discontinuation group and one out of 27 in the switching or maintenance group) and 10 patients were lost (two out of 13 in the discontinuation group and eight out of 27 in the switching or maintenance group). †Three had cancer recurrence after chemotherapy and one achieved arthritis remission after cancer treatment.

fore cancer diagnosis and one of them resumed MTX as monotherapy and the other received etanercept. The remaining one in the surgery only group who had received adalimumab before cancer diagnosis resumed adalimumab. All six patients in the chemotherapy group had received MTX-combined csDMARDs before cancer diagnosis and three of them resumed DMARDs with LEF+HCQ combination, two with MTX monotherapy and the last one with MTX+HCQ combination.

DMARDs prescription patterns at recent outpatient clinic visits

During the follow-up period, five patients died (four out of 13 in the discontinuation group, one out of 27 in the switching or maintenance group) and 10 patients were lost (two out of 13 in the discontinuation group, eight out of 27 in the switching or maintenance group). Twenty-five patients were evaluated at recent outpatient clinic visits at a median of 4.6 years (IQR 3.3, 6.7) after cancer diagnosis. Four patients were prescribed no DMARD, three MTX monotherapies, 11 csDMARDs combination therapies, and seven biologics (Table 5). MTX was used in 14 patients (MTX monotherapy in three, combination with other csDMARDs in eight, combination with biologics in three). Among the four patients with no DMARD prescription, three had cancer recurrence after chemotherapy and the remaining one achieved arthritis remission after cancer treatment. As for biologics, seven patients started biologics at a median of 17 months (IQR 5.55, 29.1) after cancer treatment and five of them were newly prescribed biologics after cancer diagnosis. Remaining two had been receiving biologics at the time of cancer diagnosis. One of them continued etanercept after cancer diagnosis and the other discontinued adalimumab after cancer diagnosis and resumed it during follow-up. In addition, evaluation of patient receiving biologics at recent outpatient clinic visit according to DMARDs prescription pattern right after cancer diagnosis (Table 6) showed that the proportion of patients receiving biologics was higher in the discontinuation group

(3/7, 42.8%) than in the switching or maintenance group (4/18, 22.2%) ($p<0.05$).

Cancer recurrence in patients with rheumatoid arthritis

During follow-up, relapses were confirmed in eight patients at a median of 1.6 years (IQR 1.0, 2.3) after the initial cancer diagnosis (Table 7). Two of them had been receiving biologics before cancer relapse, both adalimumab. A male with stage 4 lung cancer, who had discontinued DMARD right after cancer diagnosis, resumed HCQ monotherapy after chemotherapy and died due to cancer progression. A female with stage 3 CBD cancer had stopped DMARD right after cancer diagnosis and then no DMARD was prescribed. A female with stage 1 cervical cancer switched from MTX+adalimumab to LEF+TC+HCQ combination right after cancer diagnosis and continued it after initial cancer treatment. After cancer relapse, her DMARDs were switched to LEF+HCQ combination and then stopped. A female with stage 3 colon cancer switched to SSZ+HCQ combination right after cancer diagnosis. Later, she was prescribed MTX+adalimumab, which was stopped after cancer recurrence. A male with CML discontinued DMARD right after CML diagnosis and then no DMARD was prescribed. A female with stage 1 stomach cancer discontinued DMARD right after cancer diagnosis. Later, she was prescribed adalimumab, which was switched to tocilizumab after cancer recurrence. A female with stage 2 lung cancer switched to HCQ monotherapy right after cancer diagnosis and then to MTX+HCQ combination after cancer treatment. A male with stage 1 bladder cancer maintained tocilizumab right after cancer diagnosis and then

Table 6. DMARDs prescription patterns at recent outpatient clinic visit according to DMARDs prescription pattern right after cancer diagnosis

DMARDs prescription patterns	Discontinuation (n=7)	Switching or Maintenance (n=18)
No DMARD (n=4)	1 (14.3)	3 (16.7)
csDMARDs (n=14)	3 (42.8)	11 (61.1)
Monotherapy (all MTX) (n=3)	1	2
Combination MTX (+) (n=8)	2	6
MTX (–) (n=3)	0	3
Biologics (n=7)	3 (42.8)	4 (22.2)

Values are presented as number (%) or number only. DMARDs: disease modifying anti-rheumatic drugs, csDMARDs: conventional synthetic DMARDs, MTX: methotrexate.

Table 7. Patients with cancer recurrence and progression

No.	Sex/ Age (yr)	Cancer	Stage	DMARDs before cancer diagnosis	DMARDs right after cancer diagnosis	Cancer treatment	DMARDs before recurrence	Relapse time (yr)	Cancer treatment after recurrence	DMARDs after recurrence	FU (yr)	Current RA treatment
1	M/72	Lung	IV (T4aN0M0)	MTX+LEF+HCQ	Discontinuation	C	HCQ	1.7	C	HCQ	2.6	Death
2	F/71	CBD	III	MTX+SSZ+HCQ	Discontinuation	S+C	No DMARD	0.9	C	No DMARD	1.2	FU loss
3	F/39	Cervix	I	MTX+ADA	Switching→LEF+TC+HCQ	S+C	LEF+TC+HCQ	1.5	C	LEF+HCQ	7.1	No DMARD
4	F/57	Colon	III	MTX+SSZ+HCQ	Switching→ SSZ+HCQ	S+C	MTX+ADA	2.3	C	No DMARD	6.6	No DMARD
5	M/50	CML	Accelerated	MTX+HCQ	Discontinuation	C	No DMARD	2.4	C	No DMARD	8.0	No DMARD
6	F/67	Stomach	I	MTX+LEF	Discontinuation	S	ADA	2.1	S	ADA	7.1	TCZ
7	F/66	Lung	II	MTX+LEF+HCQ	Switching → HCQ	S+C	MTX+HCQ	1.3	C	MTX+HCQ	4.4	MTX+HCQ
8	M/80	Bladder	I	TCZ	Maintenance	S	MTX+LEF	0.7	S+C	LEF	4.6	MTX

F: female, M: male, CBD: common bile duct, CML: chronic myelogenous leukemia, DMARDs: disease modifying antirheumatic drugs, MTX: methotrexate, LEF: leflunomide, TCZ: tocilizumab, ADA: adalimumab, HCQ: hydroxychloroquine, SSZ: sulfasalazine, S: surgical therapy, C: chemotherapy, FU: follow-up, RA: rheumatoid arthritis.

switched to MTX+LEF combination. After cancer relapse, his DMARD was switched to LEF monotherapy, and then MTX monotherapy.

When it comes to the prognosis of nine patients who received biologics before cancer diagnosis, two died, one was lost to follow up, one survived cancer relapse, and the remaining five had no significant cancer-related problems.

DISCUSSION

Patients with RA have a higher risk of malignancies, especially lung cancer and lymphoma, than the general population [1-3]. Although malignancies are common in RA patients, a guideline for the treatment of RA patients with cancer has not yet been established [4-7].

We retrospectively examined DMARDs prescription patterns at three time points (before and right after cancer diagnosis and recent outpatient clinic visits) in RA patients who developed cancer while being treated for RA. Right after cancer diagnosis, only about one third of the patients stopped DMARDs and the remaining two thirds switched or maintained DMARDs (Figure 1). Among csDMARDs, HCQ, which is known to be the safest one, was prescribed the most right after cancer diagnosis. Although the number of patients receiving MTX or biologics largely decreased right after cancer diagnosis (MTX from 30 to 14 and biologics from nine to two), a significant number of patients (16/40, 40.0%) were still receiving MTX or biologics. In particular, nine out of the 13 patients who discontinued DMARDs right after cancer diagnosis resumed DMARDs at a median of 5.5 months after cancer diagnosis. At recent outpatient clinic visits (at a median of 4.6 years after cancer diagnosis), 21 out of 25 patients (84.0%) were prescribed DMARDs including seven patients receiving biologics (Figure 1). In particular, five of the seven patients receiving biologics at recent outpatient clinic visits were those who newly started biologics after cancer diagnosis. Our study showed that a significant number of RA patients who developed cancer during RA treatment were still receiving DMARDs including biologics after cancer diagnosis.

When cancer develops during the treatment of RA, it is usual to discontinue DMARDs such as MTX and biologics which have immunosuppressive effects. However, little is known about the changes in RA disease activity after stopping DMARDs. Even though DMARDs are not used, chemotherapy may control autoimmune inflammation. In patients with inflammatory bowel disease (IBD) with cancer, chemotherapy decreased the frequency of IBD flares and the use of drugs for the treatment of IBD [14]. However, there is no such study on RA. In real practice, we occasionally saw RA disease flares after the discontinuation of DMARDs in RA patients undergoing cancer treatment. In our study, nine out of the 13 patients who discontinued DMARDs right after cancer diagnosis resumed DMARDs due to the aggravation of arthritis at a median of 5.5 months after cancer diagnosis. Of note, six of them were in the chemotherapy group.

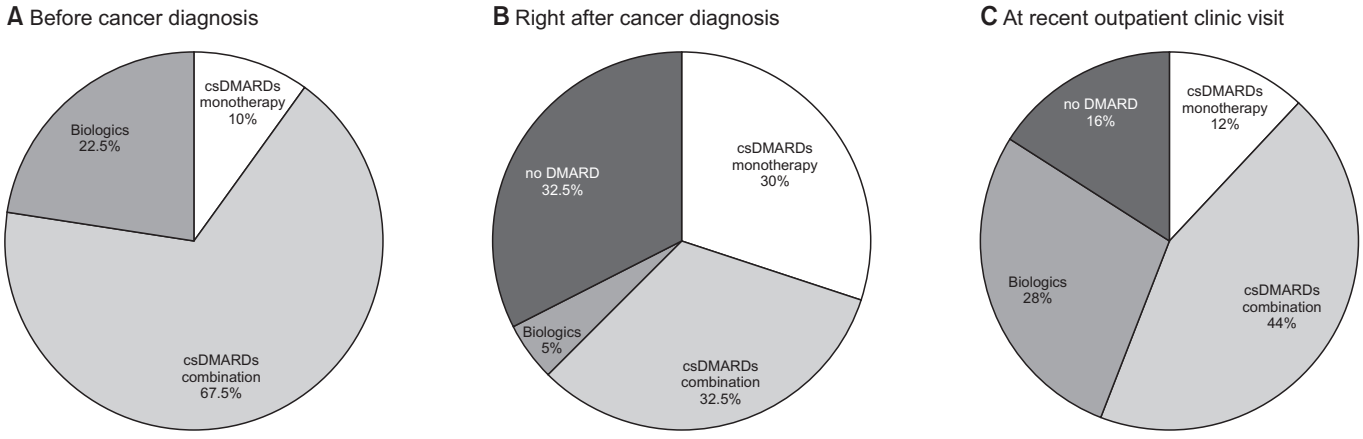

Figure 1. DMARDs prescription patterns before and after cancer diagnosis in RA patients. (A) Before cancer diagnosis (n=40); 27 patients were treated with csDMARDs combination (67.5%), 4 with csDMARDs monotherapy (10%), and 9 with biologics (22.5%). (B) Right after cancer diagnosis (n=40); 13 patients discontinued DMARDs (32.5%) and 13 patients were treated with csDMARDs combination (32.5%), 12 with csDMARDs monotherapy (30%), and 2 with biologics (5%). (C) At recent outpatient clinic visit (median 4.6 years [IQR 3.3, 6.7] after cancer diagnosis) (n=25): 4 patients were prescribed no DMARD (16%), 11 csDMARDs combination (44%), 3 csDMARDs monotherapy (12%), and 7 biologics (28%). RA: rheumatoid arthritis, csDMARDs: conventional synthetic DMARDs, IQR: interquartile range.

One of the reasons for the reluctance to administer DMARDs in RA patients with current cancer or cancer history is that DMARDs can suppress anti-tumor immune response and thereby interfere with cancer treatment and increase the risk of cancer recurrence. However, biologics such as TNF inhibitors don't seem to increase the risk of cancer recurrence in RA patients with a history of cancer [5-7,10-13]. Xie et al. [6] reported that biologics including TNF inhibitors, rituximab, and anakinra were not associated with an increased risk of new or recurrent cancer compared with csDMARDs in RA patients with prior cancer history. Shelton et al. [15] reported similar rates of cancer recurrence among patients with immune-mediated diseases (RA, IBD, and psoriasis) and prior cancer history who received anti-TNF therapy, immune-modulatory therapy, or no immune suppression. In our study, seven RA patients with prior cancer history were receiving biologics at recent outpatient clinic visits. Two of them had been prescribed biologics before cancer diagnosis and did well without cancer relapse. Five patients were newly prescribed biologics after cancer diagnosis and only one of them had cancer relapse while being treated with adalimumab, which was switched to tocilizumab after surgery.

Even if cancer developed, there was no difference in cancer stage or survival rate between patients who received TNF inhibitors and those who did not [16]. When it comes to the survival of RA patients who were treated with biologics after cancer diagnosis, Phillips et al. [17] reported that, in RA patients with head and neck cancer (HNC), treatment with a TNF inhibitor was not a risk factor for recurrence or HNC-attributable death. Pundole et al. [18] also found no significant differences in overall survival between RA patients with solid malignancies who received biologic DMARDs and those who did not.

As for the interval between cancer diagnosis and the resumption of biologics, it is very variable according to reports [4,6,10,11,19-23]. Lopez-Olivo et al. [4] reported that starting biological therapy is recommended for patients treated for cancers more than 5 years prior in many recommendations. However, Pappas et al. [20] reported that in real-world practice, nearly one-third of RA patients with a cancer diagnosis were treated with systemic therapy in the immediate visit after malignancy diagnosis. Mamtani et al. [21] reported that starting anti-TNF therapy 1 year after primary breast cancer surgery did not significantly increase the risk of breast cancer recurrence. Pundole et al. [22] reported that 26% of RA patients with cancer received biologics after cancer diagnosis and 54% of them had received biologics before cancer diagnosis and continued this therapy after cancer diagnosis. Furthermore, Phan et al. [23] observed that there were no differences in survival and recurrence rates at 1, 2, and 5 years between patients who received TNF inhibitors and those who did not and suggested that TNF inhibitors may be used safely in select inflammatory disease patients with concurrent cancer if therapy is needed for proper disease control. In our study, seven patients who were receiving biologics at recent outpatient clinic visits started biologics at a median of 17 months (IQR 5.55, 29.1) after cancer treatment.

What is more problematic is that management of arthritis could be suboptimal with the fear of cancer recurrence in RA patients with cancer history [8]. It was reported that cancer patients with RA have a worse prognosis than those without and RA seemed to contribute to the increase in the mortality rate of cancer patients with RA independently of the cancer [24-26]. Moreover, high RA disease activity is associated with a high risk of cancer such as lymphoma [9,27,28], which suggests that suboptimal management of arthritis in RA patients with cancer history could increase the risk of cancer recurrence.

When it comes to targeted synthetic DMARDs such as JAK inhibitors, the United States Food & Drug Administration (FDA) cautioned about the increased risk of cancer [29]. In a large randomized safety clinical trial of tofacitinib, lymphomas and lung cancers were observed at a higher rate in patients treated with tofacitinib compared to those treated with TNF blockers. In particular, current or past smokers treated with tofacitinib had a higher rate of lung cancer and additional increased risk of overall cancers. The FDA considered that two other JAK inhibitors, baricitinib and upadacitinib, may have similar risks as seen in the tofacitinib safety trial because they share mechanisms of action with tofacitinib.

There are several limitations to our study. First, classification of DMARDs prescription pattern into only three categories of csDMARDs monotherapy, csDMARDs combination therapy, and biologics may be oversimplified. For example, patients receiving SSZ+HCQ and those receiving triple therapy including strong csDMARDs such as MTX, LEF, or TC could have different clinical status but are classified into the same group of csDMARDs combination therapy in our study. However, it was difficult to group patients according to specific csDMARDs in more detail because of the small number of enrolled patients. Secondly, examination of prescription pattern of each csDMARDs separately could have given more relevant information,

although we tried to describe the use of MTX and other csDMARDs as specific as possible. Third, due to retrospective study design, RA disease activity score (DAS) 28 was measured not in all patients but only in those patients who were prescribed biologics according to the Korea Health Insurance & Assessment Service reimbursement guideline for biologics, and therefore it was not possible to directly see the relationship between RA disease activity and changes in DMARDs prescription patterns. However, since DMARDs prescription was determined according to clinical needs in everyday practice, we thought there might be a relationship between DMARDs prescription patterns and RA disease activity. For example, if biologics and strong csDMARDs such as MTX, LEF, and immunusuppressants were used, we supposed that RA disease activity would have been high. Lastly, large-scale studies, for example big registry studies, are necessary to make practical guidelines for the management of RA patients who are diagnosed with cancer or have prior cancer history.

It is a complex problem to optimally treat RA patients who developed cancer or have a history of cancer. First of all, cancer types and stages at the time of cancer diagnosis, risk of recurrence, and prognosis are all different for each patient and a tailored therapeutic approach is necessary [4,6,7]. In addition, it has been known that newer cancer immunotherapies can stimulate the immune system and cause autoimmune manifestations including flares of RA disease activity. In particular, immune checkpoint inhibitors have been reported to induce inflammatory arthritis in 50% of patients treated with these drugs as immune-related adverse events [30,31]. These mean that further research on how to treat RA patients who developed cancer or have a prior cancer history is necessary and close cooperation with oncologists is essential.

CONCLUSION

Our study showed that a significant number of RA patients who developed cancer during RA treatment were still receiving DMARDs including biologics after cancer diagnosis. This suggests that a significant number of patients require active treatment of RA with DMARDs even after cancer diagnosis.

FUNDING

None.

CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

Y.B.J. and K.S.P. concepted and designed the work and acquired, analyzed, and interpretated data for the work. Y.B.J., K.S.P., S.M.J., Y.J.P., and K.J.K. drafted the work or revised it critically for important intellectual content.

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