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Review Article

The Use of Biological Disease-modifying Antirheumatic Drugs for Inflammatory Arthritis in Korea: Results of a Korean Expert Consensus

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Biological disease-modifying antirheumatic drugs (bDMARDs) are highly effective agents for the treatment of inflammatory arthritis; however, they also possess a potential risk for serious infection. Recently, with the rapid expansion of the bDMARDs market in Korea, reports of serious adverse events related to the agents have also increased, necessitating guidance for the use of bDMARDs. Current work entitled, "Expert Consensus for the Use of bDMARDs Drugs for Inflammatory Arthritis in Korea," is the first to describe the appropriate use of bDMARDs in the management of inflammatory arthritis in Korea, with an aim to provide guidance for the local medical community to improve the quality of clinical care. Twelve consensus statements regarding the use of bDMARDs for the management of rheumatoid arthritis and ankylosing spondylitis were generated. In this review, we provide detailed guidance on bDMARDs use based on expert consensus, including who should prescribe, the role of education, indications for use, and monitoring strategies for safety. **(J Rheum Dis 2020;27:4-21)**

Key Words. Expert consensus, bDMARDs, Inflammatory arthritis, Rheumatoid arthritis, Ankylosing spondylitis

INTRODUCTION

Inflammatory arthritis including rheumatoid arthritis (RA) and ankylosing spondylitis (AS) is a chronic autoimmune disease, which creates a major health burden with negative impact on activities of daily living, quality of life, and utilization of health care resources [1-6]. However, there was a dramatic improvement in the lives of many patients with inflammatory arthritis after the introduction of highly effective agents for treatment, i.e. biological disease-modifying antirheumatic drugs (bDMARDs) [7-13]. Due to their high efficacy, bDMARDs are used increasingly in the treatment of inflammatory arthritis in a recent decade, but the issues regarding appropriate use, safety and cost have been also raised in parallel [14-17]. The global rheumatology community has realized the importance of these issues regarding bDMARDs use, facilitating the development of several recommendations and guidelines from the major rheumatology societies including the American College of Rheumatology (ACR) [9,10], the European League Against Rheumatism (EULAR) [12,18] and Asia Pacific League of Associations for

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Rheumatology (APLAR) [13]. As observed globally, reports of inappropriate use and serious adverse events related to bDMARDs were increasingly observed in Korea, with the rapid expansion of the bDMARDs market in the region. The Korean College of Rheumatology (KCR) recognized the urgent need for the development of regional guideline based on scientific evidences to guide the practitioners to use bDMARDs effectively and safely, since the differences in disease manifestations, healthcare resources, and medical insurance systems among countries preclude direct application of international guidelines. In 2018, the task force team has been organized under the auspice of the KCR Heath Policy Affairs Committee to develop an expert consensus for the appropriate use of bDMARDs for inflammatory arthritis in Korea.

In this review, we provide detailed guidance on bDMARDs use in adults with inflammatory arthritis, based on the "Expert Consensus for the Use of bDMARDs for inflammatory arthritis in Korea" developed by the KCR. Twelve consensus statements regarding the use of bDMARDs for the management of RA and AS were generated, in consideration of local medical circumstance. The quality of evidence was evaluated using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system (Table 1) [19,20]. We focused on RA and AS because these are the most common inflammatory arthritis in terms of incidence of diseases and the use of biologics agent for treatment [11,14,15]. The statements covered 4 topics: 1) who should prescribe, 2) the role of education, 3) indications for use, and 4) required evaluations before and during use for safety (Table 2). The current consensus statements are the first to describe the appropriate use of bDMARDs in the management of inflammatory arthritis in Korea, with an aim to provide guidance for the local medical community to improve the quality of clinical care.

MAIN SUBJECTS

Developmental process

1) Korean College of Rheumatology working group

To develop the expert opinion for use of bDMARDs in patients with inflammatory arthritis, the development group was established on behalf of the KCR. The development group consisted of 6 rheumatologists and 1 expert in literature search to collect and evaluate the evidences, and draft the consensus statement. The consensus group consisting of representatives from the relevant stakeholders participated in a voting process to reach a clinical consensus.

2) Scope of clinical consensus statements

The clinical consensus statement was developed to improve the quality of health care in patients with RA and AS. The clinical research question was determined using the PIPOH instrument as follows:

Population: Adult patients who were diagnosed with RA or AS according to the previous or current classification criteria [21-24]

Intervention: Treatment with bDMARDs

Professionals: Physicians who treat patients using bDMARDs

Outcomes: Improving the quality of care (efficacy and safety)

Health care setting: all medical settings that prescribe bDMARDs, including community and academic practice setting

This clinical consensus statement covered all currently available bDMARDs in Korea: anti-tumor necrosis factor (TNF) inhibitors including infliximab, etanercept, adalimumab, and golimumab, and anti-B-cell agent (rituximab), co-stimulation inhibitor (abatacept), and interleukin (IL)-6 receptor blocker (tocilizumab) for treatment

Table 1. Significance of the quality of evidence according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system [19,20]

Quality level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 2. Expert opinion for the management of inflammatory arthritis in adults with biological disease-modifying antirheumatic drugs* in South Korea

Recommendation	Appropriateness[†] / Median Likert Scale score	Level of agreement[‡] (%, agreement)
1. bDAMRDs should be prescribed by an expert experienced in the diagnosing and managing rheumatic diseases, who can monitor disease activity using standardized assessment tools, and perform safety monitoring (LOE: low, SOR: strongly recommended)	A/9	High agreement (100)
2. Patients should be provided with education about their treatment with bDMARDs (LOE: moderate, SOR: strongly recommended)	A/9	High agreement (100)
3. In RA, if the treatment target is not achieved with the first csDMARDs strategy, when poor prognostic factors[§] are present, addition of a bDMARD should be considered (LOE: moderate, SOR: strongly recommended)	A/9	High agreement (100)
4. In AS, bDMARDs should be considered in patients with persistently high disease activity despite conventional treatments including NSAIDs; current practice is to start with TNFi therapy (LOE: high for TNFi/Moderate for IL-17 inhibitor, SOR: strongly recommended)	A/9	High agreement (100)
5. In RA, bDMARDs should be combined with a csDMARDs such as MTX (LOE: high, SOR: strongly recommended)	A/9	High agreement (100)
6. In AS, bDMARD monotherapy without csDMARDs is recommended patients with purely axial disease (LOE: high, SOR: strongly recommended)	A/9	High agreement (93.8)
7. In RA, if a bDMARD has failed, switching to another bDMARD should be considered (LOE: high, SOR: strongly recommended)	A/9	High agreement (100)
8. In AS, if the treatment with the first TNF inhibitor has failed, switching to another TNF ihibitors or IL-17 in-hibitor should be considered (LOE: low for TNF inhibitor/moderate for IL-17 inhibitor; SOR: weakly recommended for TNF inhibitors, strongly recommended for IL-17 inhibitor)	A/9	High agreement (100)
9. Prior to initiating bDMARDs, disease activity, joint damage, functional capacity, extra-articular manifestations, comorbidities, vaccination history, and pregnancy status should be assessed in all patients with inflammatory arthritis (LOE: low, SOR: strongly recommended)	A/9	High agreement (100)
10. All patients should be screened for active or latent tuberculosis before starting bDMARDs, and if tuberculosis is detected, patients should receive adequate anti-tuberculosis treatment, appropriately (LOE: low, SOR: strongly recommended)	A/9	High agreement (100)
11. All patients should be screened for hepatitis B virus infection before starting bDMARDs, and if hepatitis B virus infection is identified, proper antiviral therapy should be considered (LOE: high for screening/low for antiviral therapy, SOR: strongly recommended)	A/9	High agreement (100)
12. All patients receiving bDMARDs should be monitored for disease activity, joint damage, functional capacity, extra-articular manifestations, comorbidities, and drug side effects and toxicity (LOE: low, SOR: strongly recommended)	A/9	High agreement (100)

bDMARDs: biologic disease modifying antirheumatic drugs, LOE: level of evidence, SOR: strength of recommendation, RA: rheumatoid arthritis, AS: ankylosing spondylitis, NSAIDs: non-steroidal anti-inflammatory drugs, TNFi: tumor necrosis factor inhibitor, MTX: methotrexate, csDMARDs: conventional synthetic disease modifying antirheumatic drugs, IL-17i: interleukin-17 inhibitor, A: appropriateness. *TNF-inhibitors (adalimumab, etanercept, golimumab, or infliximab), abatacept, rituximab, tocilizumab, or the respective European Medicines Agency (EMA)-approved/Food and Drug Administration (FDA)-approved biosimilars for the patients with RA; TNF-inhibitors (adalimumab, etanercept, golimumab, infliximab, or the respective EMA-approved/FDA-approved biosimilars) or IL-17 inhibitors for the patients with AS. [†]Appropriateness was evaluated according to RAND/University of California Los Angeles (ULCA) appropriateness method; Appropriate (A) was defined as median score ranged 7～9 without disagreement. [‡]Level of agreement was evaluated according to 9-point Likert scale; high agreement was defined as agreement scored between 7 and 9. [§]Positivity of rheumatoid factor or anti-citrullinated protein antibodies, joint damage, high disease activity, failure of ≥2 csDMARDs.

of RA; TNF inhibitors and IL-17 inhibitor (secukinumab) for treatment of AS, and European Medicines Agency (EMA), Food and Drug Administration (FDA) or Ministry of Food and Drug Safety-approved biosimilar DMARDs (bsDMARDs). The targeted synthetic DMARDs were not discussed here. The improvement of the quality of care included both efficacy and safety of bDMARDs.

3) Literature search

We searched the existing literature for systematic review, clinical consensus statement, recommendations, and clinical practice guidelines. Literature search was performed under the following principles: 1) guidelines should be developed by the international network or the national association of rheumatology; 2) guidelines should be published after 2015; 3) guidelines should be written in English or Korean. Following the review, 6 guidelines were selected for the management of RA and AS [9,10,12,17,18,25,26]. The Korean guidelines for tuberculosis and hepatitis B virus infection, published by the Korean Academy of Tuberculosis and Respiratory Diseases (KATRD) and the Korean Association for the Study of the Liver, respectively, were also included in the development of the clinical consensus statement [27,28].

Because the evidence supporting the guidelines is rapidly evolving, further literature search was performed to confirm the currency of recommendations. The working group selected the relevant evidence and evaluated the current evidence. Based on these processes, the consensus statement was updated.

4) Development of statements

To evaluate the quality of evidence, we used the GRADE system (Table 1) [19,20]. The evidence from the reference studies was reviewed by the working group to grade the quality of evidence. The strength of recommendations was determined based on the estimated effect, overall quality of evidence, values and preference, and resource use [29].

5) Agreement of statement

The members of the consensus group voted for the appropriateness of 12 statements. The survey was performed with Internet-based software according to the modified Delphi technique. The members rated their agreement of 12 statements on a 9-point Likert scale (1: strongly disagree; 3: disagree; 5: neutral; 7: agree; 9: strongly agree). The median score of $\geq$ 7.0 on a 9-point Likert scale was considered appropriate for consensus statement [30]. As with the ballot, different opinions were also collected.

Following the initial Delphi round, the consensus statement was modified based on the expert opinion from the consensus group. The modified statement was confirmed through another Delphi round.

6) Approval of clinical consensus statement

The draft statement was approved by all members of the consensus group and the development group. The draft of 12 consensus statements was presented on the 2018 KCR Annual Scientific Meeting, and feedback from the target users was used to finalize the clinical consensus statement. The final manuscript was officially endorsed by KCR. The final version of clinical consensus statement was released on web-site of KCR at 2019 (www.rheum.or.kr).

Expert opinion for the management of inflammatory arthritis in adults with bDMARDs in South Korea

1) General principles of bDMARDs treatment

(1) bDMARDs should be prescribed by an expert experienced in the diagnosing and managing rheumatic diseases, who can monitor disease activity using standardized assessment tools, and perform safety monitoring (level of evidence [LOE]: low, strength of recommendation [SOR]: strongly recommended)

This statement indicates the importance of an expert care in the treatment of rheumatic diseases, in particular, with bDMARDs. The care by an expert in rheumatic diseases, such as a rheumatologist, should be seriously considered and emphasized, because it allows the severity of disease to be estimated, a plan of care to be developed and initiated, and the patient's response to the treatment to be assessed properly [12,31]. In addition, the management with bDMARDs may lead to various adverse events which include injection site reactions, infusion reactions, exacerbation of heart failure, cytopenia, infections including lethal tuberculosis and fungal infections, demyelinating diseases, increased risk of cancer, anaphylaxis and even death [15,32-37]. Thus, meticulous monitoring by an expert for any new or developing conditions is essential to minimize the potential of harm caused by these agents [10,18,38,39].

In this regard, this statement emphasizes that the treating physician should have extensive knowledge of the en-

tire rheumatic disease spectrum and is capable of providing comprehensive management, taking into account not only efficacy but also risks associated with the therapy. The expert panel reached 100% of agreement and strongly recommended this statement pertaining to the qualification of an expert for use of bDMARDs.

(2) Patients should be provided with education about their treatment with bDMARDs (LOE: moderate, SOR: strongly recommended)

To standardize the management of inflammatory arthritis including RA and AS, clinical practice guidelines and recommendations have been published in many countries [7,9-13,18]. Many of these emphasize that patient education is as important as pharmacological and non-pharmacological treatment because patients play a central role in managing their disease. Patients' awareness about their diseases and management can promote long-term treatment adherence [7]. Therefore, it is crucial to communicate with patients by giving relevant information and education about their disease, its management, risks, and coping skills. In addition, clinicians should provide information tailored to meet the needs of each patient at different stages of their disease and associated comorbidities [40].

Thus, the expert panel reached 100% agreement and strongly recommended that patients should be provided with education about their treatment with bDMARD.

2) Indications for initiation of bDMARDs in patients with RA and AS

(3) In RA, if the treatment target is not achieved with the first conventional synthetic DMARDs (csDMARDs) strategy, when poor prognostic factors are present, addition of a bDMARD should be considered (LOE: moderate, SOR: strongly recommended)

Conventional synthetic DMARDs (csDMARDs) in this expert opinion include methotrexate (MTX), leflunomide (LEF), sulfasalazine (SSZ), and hydroxychloroquine (HCQ). It does not include targeted synthetic DMARDs (tsDMARDs), namely the Janus kinase inhibitors (Jak-inhibitors) such as tofacitinib or baricitinib. All bDMARDs mentioned in this expert opinion were bDMARDs currently approved for management of RA. Currently approved bDMARDs for use in Korea are TNF inhibitors (adalimumab, etanercept, golimumab, and infliximab); a co-stimulation inhibitor (abatacept); an IL-6 receptor blocker (tocilizumab); an anti-B-cell agent (rituximab); an IL-17 inhibitor (secukinumab), and EMA, FDA or Ministry of Food and Drug Safety-approved bsDMARDs.

All bDMARDs approved for treatment of RA had showed efficacy in RA patients with inadequate response to MTX (MTX-IR). ACR response at 24 weeks after addition of bDMARDs in MTX-IR patients was significantly superior to those treated with MTX plus placebo [41-55]. Remission rate at 6 months after addition for adalimumab [48], abatacept [56] and rituximab [41] in patient with RA that had remained active despite MTX treatment was significantly higher compared to that in patients with placebo pulse MTX. Remission rates at 12 months in MTX-IR RA patients with abatacept [56,57] and tocilizumab [58] were superior to that in MTX-IR RA patients with placebo. In addition, radiographic progression at 12 months in patients with RA who remained active despite of MTX treatment was halted when they received bDMARDs [46,48,57-59]. ACR response at 6 months of etanercept [60], adalimumab [51], and tocilizumab [61], and ACR response at 12 months of etanercept were superior to that of placebo in RA patients with active disease despite of csDMARDs other than MTX [62].

The bDMARDs including biologic originator DMARDs (boDMARDs) and bsDMARDs are recommended without specific preference in RA patients who have inadequate response according to a validated composite measure, or intolerance to csDMARDs. There is no difference in efficacy and safety, irrespective of their target, among the bDMARDs in head-to-head trials, meta-analysis, or the results of the systemic literature reviews (SLR) [11,14-16,63-65].

Rituximab was approved for use in RA patients who failed to TNF inhibitors although it is effective in bDMARDs-naïve RA patients. Rituximab was significantly effective and well tolerated when combined with MTX therapy in RA patients IR to MTX compared with placebo in ACR20, ACR50, ACR70 response, and the Health Assessment Questionnaire (HAQ) score at 24 weeks [66]. Initial treatment with rituximab was non-inferior to initial TNF inhibitor treatment in randomized controlled trial (RCT) in patients with seropositive RA who were naïve to treatment with bDMARDs [67]. Of note, it is frequently used for RA patients IR to csDMARDs, in particular when the patients have specific contraindications to other bDMARDs such as lymphoma, or demyelinating disorder [47,68].

Some factors indicating moderate to high disease activity according to composite measures after csDMARDs

therapy [69] such as the presence of rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA) [60,70], presence of early erosion [60], high swollen joint counts [60,71,72] or high acute phase reactant level [60,72] were proven to be associated with poor disease outcome in patients with RA. In addition, a further csDMARDs may have only minimal impact if RA patients have failed to respond to two or more csDMARDs [73,74], therefore EULAR recommendation included failure to two or more csDMARDs as a poor prognostic factor [12].

This statement received 100% agreement by the expert panel's vote and is strongly recommended despite moderate evidence.

(4) In AS, bDMARDs should be considered in patients with persistently high disease activity despite conventional treatments including non-steroidal anti-rheumatic drugs (NSAIDs); current practice is to start with TNF inhibitors therapy (LOE: high for TNF inhibitors, moderate for IL-17 inhibitors, SOR: strongly recommended)

Conventional treatment in AS includes not only NSAIDs but also non-pharmacological management, a local glucocorticoid injection in patients with peripheral symptoms, and a treatment with SSZ in case of peripheral arthritis [18]. In most patients with symptomatic AS, however, initial therapy with NSAIDs alone is generally recommended [10,18,38,75,76]. This recommendation based on the evidence of the Assessment in Ankylosing Spondylitis response criteria (ASAS) 20 response of $>$ 70%, an ASAS40 response in $>$50% of the patients starting with an NSAIDs in early disease or 35% of patients in ASAS partial remission [18,75]. It was also reported that approximately 70% to 80% of AS patients experienced substantial relief of their symptoms, including back pain and stiffness, with NSAIDs [76].

An inadequate response to NSAIDs typically requires trials with at least two NSAIDs that have been taken in an adequate dose for at least two to four weeks each [10]. Current prevailing opinion for the management of AS patients with persistent high disease activity despite the initial NSAIDs therapy is to start with bDMARDs, especially TNF inhibitors [10,18,77-79]. Due to the concern of high cost and social burden, the use of a biologic agent for active AS is particularly appropriate for those with high or very high disease activity, although they are effective in patients with mild to moderate symptoms as well. High disease activity can be defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) $\geq$4.0 or Ankylosing Spondylitis Disease Activity Score (ASDAS) $\geq$2.1 [18]. Any of the TNF inhibitors is an acceptable option. The choice between them is based upon patient preferences, physician preference and experience, national regulatory and cost issues, and possible coexisting conditions such as inflammatory bowel diseases (IBD) or uveitis. TNF monoclonal antibodies such as adalimumab and infliximab are preferred over etanercept for the treatment of AS, IBD, and recurrent uveitis associated with AS [80-83]. An IL-17 inhibitor (secukinumab) is known to increase risk of the new onset or exacerbation of IBD in several studies, therefore, comorbidities and risk factors should be considered when selecting bDMARDs in active AS patients [84,85]. Substantial evidences of consistent improvements and effective clinical outcomes of TNF inhibitors in active AS patients is sufficient to support this clinical practice [10,18,38,77-79].

Secukinumab is a reasonable alternative to TNF inhibitors, with a similar level of efficacy [18,86,87]. Several clinical trials demonstrates that another IL-17 inhibitor, ixekizumab, which is available commercially for the treatment of psoriasis and psoriatic arthritis, significantly improved the signs and symptoms after 16 weeks in active AS patients who are bDMARDs-naïve, and have inadequate response to or intolerance of TNF inhibitors [88,89]. However, studies there is much more experience in clinical practice with TNF inhibitors than with IL-17 inhibitor [18].

For these reasons, the expert panel voted 100% of agreement for starting bDMARDs, particularly TNF inhibitors as first bDMARDs and IL-17 inhibitor as an alternative option, in AS patients with IR to conventional treatment, and strongly recommended.

3) Concomitant use of csDMARDs with bDMARDs in RA or AS patients

(5) In RA, bDMARDs should be combined with a csDMARDs such as MTX (LOE: high, SOR: strongly recommended)

All bDMARDs is more efficacious when combined with MTX than as monotherapy in patients with RA [14,49,62,90-92]. The combination of bDMARDs such as etanercept [62] or adalimumab [90] with MTX, was significantly better in reduction of disease activity, retardation of radiographic progression, and achieving clinical remission compared with MTX or bDMARDs alone.

Extended studies also supported this results that etanercept [93] and adalimumab in combination with MTX [94] was superior to either bDAMRDs alone in improving remission rate and inhibiting radiographic progression in patients with RA. Tocilizumab in combination with MTX in patients with early RA [95] and MTX-IR RA [96-98], conveyed better clinical efficacy and showed prevention of radiographic progression than tocilizumab alone. MTX can be used at 7.5～10 mg per week when combined with bDMARD to provide efficacy while minimizing intolerance leading to discontinuation [99,100].

Furthermore, the use of MTX as concomitant drug with bDMARDs reduces the incidence of antidrug antibody which results in secondary treatment failure in patients with RA receiving bDMARDs [99,100]. However, EULAR recommendation for management RA, updated 2016, did not recommend routine testing of antidrug antibodies and drug level because a positive clinical response would not lead to cessation of therapy even in the presence of antidrug antibodies, or low drug levels [12].

Several studies demonstrated that combination of csDMARDs, other than MTX, with bDMARDs can also be effective in patients with RA. Combination of TNF inhibitors with LEF showed comparative effectiveness to those with MTX in patients with RA [101]. In an another study, RA patients receiving adalimumab and concomitant csDMARDs (regardless of type or number of DMARDs such as HCQ, SSZ, MTX, or LEF) showed greater improvement in most of the outcome measures than patients receiving adalimumab alone [102].

For all of the above, the expert panel reached 100% agreement and strongly recommended that bDMARDs should be combined with a csDMARD such as MTX in patients with RA unless intolerant or have contraindication to csDMARDs.

(6) In AS, bDMARD monotherapy without csDMARDs is recommended patients with purely axial disease (LOE: high, SOR: strongly recommended)

This statement indicated that the combination therapy with csDMARDs is not supported by the evidence in AS patients with exclusively axial involvement on bDMARDs. Based on the Cochrane reviews and existing recommendations, there was no strong evidence of support for using csDMARDs including SSZ, MTX and LEF in patients with purely axial disease [18,39]. SSZ only, however, could be considered as a treatment option in patients with peripheral arthritis [10,18]. In addition, concomitant use of csDMARDs, such as MTX, is not recommended as most of the limited evidence indicates that this provides no additional benefit in patients with AS [18,103,104].

The expert panel agreed 93.8% in vote and strongly recommended using bDMARDs monotherapy without csDMARDs in patients with purely axial disease.

4) Treatment options after failure of or intolerance to first bDMARDs in RA or AS patients

(7) In RA, if a bDMARD has failed, switching to another bDMARD should be considered (LOE: high, SOR: strongly recommended)

In a treat-to-target strategy of RA, if a patient did not achieve adequate response with the first bDMARD, switching to another bDMARD should be instituted without a significant delay. The EULAR recommendation did not prioritize any specific bDMARDs after failure in first bDMARDs in patients with RA [12]. The EULAR recommendation state that any bDMARDs including another TNF inhibitors, could be used in RA patients whom failed TNF inhibitors, which indicates that any bDMARDs with the same or with another mode of action are recommended in case with failure to bDMARDs in RA. This was based on the data from meta-analysis, systematic literature reviews (SLRs), and prospective studies [14,15, 105]. One prospective study showed that abatacept, rituximab, and different TNF inhibitor demonstrated similar effect in patients with RA who had failed TNF inhibitor [106]. Rituximab use as second-line therapy in RA patients after TNF inhibitor failure led to improvements in the efficacy and functional variables at 6 months, with no serious adverse events [107]. Even primary non-responders to a TNF inhibitor were shown to have some response to another TNF inhibitor in several studies [108-112].

There is one randomized controlled trial showed that a non-TNF inhibitor was more effective than the 2nd TNF inhibitor in RA patient with primary failure to the first TNF inhibitor [113] and also lack studies investing the effect of TNF inhibitors as second-line bDMARDs after failure to bDMARDs with other modes of action in patients with RA. Therefore, the choice should be based on a shared decision between the patient and the physician based on patient's characteristics and preferences. The EULAR recommendation also stated that bsDMARD of any of the reference boDMARDs should not be considered in patients who have inadequate response or failed

to the respective boDMARD (or another bsDMARD of the same molecule) or vice versa [12].

Expert panel voted 100% of agreement for this part based on the above evidence and strongly recommended that switching to another bDMARDs should be considered if the first bMDARD has failed in patients with RA.

(8) In AS, if the treatment with the first TNF inhibitor has failed, switching to another TNF ihibitors or IL-17 in-hibitor should be considered (LOE: low for TNF inhibitor/moderate for IL-17 inhibitor; SOR: weakly recommended for TNF inhibitors, strongly recommended for IL-17 inhibitor)

Treatment options in patients with AS who have responded inadequately to the first TNF inhibitor are another TNF inhibitors or an IL-17 inhibitor such as secukinumab [18,114,115]. For primary failure to an initial TNF inhibitor, either the second TNF inhibitors or secukinumab could be considered. However, given the different mechanism of action, anti- IL-17 inhibitor is preferred as more reasonable option [18,115]. In patients with secondary failure, the treatment with another TNF inhibitor should be considered [18,114,115]. In general, the response rate of a second TNF inhibitors decreases compared with the first. However, the data showed good responses to subsequent TNF inhibitors in AS [116,117]. IL-17 inhibitor has also proven efficacy in patients who had failed a TNF inhibitor but this was also less than in TNF inhibitor-naïve patients [85,86].

Expert panel agreed 100% in vote for this statement, and weakly recommended an TNF inhibitor and strongly recommended an anti-IL17 inhibitor as 2nd bDMARDs in patients with failure to first TNF inhibitor.

5) Monitoring strategies before or during use of bMDARDs in patients with RA or AS

(9) Prior to initiating bDMARDs, disease activity, joint damage, functional capacity, extra-articular manifestations, comorbidities, vaccination history, and pregnancy status should be assessed in all patients with inflammatory arthritis (LOE: low, SOR: strongly recommended)

Disease activity is the fundamental criteria to determine the use of biologic agents in inflammatory arthritis, based on the treat-to-target strategy [118,119]. All of the current guidelines recommend that the disease activity and disease-related features should be evaluated in patients with inflammatory arthritis prior to initiating biologic therapy.

Although biologic therapy is proven to improve the clinical outcomes in patients with inadequate response to conventional therapy, the use of bDMARD in patients with comorbid conditions requires special caution. Several safety data regarding bDMARDs have been published [120-122]. Thereafter, the 2015 ACR and APLAR recommendations, and 2018 National Institute for Health and Care Excellence (NICE) guidelines included the management of RA in special clinical situations, such as congestive heart failure [35,123], combined hepatitis viral infection (described in detail in statement 11), past history of malignancy [124-126], and previous severe infections [127-129]. However, at the current time, the recommendations are still based on evidences of low-quality.

RA patients have an increased risk of infection when compared to the general population [130]. In addition, use of biologic therapy such as TNF inhibitor further increases the risk of infection [131,132]. Given the high risk of infection in patients receiving biologic therapy, the 2015 ACR and APLAR guidelines recommended assessment of vaccination history and completion of outstanding vaccination when possible, before initiating bDMARDs. Several RCTs studied the safety and efficacy of pneumococcus, influenza, and hepatitis B virus (HBV) vaccination in patients receiving biologic therapy [133-140]. Biologic therapy seems to be unrelated to the side effect of the killed vaccine. However, due to the theoretical risk and the limited data, the live vaccine is contraindicated during the bDMARDs therapy.

The safety of bDMARD during pregnancy was evaluated in several observation cohort studies [141]. TNF inhibitors, especially adalimumab and etanercept, showed no significant difference in miscarriage and congenital malformation compared with disease-matched controls [142-153]. Other biologic therapies still have limited safety data. Based on the currently available data, physicians can discuss the use of biologic therapy with patients during pregnancy, if the disease activity is not otherwise controlled.

Given the importance of the safety issue of bDMARDs, assessment of comorbidities, vaccination history, and pregnancy status should be emphasized in all patients receiving biologic therapy, despite of insufficient evidence.

(10) All patients should be screened for active or latent tuberculosis before starting bDMARDs, and if tuberculosis is detected, patients should receive ad-

equate anti-tuberculosis treatment, appropriately (LOE: low, SOR: strongly recommended)

Tuberculosis (TB) is an important complication following biologic therapies in patients with inflammatory diseases. The use of TNF inhibitors increases the risk of TB, especially in patients with latent TB infection [154,155]. South Korea is a country of intermediate TB burden. The annual incidence of TB is 55 per 100,000 persons in 2017 [156], and the estimated prevalence of latent TB is 33%, which is higher than those in other developed western countries [157]. The nationwide study conducted in Korea between 2005 and 2009 showed the significantly higher incidence of TB in patients who treated with TNF inhibitors, which was 1,017 per 100,000 person-years [158]. Based on the clear association between TB and TNF inhibitors, the panels strongly recommend that all patients should be screened for active or latent TB before initiating biologic therapy, and patients with active or latent TB infection should receive appropriate anti-TB therapy.

Studies have suggested that patients treated with monoclonal antibody, such as infliximab and adalimumab, had a higher risk of TB than patients treated with etanercept [158-160]. The effect of biologic therapies other than TNF inhibitors on risk of TB is largely unknown. Although data from clinical trials and national registries suggested that non-anti-TNF targeted biologics were not associated with the increased TB risk, further research would be required to reach a definite conclusion [161]. Based on the currently available data, the 2015 APLAR guideline recommended that patients with a history of TB or latent TB are preferentially treated with other biologic therapies than monoclonal antibody TNF inhibitors.

Diagnosis and treatment of latent TB can be referred to country-specific guidelines [25]. The 2017 KATRD guideline recommend that interferon-gamma releasing assay can be used alone or in combination with tuberculin skin test for diagnosis of latent TB, and biologic therapy can be started 3 weeks after latent TB treatment [27,28].

(11) All patients should be screened for hepatitis B virus infection before starting bDMARDs, and if hepatitis B virus infection is identified, proper antiviral thera-py should be considered (LOE: high for screening/low for antiviral therapy; SOR: strongly recommended)

Korea is classified into the high-prevalent region of chronic HBV infection. Although the national health program has substantially reduced the prevalence of HBV infection, the positivity rate of HBV surface antigen (HBs Ag) was still 3.4% for males and 2.6% for females in 2012 [162].

Several studies have shown that treatment with rituximab and TNF inhibitors increased the risk of reactivation of HBV [163-167]. The rate of HBV reactivation was reported to be 12.3%～39% among HBs Ag (+) patients receiving TNF inhibitors. Although the association between HBV and rituximab is unclear in patients with rheumatic diseases, the reactivation rate of HBV infection in lymphoma patients receiving rituximab-containing regimen was reported to be 24%～67%. The rate of HBV reactivation in patients with resolved HBV infection (HBs Ag [–]/anti-HBV core antibody [+]) also increased following the treatment with rituximab and TNF inhibitors [164,166,168]. The effect of other bDMARDs on HBV reactivation is largely unknown. However, the panels recommend that all patients receiving biologic therapy should be screened for HBV infection, given the increased risk of HBV reactivation in RA patients, regardless of biologic therapy [169].

The 2015 ACR, APLAR, and 2018 NICE guideline consistently emphasize the importance of screening of HBV infection prior to biologic therapy and antiviral treatment during biologic therapy. Preventive antiviral therapy significantly reduced the risk of HBV reactivation in HBs Ag (+) lymphoma patients receiving rituximab-containing chemotherapy [170-172] and HBs Ag (+) RA patients treated with TNF inhibitors [163]. Thus, based on the currently available evidence, the panels recommend that screening for HBV infection should be performed prior to biologic therapy, and preventive antiviral therapy should be considered in patients receiving biologic therapy.

(12) All patients receiving bDMARDs should be monitored for disease activity, joint damage, functional capacity, extra-articular manifestations, comorbidities, and drug side effect and toxicity (LOE: low, SOR: strongly recommended)

Based on the treat-to-target strategy, the monitoring of disease activity is important to guide the treatment in inflammatory arthritis [118,119]. The 2015 ACR, APLAR guidelines, and 2016 EULAR guideline, suggested that disease activity of RA should be monitored every 1～3 months in active disease, and at least 3～6 months in stable disease [9,12,25]. The 2016 ASAS-EULAR guideline recommended assessment of disease activity of axial

spondyloarthritis on individual basis [18]. Even though composite measures of disease activity indicate inactive disease, joint damage should be evaluated in patients with inflammatory arthritis. Radiographic progression does not necessarily correlate with the disease activity [173].

In addition, the voting panels agreed to evaluate the functional capacity and extra-articular manifestations during biologic therapy. Biologic therapy may affect the functional capacity, and extra-articular manifestation in patients with inflammatory arthritis. Likewise, these clinical features may affect the choice of certain bDMARDs.

As mentioned previously, bDMARD should be cautiously prescribed in special clinical situations, including combined infection, congestive heart failure, past history of malignancy, and pregnancy. Of note, the use of bDMARDs was associated with the increased risk of certain infections, including TB and HBV. Safety concern about malignancy is one of the major issues in patients receiving bDMARDs treatment and further prospective observational registry is needed. One study showed that cancer incidence was similar in RA patients treated with TNF inhibitors and csDMARDs, which suggested that TNF inhibitors may be a safe therapeutic option for RA treatment, in terms of malignancy [174]. Furthermore, biologic therapy is associated with various drug-related toxicities [175]. Therefore, the all patients receiving biologic therapy should be monitored for therapy-related toxicities based on the currently available evidence.

CONCLUSION

This Korean expert consensus for the use of bDMARDs in inflammatory arthritis developed by the KCR provides physicians participating in the care of inflammatory arthritis with a guidance stemming from up-to-date best evidence based on Korean health care situations. It is critical for physicians to understand the evidence-based use of bDMARDs to choose the optimal agents and to protect the patients from the harmful effects of the drug, which in turn can contribute to a better management of inflammatory arthritis in everyday practice. In addition, patients can benefit from receiving the appropriate treatment, according to the verified guidelines, for the effective management of their disease and improved quality of life. Furthermore, this expert opinion emphasizes the role of education for patients being treated with bDMARDs in inflammatory arthritis, as patient's awareness and knowledge about the course of diseases, medications, treatment goal, and prognosis improves compliance and successful outcome [7,41,176]. This expert consensus may contribute to the promotion of the standard of care in Korea for the management of inflammatory arthritis with bDMARDs, until the final development of validated guidelines on this important management issue can be realized.

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CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

Among the authors, E.J.P. was in charge of design of study, acquisition of data, analysis and/or interpretation of data, drafting and revising the manuscript. H.J.K. was responsible for acquisition of data, analysis and/or interpretation of data, drafting the manuscript. S.M.J. was responsible for acquisition of data, analysis and/or interpretation of data, drafting the manuscript. Y.K.S. took an important part in conception, design of study, analysis of data, and revising the manuscript. H.J.B. and J.S.L. contributed conception and design of study, analysis and/or interpretation of data, and revising the manuscript critically for important intellectual content.

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