2024 Thai Rheumatism Association Guideline for the Treatment of Axial Spondyloarthritis with Biologic and Targeted Synthetic Disease-Modifying Anti-Rheumatic Drugs

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Objective: To provide rheumatologists with the decisions for the appropriate and standardized treatment of patients with axial spondyloarthritis (axSpA) with biologic disease-modifying antirheumatic drugs (bDMARD) and targeted synthetic DMARDs (tsDMARD), according to current evidence and expert opinion.

Materials and Methods: The development process involved 46 rheumatologist representatives from medical schools, government hospitals, and private hospitals nationwide. Relevant clinical questions related to treatment initiation criteria, administration, evaluation, monitoring, and intensive treatment options were selected. The evidence was systematically identified and summarized. Quality of evidence was evaluated and ranked according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) scoring methodology. The recommendations were then proposed and voted on using the nominal group process. The input was collected from stakeholders through a public hearing. The final 13 recommendations were provided.

Results: The guideline addresses the criteria for starting bDMARD/tsDMARD and details the first-line drugs for specific disease profiles, including predominantly axial involvement, predominantly peripheral joint involvement, and uveitis. It also addresses the management of patients with comorbid conditions such as tuberculosis, chronic hepatitis B, malignancy, and pregnancy. Additionally, it covers monitoring and follow-up procedures, alternative treatments for first-line treatment failures, tapering treatment after remission, and reinstitution of bDMARD/tsDMARD in case of flare-up.

Conclusion: Thai Rheumatism Association has proposed a set of recommendations to outline concepts and provide guidance on the treatment of axSpA with bDMARD and tsDMARD for Thai rheumatologists.

Keywords: Axial spondyloarthritis; Biologic disease-modifying antirheumatic drug; Targeted synthetic disease-modifying antirheumatic drug; Treatment; Monitoring

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Axial spondyloarthritis (axSpA) is a chronic inflammatory joint disease of unknown etiology that predominantly affects the spine and sacroiliac joint. Although musculoskeletal manifestations are characteristic of this disease, some patients can also exhibit clinical features indicating inflammation of other organs, such as fever, fatigue, anemia, uveitis, psoriasis, or inflammatory bowel disease (IBD). Without appropriate and timely treatment, axSpA can cause joint deformities, disability, and premature death. Early diagnosis and proper treatment from the onset of the disease, before irreversible joint damage occurs, are crucial strategies for preventing

undesirable outcomes, improving quality of life, and reducing mortality rates. Current treatment approaches include non-pharmacological interventions such as warm compression, physical therapy to reduce joint deformities, and medication to reduce inflammation and pain. Standard medications for SpA include non-steroidal anti-inflammatory drugs (NSAIDs), conventional disease-modifying anti-rheumatic drugs (csDMARDs) such as sulfasalazine, methotrexate, leflunomide, and glucocorticoid injections into affected joints or entheses. In patients who do not respond to or experience side effects from standard treatments, interventions targeted at pathogenic inflammatory cytokines can be considered, including biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs). These medications effectively reduce joint inflammation, resulting in remission of the disease. Currently, tumor necrosis factor inhibitors (TNFi), one of the bDMARDs approved for SpA, are included in the national essential drug list for patients with ankylosing spondylitis (AS) in Thailand, allowing more patients to access these treatments. However, it is essential to monitor and manage the potential short-term and long-term side effects of these medications, such as serious bacterial infections, tuberculosis, pneumonia, herpes zoster, dyslipidemia, and cardiovascular disease. Additionally, these medications are expensive and may require long-term treatment. Therefore, proper, safe, and cost-effective medication management is crucial. The Thai Rheumatism Association (TRA) guideline has been developed to provide rheumatologists with the decisions for the appropriate and standardized treatment of axSpA patients with bDMARDs and tsDMARDs, aligned with current evidence and standard practice. Furthermore, these recommendations offer guidance to the National Health Security Office, the Social Security Office, the Comptroller General's Department, and other stakeholders to efficiently and appropriately manage the care of axSpA patients, thus maximizing benefits for the entire country.

Materials and Methods

The development process involved 25 rheumatologists across the country and a steering committee consisting of representatives from medical schools, government hospitals and private hospitals nationwide, totaling 15 members. Additionally, a working group consisting of 13 rheumatologists' representatives from seven medical schools were tasked with gathering and assessing quality of evidence to inform the guideline development process using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology[1]. The initial meeting of the working group took place in August 2023, where it was decided to develop guidelines specifically for rheumatologists treating patients with axSpA with bDMARDs and tsDMARDs available in Thailand up to December 2022. The bDMARDs refers to TNFi (adalimumab, etanercept, golimumab infliximab) and interleukin-17 inhibitor (IL-17i) (brodalumab, ixekizumab, secukinumab), while tsDMARDs refers to Janus kinase inhibitors (JAKi) (baricitinib, tofacitinib). Subsequently, the committee and all members worked together to generate clinical questions relevant to the guidelines. After gathering all relevant questions, a meeting was held to select those considered clinically important, significant, practical, and showing variation in practice. Eleven key clinical questions were chosen, covering the criteria for starting medication, appropriate medication selection for different patient profiles, medication administration methods, treatment evaluation and monitoring, intensive treatment options, medication adjustments for disease remission or lack of response, and medication adjustments for disease exacerbation (Table 1).

Next, the working group collaborated to systematically search and review medical literature, primarily using the Medline (PubMed®) database. The goal was to identify relevant studies that could address the selected clinical questions. Initially, systematic reviews were prioritized. However, if none were found or if the quality of available research was low or outdated, the next priority was randomized controlled trials (RCT) and observational studies involving axSpA. If no relevant studies were found for axSpA, studies involving patients with similar clinical characteristics such as psoriatic arthritis (PsA) or rheumatoid arthritis (RA) were considered to extrapolate data for the development of the guideline. Finally, the steering committee, the working group, and all members reviewed the collected evidence and proposed statements. Following subgroup discussions, a voting process was conducted using a nominal group process. Each statement was subjected to two rounds of voting based on predetermined criteria. In the first round, statements receiving at least 75% agreement were considered approved, while those with less than 75% agreement were omitted. Statements with 71% to 74.99% agreement were further discussed before a second round of

Table 1. Clinical questions

Clinical question
1. When should we start targeted therapy?
2. What is the initial choice of bDMARDs/tsDMARDs? • Axial, Peripheral involvement • Uveitis • Pregnancy, tuberculosis • Malignancy • Hepatitis B virus
3. Should bDMARDs/tsDMARDs be started as monotherapy or in combination with csDMARD?
4. If bDMARDs/tsDMARDs is started in combination with csDMARD, what should be done with the previous csDMARD?
5. How to assess response or efficacy of bDMARDs/tsDMARDs? • Type of outcome measure • Frequency to follow-up
6. What is the benefit of a tight control strategy aimed at inactive disease over usual care?
7. When patients achieve remission or inactive disease, what should be done next?
8. When patients achieve remission or inactive disease and decide to reduce or discontinue DMARDs, should csDMARDs or bDMARDs/tsDMARDs be reduced?
9. In patients who have an inadequate response to the first bDMARDs/tsDMARDs, what should we do next?
10. If patients flare after discontinuation of bDMARDs/tsDMARDs, when to re-start bDMARDs/tsDMARDs (indication)
11. If patients stop bDMARDs/tsDMARDs due to TB, what is the most appropriate bDMARDs/tsDMARDs?

bDMARD=biologic disease modifying anti-rheumatic drug; csDMARD=conventional synthetic disease modifying anti-rheumatic drug; tsDMARD=targeted synthetic disease modifying anti-rheumatic drug; TB=tuberculosis

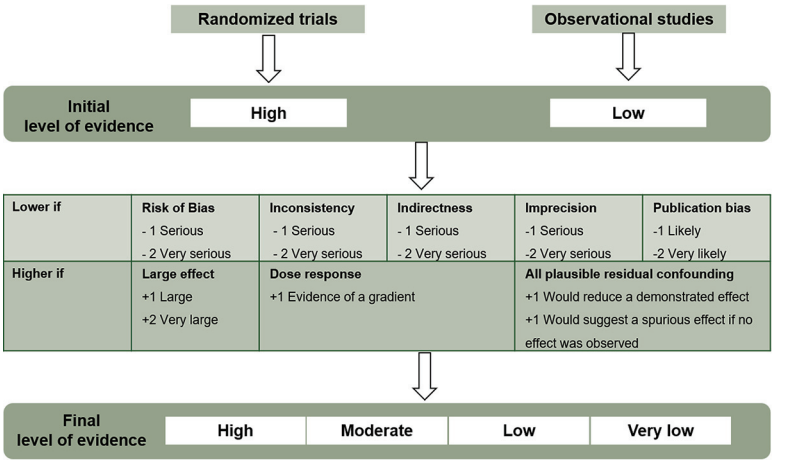

Figure 1. Level of evidence[2].

voting. Only statements with at least 75% agreement in the second round were approved. The quality of evidence or level of evidence (LoE)[2] (Figure 1) and the strength of recommendation (SoR)[3] were assessed according to the GRADE methodology. The guidelines were endorsed on the basis of consensus agreement among committee members.

After obtaining the initial clinical practice guidelines, the TRA proceeded to seek feedback on these guidelines from pertinent organizations and institutions, including the Food and Drug Administration (FDA), the National Health Security Office, the Social Security Office, the Controller General's Department, and hospitals with rheumatology departments. Furthermore, the working group presented all recommendations along with related evidence at the TRA annual meeting in March 2024. Following this presentation, there was an open discussion and independent feedback. Subsequently, the working group collected and revised the statements according to all comments and suggestions to refine and improve the current clinical practice guidelines. Finally, overarching principles were developed to support a holistic approach to

Table 2. Overarching principles

These clinical practice guidelines are not mandatory, and physicians may deviate from them as appropriate.
When selecting the appropriate treatment for each patient, the evaluation should consider cost effectiveness by comparing risks with potential benefits, the patient's characteristics, disease severity, specific manifestations of the disease (both joint and extraarticular symptoms), comorbidities, and other treatment options.
Shared decision making between the treating physician and the patient should be applied taking into account economic, social, and social costs and resources, as well as the capabilities of medical personnel and facilities.
Specialized consultations with gastroenterologists, infectious disease specialists, pulmonologists, or ophthalmologists may be necessary for collaborative treatment, depending on the capabilities of medical personnel and facilities.
The bDMARDs and tsDMARDs recommended in these guidelines cover only drugs approved by the Thai FDA until 2023, including: • bDMARDs: TNF inhibitors (adalimumab, etanercept, golimumab infliximab), IL-17 inhibitors (brodalumab, ixekizumab, secukinumab) • tsDMARDs: JAK inhibitors (tofacitinib) • TNF monoclonal antibodies refer to adalimumab, golimumab, infliximab • The TNF receptor-Fc fusion protein refers to etanercept
csDMARDs include sulfasalazine, methotrexate, and leflunomide.
Approved biosimilars can also be used in the treatment of axSpA according to this guideline, similar to their reference products.

axSpA=axial spondyloarthritis; bDMARD=biologic disease modifying antirheumatic drug; csDMARD=conventional synthetic disease modifying antirheumatic drug; FDA=Food and Drug Administration; IL-17=interleukin-17; JAK=Janus kinase; TNF=tumor necrosis factor; tsDMARD=targeted synthetic disease modifying anti-rheumatic drug

management according to this guideline (Table 2). Final recommendations along with LoE, SoR, and agreement are summarized in Table 3. The TRA plans to continuously monitor the implementation of these guidelines by collecting multi-institutional data in the future.

Recommendation 1

bDMARDs/tsDMARDs should be started when patients met all the following criteria:

- **Active disease, defined as BASDAI at 4 or above or ASDAS at 2.1 or above.**
- **Inadequate response or intolerance to NSAIDs at a tolerated dose for at least one month or having a contraindication to the use of NSAIDs.**
- **Inadequate response or intolerance to at least one csDMARD at standard dose for at least three months or having contraindications to the use of csDMARDs.**

(LoE:- very low, SoR:- weakly recommended, Agreement:- 92%)

These recommendations derived from the criteria for selecting axSpA volunteers for RCTs investigating the efficacy and safety of bDMARDs, including infliximab[4], adalimumab[5], etanercept[6], golimumab[7], secukinumab[8-11], ixekizumab[12-15], brodalumab[16,17], and tofacitinib[18]. Additionally, experts incorporated clinical practice guidelines from various international institutions, including the Assessment of SpondyloArthritis International Society-European League Against Rheumatism (ASAS/EULAR)[19], the American College of Rheumatology/Spondylitis Association of America/ Spondyloarthritis Research and Treatment Network (ACR/SAA/SPATAN)[20], the Asia-Pacific League of Associations for Rheumatology (APLAR)[21], and the Pan American League of Associations for Rheumatology (PANLAR)[22]. The criteria include:

- Patients diagnosed with axSpA according to disease classification criteria.
- Active disease based on Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) equal to or greater than 4 or Ankylosing Spondylitis Disease Activity Score (ASDAS) equal to or greater than 2.1 or elevated levels of C-reactive protein (CRP).
- Use of NSAIDs at maximum doses for axSpA treatment for at least one or two consecutive types over a period of 2 to 12 weeks.
- Patients receiving csDMARDs must receive a steady dose for at least 12 weeks.

In some cases, experts have adjusted the initiation criteria to fit the Thai population and the country context. For example, when more than half of the experts, such as 56%, suggested starting bDMARDs/tsDMARDs in cases where patients are allergic to or experience severe side effects of one NSAID, as patients may not want to risk further adverse effects related to NSAIDs. Although some experts suggested trying other NSAID groups, since the vote did not pass the 75% threshold, this recommendation did not specify the number of NSAIDs that must be received before considering treatment with bDMARDs/tsDMARDs. However, experts recommended a duration of NSAID use of at least one month and to consider starting bDMARDs/ tsDMARDs if there was no response to treatment. For csDMARDs, even though international guidelines did not recommend csDMARD treatment for patients with predominant axial symptoms due to

Table 3. Summary of recommendations

Statement	LoE	SoR	Agreement$
bDMARDs/tsDMARDs should be started when patients met all the following criteria: • Active disease, defined as BASDAI ≥4 or ASDAS ≥2.1. • Inadequate response or intolerance to NSAIDs at a tolerated dose for at least 1 month or having a contraindication to the use of NSAIDs. • Inadequate response or intolerance to at least one csDMARD at standard dose for at least 3 months or having contraindications to the use of csDMARDs.	Very low	Weakly recommended	92%
TNFi is recommended as first-line therapy in patients with predominant axial involvement.	High	Strongly recommended	97%
TNFi or IL-17i is recommended as first-line therapy in patients with predominant peripheral involvement.	Moderate to low	Strongly recommended	97%
TNFi mAb is recommended as first-line therapy in patients with active uveitis.	Very low	Weakly recommended	97%
Consider adding at least one csDMARD in conjunction with bDMARDs/tsDMARDs.	Moderate to low	Weakly recommended	94%
• In patients with a history of tuberculosis infection, IL-17i or TNF-r-Fc fusion protein is recommended as first-line therapy. • Avoid TNFi mAb in patients with active tuberculosis. • IL-17i is recommended for patients with latent tuberculosis who require bDMARD/tsDMARD treatment. • In patients with latent tuberculosis who require TNFi treatment, it is recommended to treat tuberculosis before TNFi initiation.	Moderate to very low	Weakly recommended	91%
• Patients with chronic hepatitis B virus infection are advised to receive antiviral therapy concurrently with bDMARDs/tsDMARDs, or consider consulting a gastroenterologist. • For patients with HBsAg-negative and anti-HBc IgG-positive status, bDMARDs/tsDMARDs can be administered with caution. Prophylactic antiviral therapy may be prescribed after consultation with a gastroenterologist.	Very low	Weakly recommended	94%
bDMARDs/tsDMARDs can be used with caution in patients with malignancy, especially JAKi	Moderate	Strongly recommended	94%
During pregnancy, TNFi treatment can be considered up to the second trimester.	Very low	Weakly recommended	100%
Follow-up disease activity every 3 to 6 months with validated outcome measures, including ASDAS or BASDAI, is recommended.	Low to very low	Weakly recommended	100%
Gradual dose reduction or increasing the interval of bDMARD/tsDMARD doses is recommended over abrupt discontinuation, when patients are in sustained remission for at least 6 months.	High to moderate	Strongly recommended	100%
Switching to another TNFi, IL-17i, or JAKi is recommended for patients who have had an inadequate response to TNFi.	Low to very low	Weakly recommended	100%
If the disease flares after the tapering or withdrawal of bDMARDs/tsDMARDs, consider initiating a bDMARD/tsDMARD when the ASDAS is ≥2.1 or BASDAI is ≥4, or if ASDAS increases by at least 1.1 or BASDAI increases by at least 1.5.	Very low	Weakly recommended	94%

ASDAS=Ankylosing Spondylitis Disease Activity Score; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; bDMARD=biologic disease modifying anti-rheumatic drug; csDMARD=conventional synthetic disease modifying anti-rheumatic drug; IL-17=interleukin-17 inhibitor; JAKi=Janus kinase inhibitor; LoE=level of evidence; NSAIDs=non-steroidal anti-inflammatory drugs; SoR=strength of recommendation; TNF=tumor necrosis factor; TNF mAb=tumor necrosis factor monoclonal antibody; TNF-r-Fc=tumor necrosis factor receptor-Fc; tsDMARD=targeted synthetic disease modifying anti-rheumatic drug

$ Percentage of agreement among panelists

their poor efficacy, some patients may not be able to afford bDMARDs/tsDMARDs due to their high cost. Furthermore, csDMARDs is also effective in patients with peripheral joint involvement. Therefore, treatment with standard doses of csDMARDs is initially necessary. If there was an inadequate response, treatment with bDMARDs/tsDMARDs should be considered.

Recommendation 2

TNFi is recommended as first-line therapy in patients with predominant axial involvement.

(LoE:- high, SoR:- strongly recommended, Agreement:- 97%)

In patients with predominant axial symptoms, experts recommended TNFi as first-line treatment if the patients had no contraindications or history of previous allergies to TNFi. This recommendation comes from high-quality evidence supporting the efficacy of TNFi, as evidenced by systematic reviews and network meta-analyses that compare the effectiveness of bDMARDs/tsDMARDs in axSpA. The findings indicated that TNFi was more effective than IL-17i, interleukin-6 inhibitors, interleukin 12/23 inhibitors, phosphodiesterase-4 inhibitors, sulfasalazine, and placebo. Furthermore, TNFi may cause slightly less severe adverse effects than IL-17i[23]. The confidence level in these recommendations is high due to the low bias in observational evidence, which instills confidence

among experts that these measures are highly beneficial for patients and worth considering.

Recommendation 3

TNFi or IL-17i is recommended as first-line therapy in patients with predominant peripheral involvement.

(LoE:- moderate-low, SoR:- strongly recommended, Agreement:- 97%)

Currently, there are no head-to-head comparative studies evaluating the efficacy and safety of bDMARDs/tsDMARDs in patients with axSpA with concomitant peripheral arthritis. Therefore, experts provided recommendations based on extrapolated data from studies in patients with PsA, which belongs to the SpA group and often presents with peripheral arthritis. Moderate quality RCTs and low quality open-label RCTs in patients with PsA have shown that IL-17i, such as ixekizumab and secukinumab, and TNFi, such as adalimumab, had comparable efficacy[24,25]. For JAKi, an RCT comparing the efficacy of upadacitinib versus adalimumab in PsA found that upadacitinib 30 mg/day, which is a higher dose, is more effective than adalimumab, but upadacitinib at 15 mg/day is not significantly different from adalimumab (moderate quality)[26]. However, since upadacitinib is not available in Thailand. Experts believe that the available data are insufficient to draw conclusions and recommend the selection of other current available JAKi, such as baricitinib or tofacitinib, as the first-line treatment for axSpA with peripheral joint involvement.

Recommendation 4

TNFi monoclonal antibody is recommended as first-line therapy in patients with active uveitis

(LoE:- very low, SoR:- weakly recommended, Agreement:- 97%)

Due to the lack of direct comparative studies evaluating the efficacy of bDMARDs/tsDMARDs for the treatment of uveitis in axSpA, experts provided recommendations based on data extrapolated from systematic literature reviews and network meta-analyses of RCTs. This review aimed to assess the incidence of uveitis in axSpA treated with bDMARDs/tsDMARDs. The findings indicated that the incidence of uveitis in patients treated with tumor necrosis factor inhibitor monoclonal antibody (TNFi mAb) is lower than in those treated with TNF receptor-Fc (TNF-r-Fc) fusion protein fusion protein, IL-17i, and placebo, with no statistically significant difference, and the incidence was similar to JAKi (moderate quality)[27]. However, experts considered that the studies included in this systematic review could be subjective to selection bias, as patients who had previously experienced uveitis often did not participate in the IL-17i or JAKi studies, while those with a history of uveitis were more likely to enroll in TNFi mAb studies because TNFi mAb have been reported to be effective in treating uveitis. Therefore, the incidence of uveitis in these studies may not be distinctly different. Experts suggested that in axSpA patients with concomitant uveitis, TNFi mAb should be the first-line treatment. In cases where TNFi mAb is contraindicated or intolerable due to side effects, IL-17i or JAKi can be considered as an alternative treatment.

Recommendation 5

Consider adding at least one csDMARD in conjunction with bDMARDs or tsDMARDs.

(LoE:- moderate-low, SoR:- weakly recommended, Agreement:- 94%)

An open-labeled RCT in AS has revealed that individuals treated with adalimumab in combination with methotrexate exhibited a statistically significant lower incidence of antidrug antibodies compared to those treated with adalimumab monotherapy. However, there were no differences in response to treatment between the two groups (moderate quality)[28]. Furthermore, pharmacokinetic and pharmacodynamic studies (low quality)[29,30], and clinical studies (moderate quality)[31] did not find any significant differences between individuals treated with infliximab alone or in combination with methotrexate. However, the findings of observational studies from large registry databases suggested that the addition of methotrexate, sulfasalazine, or methotrexate+sulfasalazine to TNFi prolonged the maintenance of TNFi therapy and resulted in a higher remission rate compared to the group that received TNFi alone (low quality)[32-34]. On the contrary, another study did not find any difference between the group receiving TNFi therapy in combination with a csDMARD and the group receiving TNFi therapy alone (low quality)[35].

Given the conditional nature of these recommendations, experts had low confidence in recommending csDMARDs in combination with bDMARDs/tsDMARDs due to the unclear clinical benefits of combining csDMARDs with bDMARDs, inconsistent findings, and limited data specific to only TNFi therapy. Furthermore, the quality of evidence ranged from moderate to low. Therefore, in cases

where patients experience side effects or cannot tolerate the side effects of csDMARDs, bDMARDs/tsDMARDs treatment as monotherapy may be considered.

Recommendation 6

- **In patients with a history of tuberculosis infection, IL-17i or TNF-r-Fc fusion protein is recommended as first-line therapy.**
- **Avoid TNFi mAb in patients with active tuberculosis.**
- **IL-17i is recommended for patients with latent tuberculosis who require bDMARD or tsDMARD treatment.**
- **In patients with latent tuberculosis who require TNFi treatment, it is recommended to treat tuberculosis before TNFi initiation.**

(LoE:- moderate-low, SoR:- weakly recommended, Agreement:- 91%)

A systematic review of RCTs in axSpA found that those treated with TNFi had a significantly higher risk of tuberculosis (TB) compared to those receiving NSAIDs and csDMARDs, especially TNFi mAb[36]. For IL-17i, a nested case-control study in axSpA, PsA, and psoriasis showed a significantly lower risk of TB compared to TNFi[37]. Regarding tsDMARDs, there are no direct studies on this issue in axSpA. Meanwhile, data in RA showed that tsDMARDs did not increase the risk of TB compared to placebo and TNFi, as adalimumab, (moderate quality)[38]. However, most experts (90%) currently disagree with the recommendation of JAKi for patients with TB, as direct evidence from studies on tsDMARDs in axSpA is lacking. Furthermore, baricitinib is not yet approved by the Thai FDA for axSpA. bDMARDs/tsDMARDs should be avoided in patients with axSpA who have active TB infection, especially TNFi mAb, in those with current or previous TB infection or latent TB. However, if severe disease exacerbations occur and there are no other options, the IL-17i or TNF-r–Fc fusion protein may be considered alongside TB treatment. The decision depends on the patient and physician's discretion and can involve consulting specialists such as infectious disease specialists or pulmonologists.

Recommendation 7

- **Patients with chronic hepatitis B infection are advised to receive antiviral therapy concurrently with bDMARDs or tsDMARDs, or consider consulting a gastroenterologist.**
- **For patients with HBsAg-negative and anti-HBc IgG-positive status, bDMARDs or tsDMARDs can be administered with caution. Prophylactic antiviral therapy may be prescribed after consultation with a gastroenterologist.**

(LoE:- very low, SoR:- weakly recommended, Agreement:- 94%)

Data from patients with RA, psoriasis, and IBD treated with bDMARDs suggested that people with chronic hepatitis B virus (HBV) infection, indicated by the presence of hepatitis B surface antigen (HBsAg), have a higher risk of reactivation of HBV at 17% to 41%, compared to those who have resolved HBV infection, indicated by the absence of HBsAg (HBsAg-), but the presence of anti-hepatitis B core immunoglobulin G (anti-HBc IgG+) at 3% to 6% (very low quality)[39]. In patients with resolved HBV infection, the rate of reactivation in patients treated with TNFi was 1.4%[40] and JAKi was 1%[41], which was lower than other types of bDMARDs at 6% and similar to csDMARDs at 1.7% (very low quality)[40]. The rate of HBV reactivation in patients with chronic HBV infection decreased when antiviral therapy was administered in combination with bDMARDs (very low quality)[40]. For secukinumab, the risk of HBV reactivation in resolved HBV infection was quite low, while cases of chronic HBV reactivation were reported despite receiving antiviral prophylaxis (very low quality)[42]. The U.S. FDA's drug safety monitoring report spanning between 2012 and 2022 reported that tofacitinib did not increase the risk of HBV reactivation (very low quality)[43]. Additionally, an observational study in Taiwan involving RA patients treated with tofacitinib showed that among patients with chronic HBV infection who did not receive antiviral therapy, the incidence of HBV reactivation was as high as 33%, while no reactivation was observed in patients who received antiviral prophylaxis. Regarding resolved HBV infection, the incidence of HBV reactivation was 3.1% (very low quality)[44].

In addition, seeking the advice of a gastroenterologist for the management and monitoring of HBV reactivation could be beneficial. This recommendation is conditional as consulting a gastroenterologist may not be feasible in some cases. This depends on the discretion of the physicians, the patients, and the potential resources of the healthcare facility.

Recommendation 8

bDMARDs or tsDMARDs can be used with caution in patients with malignancy, especially JAKi.

(LoE:- moderate, SoR:- strongly recommended,

Agreement:- 94%)

This recommendation is based on RCTs demonstrating that patients with axSpA treated with TNFi and IL-17i for at least 24 weeks had a non-significantly higher risk of cancer compared to those receiving placebo, NSAIDs, and csDMARDs (moderate quality)[36,45], except for TNF-r-Fc fusion drugs, which have a statistically significant higher risk of cancer than placebo and TNFi mAbs. Regarding tsDMARDs, the RCT data in RA, psoriasis, and IBD found no difference in cancer risk compared to placebo and methotrexate, but when compared to TNFi, patients treated with tofacitinib had a statistically significant higher risk of all types of cancer, except non-melanoma skin cancer[46]. Although bDMARDs/tsDMARDs may increase the risk of cancer, the incidence of cancer in these studies was relatively low, less than 1%. Therefore, in situations where patients require treatment with bDMARDs/tsDMARDs, they can be administered, but cancer should be monitored, especially in patients treated with JAKi.

Recommendation 9

During pregnancy, TNFi treatment can be considered up to the second trimester.

(LoE:- very low, SoR:- weakly recommended, Agreement:- 100%)

TNFi has been reported to significantly increase the risk of preterm birth, spontaneous abortion, and low birth weight in patients with RA, IBD, and autoimmune diseases compared to the general population. However, no differences were found compared to patients treated with other standard treatments (very low quality)[47]. For IL-17i and JAKi, evidence from post-marketing surveillance studies in axSpA, PsA, and psoriasis found that patients treated with ixekizumab[48], secukinumab[49], baricitinib[50], and tofacitinib[51] had similar rates of spontaneous abortion and congenital malformations, compared to the general population. However, most patients received these medications in the first trimester and discontinued almost entirely after becoming pregnant. Additionally, these studies lacked control groups (very low quality). Tofacitinib has a small molecular size, allowing it to pass through the placenta. Furthermore, data from animal studies showed that tofacitinib resulted in abnormal fetal development in pregnant mice and rabbits[52]. Therefore, most experts agreed that IL-17i in 75% and JAKi in 100% should not be used in pregnant women until there are sufficient safety data during pregnancy.

Recommendation 10

Follow-up of disease activity every three to six months with validated outcome measures, including ASDAS or BASDAI, is recommended.

(LoE:- low to very low, SoR:- weakly recommended, Agreement:- 100%)

To assess the results of the treatment in SpA, several dimensions are used in daily practice and research, including the disease status, function, and quality of life related to the disease. For the assessment of disease status, indices such as the BASDAI, ASDAS, and patient global assessment have been evaluated for reliability, validity, and responsiveness and were found to be at a good level[53]. Additionally, ASDAS can differentiate disease severity levels, where ASDAS less than 1.3 indicates inactive disease, ASDAS between 1.3 and less than 2.1 indicates mild disease activity, ADSAS between 2.1 and 3.5 indicates high disease activity, and ASDAS greater than 3.5 indicates very high disease activity, effectively distinguishing disease severity levels with a specificity of 90%. Regarding treatment response criteria, the clinically significant reduction in disease status is defined as the reduction in ASDAS equal to or greater than 1.1, while the major improvement is defined as the reduction in ASDAS equal to or greater than 2.0. These criteria align well with the BASDAI assessment, where reductions equal to or greater than 1.6 and 2.0 correspond to a clinically significant reduction and a major improvement, respectively[17]. Additionally, BASDAI and ASDAS are questionnaire-based tools that have been translated into Thai and validated, demonstrating quality comparable to the original English versions[54]. These questionnaires are widely used in Thailand, so Thai rheumatologists are familiar with their use. Therefore, they are suitable for evaluating the response to treatment in patients with axSpA in clinical practice.

Other disease assessment indices include mini-BASDAI[55,56], Simplified ASDAS[57-59], Alternative ASDAS[60,61], BASDAI-based ASDAS formula or BASDAS[62], total back pain, night pain[53], specific BASDAI questions 5-6[53], magnetic resonance imaging of the sacroiliac joint (MRI-SIJ)[53], MRI-spine[53], and CRP[53]. However, these indices have low reliability, validity, and treatment responsiveness ranging from moderate to low. Therefore, they are not suitable for evaluating the response to treatment in axSpA.

For functional assessment, the Bath Ankylosing Spondylitis Functional Index (BASFI) is widely used,

with high reliability, accuracy, and responsiveness to changes in disease status when assessing patients with axSpA[53]. However, it is not recommended for short-term treatment evaluation because BASFI evaluates physical function that may be affected by both disease activity and permanent damage to bone and joint structure. It does not only assess the state of the disease resulting from the response to treatment.

Although there are several high-quality quality-of-life indices such as the Assessment of SpondyloArthritis international Society Health Index (ASAS-HI)[53], SF36[53], EQ5D[63,64], and Ankylosing Spondylitis Quality of Life Scale (ASQoL)[63], quality of life depends not only on disease status but also on other factors such as mental health, economics, and social aspects. Therefore, they are not suitable to monitor treatment response.

Recommendation 11

Gradual dose reduction or increasing the interval of bDMARD or tsDMARD doses is recommended over abrupt discontinuation when patients are in sustained remission for at least six months.

(LoE:- high to moderate, SoR:- strongly recommended, Agreement:- 100%)

High-quality evidence suggested that stopping treatment with TNFi or IL-17i in patients with axSpA who achieved sustained remission, as assessed by consecutive ASDAS scores of less than 1.3 over six to twelve months, resulted in a statistically significant higher disease flare rate, compared to continuous treatment with bDMARDs[65-68]. Reducing the dose or increasing the interval of administration of bDMARDs did not lead to worse flares of the disease, compared to standard-dose bDMARD treatment[69-71]. Furthermore, severe adverse effects, including infections, cancer, cardiovascular events, or mortality, did not differ between continuous standard-dose bDMARD treatment and dose reduction[72]. Confidence in these recommendations is high because observational evidence has a low risk of bias, causing experts to be confident in the significant benefits of these treatment strategies.

Recommendation 12

Switching to another TNFi, IL-17i, or JAKi is recommended for patients who have had an inadequate response to TNFi.

(LoE:- low to very low, SoR:- weakly recommended, Agreement:- 100%)

These recommendations are conditional recommendations because currently there are no RCT that assess the effectiveness of TNFi or IL-17i, as well as tsDMARDs, in patients with axSpA who did not respond to a first-line bDMARD or tsDMARD[73]. Although the evidence from observational studies is relatively limited and of low quality, prospective cohort studies and open-label extension of the RCT found that patients with axSpA who did not respond to first-line TNFi, when switched to another TNFi or IL-17i, still show efficacy, but with lower response rates than patients naive to bDMARDs (very low quality)[74,75]. Furthermore, evidence from observational studies found that patients with axSpA who did not respond to first-line TNFi, when switched to another TNFi, showed no difference in treatment results compared to switching to IL-17i (very low quality)[76]. Meanwhile, post hoc analysis of data from RCT and open-label extension studies in patients with AS treated with tofacitinib found that non-responders to previous TNFi treatment responded to tofacitinib similarly to those who had not previously been treated with TNFi (very low quality)[77]. Because the observational evidence on the effectiveness of JAKi in TNFi inadequate responders is limited in both quantity and quality, compared to IL-17i, the level of confidence in the recommendations is moderate. However, experts still recommended JAKi as an option in cases where patients had limitations to use TNFi or IL-17i.

Recommendation 13

If the disease flares after the tapering or withdrawal of bDMARDs or tsDMARDs, consider initiating a bDMARD or tsDMARD when the ASDAS is at 2.1 or greater or BASDAI is at 4 or greater or ASDAS increases by at least 1.1 or BASDAI increases by at least 1.5.

(LoE:- very low, SoR:- weakly recommended, Agreement:- 94%)

On search, no direct supporting studies for these recommendations were identified. Therefore, experts considered issuing these recommendations based on criteria to assess disease activity used in clinical trials evaluating the results of reducing the dose of bDMARDs compared to those not reducing the dose, finding that criteria to assess disease activity include BASDAI equal to or greater than 4[78-82], ASDAS equal to or greater than 2.1[65,68,83,84], or the presence of extraarticular manifestations[81,85]. Studies used changes in disease activity indices before and after dose reduction or discontinuation, such as BASDAI increasing by at least 2[86,87] or more or 1.5[82], BASDAI increasing by more than

50%[80], or ASDAS increasing by at least 1.1[65], or the presence of extraaxial manifestations[81,83]. Experts agreed to use these criteria referenced from disease activity indices or changes in indices to resume bDMARDs/tsDMARDs. For active extraarticular or extraaxial manifestations, experts believed that exacerbations may not necessarily require bDMARDs/tsDMARDs and therefore, did not recommend initiating bDMARDs/tsDMARDs in these conditions.

Discussion

This recommendation was developed by integrating the latest available evidence with expert experience and opinions, resulting in practical guidance for everyday practice. The statement was formulated based on clinical questions identified as important and relevant by rheumatologists. However, three statements related to the administration of csDMARDs when bDMARD/tsDMARD initiation and disease remission, as well as the tight control strategy were omitted. The committee's search found no studies evaluating the strategy of administration of csDMARDs when starting bDMARDs/tsDMARDs and the effects of reducing csDMARDs compared to reducing bDMARDs/tsDMARDs in axSpA who have achieved disease remission. Therefore, experts have decided not to issue recommendations due to insufficient supporting evidence and significant variability in current practices, making it impossible to reach a consensus. Regarding the tight control strategy, the committee's search identified a moderate quality RCT comparing the effectiveness of the tight control and the treat-to-target (TC/T2T) strategy with usual care (UC). In the TC/T2T strategy, patients scheduled appointments every four weeks, with treatment adjustments aimed at achieving an ASDAS score of less than 2.1 and maintaining this regimen for one year. While in UC, patients scheduled appointments every 12 weeks and treatment adjustments were made at the discretion of the treating physician. This study did not find significant differences in efficacy at one year of follow-up, measured by a 30% improvement in ASAS-HI. However, secondary outcomes showed that patients in the TC/T2T group had significantly higher proportions of low disease activity with ASAS20 and ASAS compared to the UC group. The research concluded that TC/T2T is cost-effective compared to UC, based on a cost-utility analysis within the healthcare systems of France, the Netherlands, and Belgium[88]. Eighty-two percent of experts disagreed with the tight control strategy, as a lack of empirical evidence indicates that such a strategy clearly benefits patients. Furthermore, they noted that the strategy may not be feasible in practice due to the need for follow-up every four weeks, which is more frequent than current standard practice, and might not be cost-effective in the context of Thailand. However, the experts agreed that treatment should aim at remission or inactive disease. Given that more than 74.99% of the experts voted against it, a recommendation on this matter was finally omitted.

In conclusion, The TRA has proposed 13 recommendations to outline concepts and provide guidance on the treatment of axSpA with bDMARDs and tsDMARDs. These guidelines aim to improve the knowledge and understanding of rheumatologists, allowing them to apply these treatments appropriately and efficiently. Consequently, patients with axSpA will receive care that meets standards and maximizes the benefits of bDMARD and tsDMARD therapies. However, the development of these guidelines has limitations due to the lack of high-quality and reliable evidence in many areas. Therefore, these guidelines are not mandatory. Practitioners may deviate from them as appropriate, based on their discretion and the specific circumstances of each patient. Shared decision-making between the treating physician and the patient must always be applied considering the preference of the patients, the economic, social perspective, societal costs, and the resources, as well as the capabilities of medical personnel and facilities.

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Conflicts of interest

The authors report no conflicts of interest in this work.

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