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REVIEW

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2018 update of the APLAR recommendations for treatment of rheumatoid arthritis

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Abstract

Aim: To update recommendations based on current best evidence concerning the treatment of rheumatoid arthritis (RA), focusing particularly on the role of targeted therapies, to inform clinicians on new developments that will impact their current practice.

Materials and methods: A search of relevant literature from 2014 to 2016 concerning targeted therapies in RA was conducted. The RA Update Working Group evaluated the evidence and proposed updated recommendations using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach, to describe the quality of evidence and strength of recommendations. Recommendations were finalized through consensus using the Delphi technique.

Results: This update provides 16 RA treatment recommendations based on current best evidence and expert clinical opinion. Recommendations 1-3 deal with the use of conventional synthetic disease-modifying antirheumatic drugs. The next three recommendations (4-6) cover the need for screening and management of infections and comorbid conditions prior to starting targeted therapy, while the following seven recommendations focus on use of these agents. We address choice of targeted therapy, switch, tapering and discontinuation. The last three recommendations elaborate on targeted therapy for RA in special situations such as pregnancy, cancer, and major surgery.

Conclusion: Rheumatoid arthritis remains a significant health problem in the Asia-Pacific region. Patients with RA can benefit from the availability of effective targeted therapies, and these updated recommendations provide clinicians with guidance on their use.

KEYWORDS

biological disease-modifying antirheumatic drugs, disease-modifying antirheumatic drugs, DMARDs, rheumatoid arthritis, targeted therapy, treatment

1 | INTRODUCTION

Rheumatoid arthritis (RA) continues to be a major health burden that affects quality of life and consumes healthcare resources, particularly in low- and middle-income countries such as developing countries in Asia.[1,2] Better strategic use of agents that delay disease progression, termed disease-modifying anti-rheumatic drugs or DMARDs, has improved outcomes in the past 2 decades. In parallel, development of DMARDs that directly target pro-inflammatory molecules has increased the range of DMARD options available.

DMARDs can be classified into conventional synthetic DMARDs (csDMARDs) and specific targeted DMARDs. csDMARDs include methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), hydroxychloroquine (HCQ), cyclosporine, gold salts, D-penicillamine, and azathioprine (AZA). MTX is the cornerstone of RA treatment regimens and is widely used.

Specific targeted therapies include biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs). The bDMARDs comprise monoclonal antibodies and other biologic receptor constructs that block pro-inflammatory cytokines or cell subsets that are implicated in RA pathogenesis. Typically, they are grouped in the literature according to their target. Tumor necrosis factor inhibitors (TNFi) include adalimumab (ADA), certolizumab (CZP), etanercept (ETN), golimumab (GOL) and infliximab (IFX). Non-TNFi biologic agents include abatacept (ABA; a cytotoxic T lymphocyte antigen 4[T-cell co-stimulation inhibitor]), anakinra (ANK; an anti-interleukin-1 receptor blocker), rituximab (RTX; an anti-CD20), and tocilizumab (TCZ; an anti-interleukin-6 receptor [IL-6R] blocker)[3,4]; newer IL-6R inhibitors exist (eg, sarilumab), as well as agents targeting other cytokine-mediated pathways,[3] but the studies supporting their use were published beyond the time scope of this review. Janus kinases (JAKs) represent another therapeutic target in RA—the oral JAK inhibitor tofacitinib (TOF) was the first tsDMARD approved for RA,[4,5] with other JAK inhibitors (eg, baricitinib) subsequently becoming available. For this update, we focused on guidance on the use of bDMARDs and TOF.

With the number of available targeted agents now in the market, guidance on their use will be critical for clinicians who care for patients with RA. Guidelines from the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) that provide frameworks for optimum use of these agents are published elsewhere.[6,7] In 2013, the Asia-Pacific League of Associations for Rheumatology (APLAR) convened a Steering Committee to develop recommendations on pharmacological treatment of RA that would serve as a reference for best RA management practices in the region, focusing on local issues in the region; these recommendations were published in 2015.[8] This update builds on the 2015 document by presenting a review of literature which had emerged since the development and subsequent publication of the original recommendations. We focused specifically on the role of targeted therapies to address the outstanding questions practitioners may have on the use of these agents.

2 | MATERIALS AND METHODS

Our original document of treatment recommendations covered clinical practice guidelines for RA from January 2000 to December 2013.[8] We used the ADAPTE framework with the aim of adapting international guidelines for use in the Asia-Pacific region. To assess the quality of each guideline, we used the Appraisal of Guidelines, Research and Evaluation (AGREE) instrument.

Members of the Steering Committee involved in the development of the 2015 document were called upon to form the Working Group for this update. During the first meeting, the group re-evaluated the list of clinical questions on which the literature search for the original set of recommendations was based. The group agreed on a list of 10 relevant questions on the use of targeted therapy, that formed the basis of the literature search strategies for this update.

Because new studies had been conducted since the publication of our original document, we searched MEDLINE through PubMed, EMBASE and the Cochrane Library for randomized controlled trials (RCTs), observational studies, and meta-analyses, limited to research in humans, publications in English, from January 2014 to December 2016. The articles were assigned for review to members of the Working Group. To evaluate the evidence from these publications, the group employed the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach to evaluate the evidence from these publications. The GRADE approach is widely seen as the most effective method of linking evidence-quality evaluations to clinical recommendations.[9,10]

Over the next two meetings, the evidence was presented and discussed. According to the GRADE approach, the strength of a recommendation and quality of evidence ("very low", "low", "moderate" and "high") were assigned grades to yield 1 overall grade (Table 1).[9,10] If the Working Group judged that a recommendation lacked sufficiently strong evidence, they agreed to provide their best expert advice but left such recommendations ungraded. The members drafted recommendation statements and refined these as the discussion of evidence proceeded. After the 2nd meeting (3rd overall), the group generated a final set of 16 recommendations for the use of targeted therapy in RA.

A voting group was then convened from APLAR country representatives. Utilizing the modified Delphi technique, the voting group rated their agreement with each recommendation on a 5-point Likert scale (ie, 5, strongly agree; 4, agree; 3, neither agree nor disagree; 2, disagree; 1 strongly disagree); agreement by 75% of total voting members was defined as the threshold for acceptance of a statement. The voting group achieved consensus on all statements in the 1st voting round.

Draft recommendations developed by the group were sent to Professor Iain McInnes and Professor Vibeke Strand for review and comments. The draft recommendations were also presented in an open forum during the 2018 APLAR Congress, as well as regional rheumatology conferences in China, Hong Kong and Pakistan, to seek opinions and suggestions from participants. Feedback from the respondents was used to finalize the recommendations and inform supporting text. The recommendations were also sent for review and official endorsement by APLAR.

3 | RESULTS

Sixteen recommendations are presented with their level of agreement and overall grade, each followed by a discussion of the past and current evidence that support it (Table 2).

3.1 | Recommendations

1. Starting treatment with csDMARD monotherapy, preferably MTX, is recommended as soon as the diagnosis of RA is made. (100% agreement; grade of evidence moderate)

The 2016 update to the EULAR RA management recommendations and the 2015 ACR RA treatment guidelines both state that DMARDs should be 1st-line therapy for RA.[6,7] Treatment should be started with MTX as monotherapy, instead of double or triple DMARD combination therapy. A 2014 systematic review of seven studies showed that MTX monotherapy for RA was significantly more effective than placebo in improving outcomes such as the ACR response criteria of 50% improvement (ACR50) and the Health Assessment Questionnaire Disability Index (HAQ-DI).[11] Moderate-quality evidence from individual studies further showed that combination therapy with a csDMARD does not confer an additional benefit compared with

TABLE 1 Grade for quality of evidence[16]

Grade	Quality of evidence	Meaning
A	High	We are very confident that the true effect lies close to that of the estimate of the effect
B	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
C	Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect
D	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 APLAR rheumatoid arthritis treatment recommendations: focus on targeted therapy

	Recommendation	Grade
1	Starting treatment with csDMARD monotherapy, preferably methotrexate, is recommended as soon as the diagnosis of RA is made	Moderate
2	Patients who cannot tolerate MTX may receive other csDMARDs such as LEF and SSZ as 1st-line treatment. HCQ, iguratimod, bucillamine, cyclosporine, intramuscular gold or tacrolimus may also be considered depending on availability	Moderate
3	In patients with high disease activity, combination csDMARD therapy should be considered, with close monitoring of therapy-related toxicities	Low
4	Prior to starting targeted therapy, all patients should be evaluated for the presence of active or inter-current infections, comorbidities including lymphoproliferative disorders and skin cancers, vaccinations, pregnancy, and possible contraindications	Not graded
5	A All patients should be screened for infections including TB, HBV, HCV and HIV (high-risk population) infections before initiating targeted therapy. Patients with active or latent infections should receive adequate therapy. B For RA patients with latent TB, prophylaxis treatment according to country-specific guidelines is recommended to prevent TB reactivation. C For RA patients with HBV infection (active or occult), antiviral therapy should be prescribed to prevent HBV reactivation.	Low
6	A Vaccination should be undertaken prior to initiating targeted therapy. B During targeted therapy, live attenuated virus vaccines are contraindicated. Pneumococcal and influenza vaccines are recommended. Vaccines for HBV, HPV and meningococcal infections are conditionally recommended.	Moderate
7	Targeted therapies, including TNFi, non-TNFi and JAK inhibitors, can be prescribed to patients who have moderate or high disease activity despite adequate treatment with csDMARD, or in patients with intolerance to csDMARD	Moderate
8	Based on currently available evidence, all targeted therapies are equally effective in the treatment of RA when combined with MTX or csDMARDs	Moderate
9	All patients receiving targeted therapy should be closely monitored for therapy-related toxicities	Not graded
10	For RA patients with a history of TB or latent TB (or in whom the risk remains high despite negative screening), targeted therapies other than monoclonal Ab TNFi are preferred	Low
11	In RA patients at increased risk of HBV reactivation, targeted therapies other than RTX are preferred	Low
12	Modification of targeted therapy should be performed for failure to achieve remission or low disease activity after 6 mo	Not graded
13	In patients with established RA, consideration of tapering or discontinuation of targeted therapy should only be made when the disease is in remission for over 12 mo, especially if the patient is receiving concomitant csDMARD	Moderate
14	For patients with a past history of treated solid cancer, targeted therapies may be used with caution	Very low
15	For patients undergoing major surgery, we recommend temporary discontinuation of targeted therapy and resumption when wound healing is satisfactory	Low
16	For patients with established RA in whom disease cannot otherwise be controlled, TNFi (preferably ETN or CZP) may be continued throughout pregnancy	Low

APLAR, Asia Pacific League of Associations for Rheumatology; bDMARD, biological DMARD; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; CZP, certolizumab; ETN, etanercept; HBV, hepatitis B virus; HCQ, hydroxychloroquine; HCV, hepatitis C virus; HPV, human papilloma virus; JAK, Janus kinase; LEF, leflunomide; MTX; methotrexate; NSAID, nonsteroidal anti-inflammatory drugs; RA, rheumatoid arthritis; RTX, rituximab; SSZ, sulfasalazine; TB, tuberculosis; TNFi, tumor necrosis factor inhibitor.

monotherapy alone (SSZ + MTX vs individual components[12-14]; MTX + LEF vs MTX[15]) in terms of disease activity score (DAS), ACR50, and HAQ score.

Results from systematic reviews also suggested no additional benefit from combination csDMARD therapy. One review found that the ACR50 response rate in MTX-naive patients was similar in both the MTX-alone and csDMARD combination group.[16] Also, a EULAR review found that combination treatments with MTX offered no significant advantage over MTX monotherapy based on pain, HAQ, and ACR20, 50, or 70 response criteria.[17] In addition, results from the latter revealed that MTX monotherapy was more efficacious than other csDMARDs pooled in reduction of signs and symptoms, disability, and structural damage. Two other studies that compared combination csDMARD therapy (MTX + SSZ + HCQ, MTX + SSZ and MTX + LEF) and MTX, with corticosteroids in both arms, showed no difference in efficacy between each treatment group.[18,19]

Our 2015 publication presented two strong recommendations on csDMARDs as 1st-line RA treatment, that is, that csDMARDs

can be started as monotherapy or in combination, and that MTX is the preferred csDMARD.[8] With current and past evidence evaluated as moderate quality based on the GRADE approach, our present recommendation modifies previous statements and integrates them into 1 recommendation—patients should be started on csDMARD monotherapy, preferably MTX, as soon as they are diagnosed with RA.

2. Patients who cannot tolerate MTX may receive other csDMARDs such as LEF or SSZ as first-line treatment. HCQ, iguratimod, bucillamine, cyclosporine, intramuscular gold or tacrolimus may also be considered depending on availability (100% agreement; grade of evidence moderate).

For patients who cannot tolerate MTX, we recommend use of SSZ or LEF as 1st-line treatment, as they have been shown to improve the signs and symptoms of RA as well as retard radiographic progression. This is consistent with our 2015 recommendations, except that the stated options now do not include HCQ. This strategy is also recommended in the 2016 EULAR RA management recommendations.[7]

The evidence for the efficacy of LEF was presented in three systematic reviews: a Cochrane review showed that LEF was better than placebo with regard to ACR50, HAQ, and radiological progression, and compared with MTX, its use led to similar improvements in ACR50 and reduction of Sharp score progression.[20] The EULAR review and a more recent publication likewise suggested that LEF was as effective as MTX.[17,21] As early as 1999, LEF was shown to be superior to placebo and as effective as MTX in a RCT in improving RA signs and symptoms, delaying disease progression and improving quality of life.[22] In a subsequent analysis, the safety and efficacy of LEF was sustained over 2 years.[23] After 24 months, LEF was superior to MTX in improving physical function.

SSZ as an alternative to MTX is supported by results from early studies and from recent reviews. A 1998 review showed a statistically significant benefit for SSZ over placebo in improvement of tender and swollen joint scores, and pain.[24] In addition, two RCTs showed no difference in terms of the mean change in DAS and HAQ between MTX and SSZ treatment groups over 1 year.[13,14] Slowing of radiographic progression was seen in observational studies.[25] More recently, direct comparison of SSZ and MTX in the EULAR review suggested no significant differences in terms of swollen joint count, ACR50, and disability,[17] while the 2002 Cochrane review showed that SSZ had a similar ACR50 response compared with LEF.[20]

The csDMARDs cyclosporine,[26-29] injectable gold,[29-32] tacrolimus,[33,34] AZA,[35-37] iguratimod,[38-43] and bucillamine[44-46] have been shown to improve signs and symptoms of RA with limited data showing efficacy in the retardation of radiographic progression. In contrast, HCQ has been shown to improve the signs and symptoms of RA without inhibiting radiographic progression.[32,47-50] Our group thus suggests considering their use only if 1st-line csDMARDs are not tolerated.[17,25]

3. In patients with high disease activity, combination csDMARD therapy should be considered, with close monitoring of therapy-related toxicities (95% agreement; grade of evidence low).

Following the review of the efficacy of csDMARD monotherapy, the group explored a scenario in which patients might need combination therapy. The evidence base consisted of RCTs conducted in early RA or in RA that had progressed. In RA patients with active disease who are csDMARD-naive, combination therapy was found to be more efficacious than monotherapy in reducing disease activity but was associated with an increase in hepatotoxicity (defined by elevation of liver enzymes to greater than twice the upper limit of normal). Low- to high-quality evidence from 4 RCTs showed that triple therapy was better than monotherapy in achieving an ACR50 response rate, but this was accompanied by a higher incidence of hepatotoxicity.[18,51,52] Moderate-quality evidence from seven RCTs also showed superior efficacy of double or triple therapy vs monotherapy in achieving an ACR50 response rate and reducing the DAS28 score; however, this was also associated with a higher incidence of hepatotoxicity.[12-14,18,51] All trials utilized SSZ or MTX as comparison monotherapy; two studies used the step-up approach by adding a DMARD in each step.[51,53] A recently published RCT from China showed that up to 54.1% of patients on an intensive combination csDMARD regimen (MTX + LEF + HCQ) achieved a good EULAR response after 36 weeks of treatment.[54] The previously cited 2002 Cochrane review on LEF also showed that the proportion of patients achieving ACR50 was higher in the combination LEF + MTX group compared with MTX alone.[20]

Based on low- to high-quality evidence, we consider combination csDMARD therapy as a viable option for progressive RA or RA with high disease activity. The combination of csDMARDs may still be a practical approach for patients in the Asia-Pacific who require affordable therapies.

4. Prior to starting targeted therapy, all patients should be evaluated for the presence of active or inter-current infections, comorbidities including lymphoproliferative disorders and skin cancers, vaccinations, pregnancy, and possible contraindications (100% agreement; evidence not graded).

The use of targeted therapy has greatly improved RA treatment but has been shown to increase risk of infections, including reactivation of latent viruses.[55,56] This is relevant particularly in the Asia-Pacific, which has a high prevalence of tuberculosis (TB) and hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections.[59,60]

The risk for infections is already higher in individuals with RA. For example, a cohort study from Taiwan showed an increased risk of HBV infection in those with RA compared with non-RA individuals.[62] The use of targeted agents may raise this risk, as shown by a data review of a TOF development program, in which a high incidence rate of TB in regions endemic for TB was associated with TOF use.[63]

Also, studies have suggested a higher risk of cancer in individuals with RA than in the general population.[64,65] A Swedish cohort study found an increased risk in basal cell carcinoma and squamous cell carcinoma in bDMARD-naive patients with RA compared with the general population.[64] Moreover, results of a meta-analysis of 9 studies showed that patients with RA carry a modest increased risk in overall malignancy, and an increased risk of lymphoma and lung cancer, compared with the general population, although standardized incidence ratio estimates for colorectal and breast cancers showed a decrease in risk.[65] Severe inflammation in immune-mediated diseases is believed to contribute to cellular changes that lead to tumor formation, in which TNF plays a role,[66] but further studies are needed to investigate the underlying mechanisms for the increased or decreased risk of specific cancers observed.[65]

The safety of targeted therapy such as TNFi in pregnancy is understandably of considerable importance, but data from well-controlled studies in humans is lacking. Although safety data from the British Society for Rheumatology Biologics Register (BSRBR) suggest an increased rate of spontaneous abortion associated with TNFi use at conception for arthritis-related diseases, no firm conclusions can be drawn about restricting TNFi use due to confounding factors, such as arthritis severity.[67]

No studies on safety outcomes after vaccination with bDMARD exposure were found. Theoretically though, vaccination can alter the immune response of individuals with inflammatory diseases like RA who take immune-suppressing agents, such as bDMARDs.

Given the potential safety issues, treatment planning with targeted therapy should therefore begin with taking a detailed medical history and examination. Eliciting relevant past diseases or conditions may facilitate the selection of a specific agent.

5. A All patients should be screened for infections including TB, HBV, HCV and HIV (high-risk population) infections before initiating targeted therapy. Patients with active or latent infections should receive adequate therapy.

B For RA patients with latent TB, prophylaxis treatment according to country-specific guidelines is recommended to prevent TB reactivation.

C For RA patients with HBV infection (active or occult), antiviral therapy should be prescribed to prevent HBV reactivation (100% agreement; grade of evidence low).

3.2 | TB

The earliest reports of increased TB infection with biological DMARDs for RA, specifically TNFi, were from IFX use.[68,69] ETN and ANK were also linked to an increased risk of TB.[70,71] Retrospective studies, including those from Taiwan, Hong Kong, and Korea, showed a higher risk of TB with bDMARDs in patients with RA.[72,73] Meta-analyses demonstrated an increased risk of TB in patients with RA treated with TNFi.[56,78]

One of these analyses showed that TB incidence rate (IR) was 3.17 times higher in patients with RA than in the general population. Furthermore, TB IR was 17.07 times higher in patients with RA treated with TNFi than the general population.[78] The researchers also evaluated the efficacy of the chemoprophylaxis for latent TB infection (LTBI) by focusing on four observational studies in which patients were screened, and then offered chemoprophylaxis prior to TNFi. The relative risk (RR) of patients treated for LTBI was 0.35 times (95% confidence interval [CI] 0.15-0.82) than that of patients with LTBI who did not receive treatment, suggesting that preventive treatment lowered TB risk by 65%.[76] In Japan, a case-cohort study showed that patients with RA and LTBI who received TB prophylaxis did not develop TB after ADA treatment.[79] Although we judged the preceding evidence as low quality, the group could not overlook the value of LTBI screening and prophylaxis pre-bDMARD in this TB-endemic region.

The initial screening assessment for TB should include both clinical evaluation and complementary tests. A detailed clinical history and contact history are helpful for TB risk assessment. Symptoms and physical signs are suggestive of active TB. Complementary tests for TB screening include chest X-ray, tuberculin skin test (TST) and interfereon-γ release assays (IGRA).[80] One observational study demonstrated increased LTBI detection with TST and booster test.[81] IGRA is recommended for use in individuals with bacille Calmette-Guerin (BCG) vaccination.[80] The concordance of TST and IGRA results are still being evaluated, but generally, clinicians should pay close attention to the potential for false-negative or indeterminate results and consider each individual's clinical situation.

Several international guidelines cite isoniazid (INH) for 6-9 months as standard LTBI treatment for bDMARD candidates. They also recommend prophylaxis 1-2 months before starting bDMARD treatment.[80]

3.3 | HBV

Asian and European guidelines contain specific recommendations on HBV infection status while on immunosuppressive therapy, given the risk of HBV reactivation (HBVr).[82,83] They state that hepatitis B surface antigen-positive (HBsAg+) individuals who are candidates for immunosuppressive therapy should receive antiviral prophylaxis at the onset of treatment, and maintain this for 6-12 months after the conclusion of treatment. The guidelines also recommend testing for HBV markers (HBsAg, hepatitis B surface antibody [anti-HBs], and hepatitis B core antibody [anti-HBc]).[82,83]

Considering that the incidence of HBVr is high among those with chronic HBV infection (HBsAg+) who received bDMARDs, antiviral prophylaxis is thus recommended.[86,87] HBV serology prior to bDMARD use, to screen for HBV infection status, is also sensible in our setting. The prophylaxis plan will depend on the individual's status. When indicated, antiviral prophylaxis should be started at least 7 days before initiating immunosuppressive therapy and for at least 6 months (12 months for rituximab) after completion of immunosuppressive treatment.[88]

Individuals with anti-HBs+/anti-HBc+ state are typically considered immune to the virus. Although certain bDMARDs can decrease anti-HBs titer, the majority of levels observed are still above what

is considered the protective level.[89,90] Measuring HBV DNA is recommended, but the test entails considerable cost. The optimal frequency of testing is also undetermined.

Individuals with anti-HBs-/anti-HBc+ state, or latent HBV infection, have a relatively low risk of HBVr. In this case, the recommendation is to monitor HBV DNA and start antiviral therapy with evidence of HBV DNA level increase, but cost, and lack of a recommended frequency of testing, may make this impractical in our region. In practice, some gastroenterologists may prescribe anti-viral prophylaxis, for example, lamivudine, instead of testing for HBV DNA.[55] Because rituximab provides the highest risk of reactivation, patients who are HBsAg- but anti-HBc+ should start antiviral prophylaxis if the patient is to start anti-CD20 therapy like rituximab.[88]

For prophylaxis, guidelines typically recommend a nucleos(t)ide analog (eg lamivudine, entecavir), based on studies that involved chemotherapy or immunosuppression.[82,83] Recently, a small RCT from Taiwan showed efficacy of entacavir prophylaxis in preventing HBVr in patients with rheumatic diseases and inactive HBV who were candidates for bDMARDs.[93]

3.4 | HCV

The risk of reactivation (HCVr) is low in patients with HCV infection. Studies also suggest that the incidence of HVCr in patients with RA receiving bDMARDs is not as high as HBVr.[94,95] The suggestion is to determine HCV RNA periodically, but cost is also prohibitive.

No definitive guidelines exist for screening for HCV prior to DMARD use.[100] However, it is important for rheumatologists to screen for HCV in their patients because treatment of concomitant HCV or HCV-induced rheumatic disease is quite challenging. The fear of exacerbating side effects from HCV treatment may prevent use of bDMARDs, which lack safety data in this scenario,[101] and lead to undertreatment of the symptoms of rheumatic disease. More data are needed—case reports have suggested that TCZ can be safely used for RA with concomitant chronic HCV infection[98,99,102]; an RCT showed that patients with RA and chronic HCV had reduced DAS44 and HAQ with MTX, ETN, or the combination, without increased viral load or hepatotoxicity[103]; and a retrospective review of the safety of bDMARDs in 26 patients (ETN, GOL, ADA, RTX) showed reduction in DAS28, also without elevation of HCV viral load and liver transaminases.[104] A systematic review of 37 publications suggested the safety of TNFi (eg ETN) in patients with rheumatic disease and chronic HCV infection.[94]

3.5 | HIV

There is a lack of data regarding safety of bDMARDs and tsDMARDs for RA in individuals with HIV. Despite this, screening for HIV may be useful in our region for proper treatment planning. IFX, ETN and ADA appear to be well-tolerated in HIV+ patients, based on t2 case series.[105,106] TNFi may also be safe for concomitant HBV and HCV.[101,107] Patients with chronic HBV and HIV co-infection should be referred to an infectious diseases specialist. The initial HIV regimen generally includes three antiretroviral drugs from at least two different HIV drug classes.

6. A Vaccination should be undertaken prior to initiating targeted therapy.
   B During targeted therapy, live attenuated virus vaccines are contraindicated. Pneumococcal, influenza, and non-live zoster vaccines are recommended. Vaccines for HBV, human papilloma virus (HPV) and meningococcal infections are conditionally recommended (100% agreement; grade of evidence moderate).

In the RA population, the general risk of infection is raised to about twice that of the general population.[108] The sites of infection include bone, joints, skin, soft tissues, and the respiratory tract. Important reasons include impaired immunity due to RA and use of long-term steroids and other immunosuppressive therapies. With targeted therapies, the infection risk is increased further. The BSRBR reported an adjusted hazard ratio (HR) of 1.2 (95% CI 1.1-1.5) for serious infections in their TNFi cohort.[109] A meta-analysis of five cohort studies and two nested case-control studies reported increased risk of infections in RA patients taking TNFi (pooled adjusted RR 1.37, 95% CI 1.18-1.60).[110] While not all of infections may be vaccine-preventable, it is prudent to plan for protection against those that occur most frequently in patients with RA. The ACR recommends vaccination against the following: *Pneumococcus*, influenza, HBV, HPV and herpes zoster.[6]

Ideally, vaccinations should be completed before starting any type of targeted therapy; however, in clinical practice, targeted therapy often needs to be started without delay. Vaccine administration in patients receiving targeted therapy concomitantly poses two challenges: the vaccine response may be compromised by ongoing targeted therapy, which can suppress the immune system; and a live attenuated vaccine carries the risk of disseminated infection by the vaccine virus strain in an immunocompromised individual.

Four RCTs were considered suitable for this update.[111,112] In addition, data from three earlier RCTs were pooled for the analysis because of similarity of methodology and reporting of results.[114,115]

3.6 | Pneumococcal vaccine

Three RCTs studied the effect of TNFi (CZP, ADA, IFX) on the immunogenicity of pneumococcal polysaccharide vaccine (PPSV-23)[108,111,117]; two of these also studied the influenza vaccine.[111,116] Patients in the intervention groups were already on TNFi when vaccine was administered. The control groups consisted of patients with RA who had not been on TNFi (or any form of targeted therapy) in the last 6 months and were continued on csDMARDs. A 2-fold rise in titer defined the vaccine response in all three studies. Pooled results showed that there was no significant difference in vaccine response between TNFi and control groups. Adverse effects were monitored up to 6 months in 2 of the 3 studies and no significant difference was observed.

Three RCTs studied the effect of non-TNFi (TCZ, TOF, RTX) on immunogenicity of PPSV-23.[112,114,115] In the TCZ trial, the intervention group received TCZ + MTX, while the control group received

MTX alone.[112] PPSV-23 was administered at week 3, then at week 8 (5 weeks after vaccination), and serum was collected for measurement of post-immunization antibody levels. The difference between TCZ and control groups was not significant. The former had a substantially higher frequency of adverse effects, as was expected.

In the TOF trial, TOF-naive RA patients were randomized to TOF 10 mg twice daily or placebo, stratified by background MTX and vaccinated 4 weeks later.[114] Antibody titers were measured 35 days after vaccination. Primary endpoints were the proportion of patients achieving a satisfactory response to *Pneumococcus* (2-fold or more titer increase against 6 or more of 12 pneumococcal serotypes). Fewer TOF patients (45.1%) developed satisfactory pneumococcal responses vs placebo (68.4%). This study did not describe adverse effects of TOF.

The 3rd non-TNFi study indicates that RTX appeared to impair the immunogenicity of the vaccine. In the study, patients received RTX + MTX for 36 weeks, or MTX alone for 12 weeks.[115] The former received PPSV-23 at week 28, and the latter, at week 4. RTX-treated patients had decreased responses to PPSV-23; 57% of patients had a 2-fold rise in titer in response to >1 serotype, compared with 82% of patients treated with MTX alone.

Patients with RA in a Japanese RCT who had been treated with biological or immunosuppressive agents were randomly assigned PPSV-23 or placebo (sodium chloride) in a Japanese RCT that evaluated vaccine protection.[118] The primary endpoints were the incidences of all-cause pneumonia and pneumococcal pneumonia. A subgroup of 3.7% (17/464) in the vaccine group and 3.4% (15/436) in the placebo group developed pneumonia—there was no difference in the rates of pneumonia between the two study groups. The authors concluded that PPSV-23 does not protect against pneumonia overall in RA patients.

3.7 | Influenza vaccine

Three RCTs evaluated the immunogenicity of the influenza vaccine with use of targeted agents (CZP, TOF, ADA).[111,114,116] A 4-fold increase in antibody titer after 4 weeks for the CZP and ADA trials, and after 5 weeks for the TOF trial, was considered as a vaccine response. The pooled results showed no evidence of impairment of vaccine immunogenicity. Also, there was no increase in adverse effects in the targeted therapy group as compared to control group. It is noteworthy that temporary discontinuation of MTX (which is often combined with targeted therapies in RA) 2 weeks before and after influenza vaccination improves the immunogenicity of influenza vaccine.[109]

3.8 | Zoster vaccine

Zoster vaccine is of paramount importance in RA patients treated with JAK inhibitors. A phase II, 14-week, placebo-controlled trial evaluated live zoster vaccine (LZV) in RA patients receiving TOF.[113] Patients aged >50 years with active RA on background MTX were given LZV and randomized to receive TOF 5 mg twice daily or placebo, 2-3 weeks post-vaccination. Investigators measured humoral and cell-mediated responses to varicella-zoster virus (VZV) at baseline and post-vaccination. Six weeks post-vaccination, these VZV-specific responses were found to be similar in both TOF and placebo groups. Serious adverse events (AEs) occurred in 3 (5.5%) TOF patients and 0 (0%) placebo patients. One patient who lacked pre-existing VZV immunity developed cutaneous vaccine dissemination 2 days after starting TOF (16 days post-vaccination). This resolved after TOF discontinuation and antiviral therapy.

A non-live zoster vaccine (Shingrix) was approved by the US Food and Drug Administration in October 2017[119] and is now available in the USA and other countries since March 2018. The US Centers for Disease Control and Prevention recommend 2 doses of this vaccine, 2-6 months apart, in subjects aged 50 years and older. Potentially, safety concerns related to the live attenuated zoster vaccine have been addressed with this new product; however, no trial data on Shingrix in patients with RA taking targeted therapies are available yet, and the vaccine is not yet available in many countries in the Asia-Pacific.

3.9 | HBV vaccine

A study was presented in the EULAR conference in 2015 on the efficacy of HBV vaccine in patients with RA.[120] The HBVAXPRO-10 regimen, with vaccination at 0, 1, and 6 months, was completed by 47 patients with RA and 156 healthy control subjects. Investigators assessed anti-HBs titers 28 weeks after the last of the three doses was administered. Patients whose titer levels were above 10 IU/L at 28 weeks were considered to be responders and were deemed to be protected against hepatitis B infection. Only 11% of the RA group (5/47) achieved an adequate response to the vaccination at 28 weeks. In contrast, 83% of the control group (129/156) were responders. A previous study had shown that immune responses in patients with RA are better with Engerix-B than with HBVAXPRO-10.[121]

3.10 | HPV and meningococcal vaccine

No RCT on immunogenicity of HPV and meningococcal vaccine in patients with RA taking targeted therapy was found in the literature.

7. Targeted therapies, including TNFi, non-TNFi and JAK inhibitors, can be prescribed to patients who have moderate or high disease activity despite adequate treatment with csDMARD, or in patients with intolerance to csDMARD (100% agreement; grade of evidence moderate).

Targeted therapies are options for patients who continue to have moderate or high disease activity despite previous csDMARD therapy, or for those who are intolerant to csDMARD. Their efficacy in improving disease outcomes as monotherapy and in combination with csDMARDs, and in early and established RA, has been confirmed in RCTs and Cochrane reviews.

In the MTX-naive population, moderate-quality evidence from a Cochrane review confirmed the efficacy of bDMARDs (TNFi ADA, ETN, GOL, and IFX; and non-TNFi ABA, RTX) plus MTX in improving ACR50, HAQ scores, and RA remission rates. However, same-quality evidence showed no difference between TNFi monotherapy (no data for non-TNFi) and MTX. The evidence for slowing of radiographic progression by bDMARD plus MTX was considered as low quality.[122]

The efficacy of the JAK inhibitor TOF as monotherapy vs MTX, also in MTX-naive patients, was demonstrated by a double-blind, randomized, placebo-controlled trial.[123] Mean changes in the modified total Sharp score from baseline to month 6 were significantly smaller with TOF than with MTX. Furthermore, the number of patients achieving ACR70 response was significantly greater for the TOF group than the MTX group.

A double-blind, placebo-controlled RCT in early, DMARD-naive RA showed that more patients who started treatment with non-TNFi TCZ with or without MTX were in sustained remission (measured by DAS28) than those who received MTX monotherapy.[124]

Cochrane reviews of the use of bDMARDs or TOF for RA in both csDMARD-experienced patients who failed on csDMARDS (including MTX), and incomplete responders to MTX and other csDMARDS, supported the efficacy of these agents in providing clinically meaningful improvements in ACR50, HAQ scores, and RA remission rates.[125,126] Moderate-quality evidence was seen with monotherapy vs placebo or MTX/other DMARDs in csDMARD-experienced patients,[125] and with targeted therapy combined with MTX/other DMARDs vs comparator in those with incomplete responses to csDMARDs.[126] Study durations were from 6 to 12 months.

An open-label RCT evaluated the efficacy of TNFi vs combination csDMARD therapy. This study included patients with established RA, that is, disease duration over 12 months and active disease, that met the National Institute for Health and Care Excellence (NICE) criteria for starting biologics in England (DAS28 >5.1 × 2 after treatment with MTX and 1 other DMARD).[127] The investigators compared treatment initiation with TNFi vs combination csDMARDs. For non-responders after 6 months, they prescribed another TNFi in the TNFi-initiation group, and a new TNFi in the csDMARD combination group. HAQ scores favored combination therapy, and there was no difference in disease activity after 6 months or in radiographic damage between groups; they concluded that TNFi were as efficacious as combination csDMARDs in established RA.

A meta-analysis of 8 RCTs (from 10 publications) explored the differences between TNFi combined with a csDMARD and combination csDMARD. Patients included those with early and established RA (5 and 3 studies, respectively). Three studies were conducted in csDMARD-naive patients. Although significant differences were seen between groups in radiographic progression score, ACR50, and ACR70 responses at 6 months favouring TNFi plus csDMARD, these were lost at 24 months.[128]

Given the established efficacy of targeted therapy, we recommend their use for controlling disease after failure with csDMARD. Targeted agents may be beneficial even in MTX-naive/csDMARD-naive individuals. There is moderate-quality evidence that the combination of targeted therapy with a csDMARD is beneficial across populations, but in patients who cannot tolerate a csDMARD, two trials showed better outcomes with TOF[123] and TCZ[124] as monotherapy vs MTX in MTX-naive patients. The evidence also suggested that monotherapy may be feasible in csDMARD-experienced individuals (established RA).

8. Based on currently available evidence, all targeted therapies are equally effective in the treatment of RA when combined with MTX or csDMARDs (90% agreement; grade of evidence moderate).

Our 2015 APLAR document listed the therapeutic options for candidates for bDMARD therapy, which included TNFi, ABA, TCZ, and RTX. The role of the tsDMARD TOF was separately stated as an option for individuals who failed bDMARDs.[8] TNFi were then considered as having the strongest evidence for efficacy,[8] and typically, they are the 1st type of targeted therapy used after a csDMARD, according to the ACR.[6]

Since then, new data from studies have emerged. Cochrane reviews have looked at the use of targeted therapies in different populations of individuals with RA, including in patients who were MTX-naïve, those who failed MTX/csDMARD, and those who failed bDMARDs. Based on the Cochrane analyses, there is moderate-quality evidence that TNFi, non-TNFi, and TOF were more effective than placebo or MTX/csDMARDs for the improvement of ACR50, HAQ, and DAS remission responses. The evidence for reduction in radiographic progression was stronger (ie, moderate quality) when TNFi and non-TNFi were combined with MTX/csDMARDs than when used as monotherapy.[122,125,126,129]

Overall, across the RA populations, results of RCTs using TNFi (CZP, ETN, GOL, IFX, and ADA), non-TNFi (ABA, RTX, TCZ, and ANK), and the JAK inhibitor TOF were analyzed. Although the results of indirect comparisons from meta-analyses are inferior to those from head-to-head trials, they provide useful information; thus, we suggest that the effectiveness of various targeted agents vs placebo or an active comparator is approximately the same. Our stance is similar to the recommendation from the updated EULAR guidelines, which does not state a hierarchy for choice of a 1st-line targeted agent.[7] The initial choice, then, would be based on patient preference, tolerability and—importantly for the Asia-Pacific region—cost.

9. All patients receiving targeted therapy should be closely monitored for therapy-related toxicities (100% agreement; evidence not graded).

This recommendation was retained from our 2015 manuscript, as the safety and tolerability considerations of targeted therapies are part of the practical aspects of their use for RA.[8] Subsequent to the release of our original recommendations, a systematic review of literature was published that compared the risk of AEs among targeted agents in chronic inflammatory diseases, including RA. Ten head-to-head RCTs and 51 observational studies were eligible for analysis, 70% of which

were conducted in patients with RA. The results showed that in RA, IFX use had a higher risk of discontinuation due to AEs vs ADA or ETN, and a higher risk of serious infections vs ADA, ABA or ETN. ETN, compared with ADA, had a lower risk of discontinuation due to AEs, serious infections, and tuberculosis.[130]

The presence of anti-drug antibodies may be associated with an increase in the drug's AEs. Another systematic review of literature, this time on use of bDMARDs in rheumatic diseases, showed that up to 50% of patients treated with IFX or ADA developed anti-drug antibodies.[131]

The preceding findings can inform clinicians during the selection of targeted agents for RA. Given the lack of comparative evidence, we are unable to make a definitive recommendation on the choice of targeted agent. However, we must restate the importance of being vigilant with monitoring of AEs during use of targeted therapy in RA.

10. For RA patients with a history of TB or latent TB (or in whom the risk remains high despite negative screening), targeted therapies other than monoclonal Ab TNFi are preferred (100% agreement; grade of evidence low).

We judged the evidence for the choice of targeted therapy for this recommendation as low quality primarily due to publication bias—the evidence came mainly from meta-analyses of observational studies that suggested high rates of TB reactivation with TNFi. One analysis demonstrated an increased risk of TB in patients with RA treated with TNFi.[78] Researchers performed two evaluations: 1 on 50 RCTs using TNFi (ETN, IFX, ADA, GOL and CZP), and another on 13 cohort and registry studies. The analysis of RCTs failed to show a significant TB risk difference between the TNFi and placebo or control groups. Notably, no cases of TB were confirmed in the 9 ETN RCTs, in both the ETN and placebo groups. In contrast, based on results from registry/cohort studies, TB IR was 4.03 times higher in patients treated with TNFi than in those treated with non-biologics (95% CI 2.36-6.88). Furthermore, TB risk was 2.78 times higher with IFX (95% CI 2.10-3.69), and 3.88 times higher with ADA (95% CI 2.31-6.53) than ETN. TB risk with IFX was 1.28 times higher than with ADA, but this was not significant (95% CI 0.87-1.89). This study demonstrated a significant increase in TB risk in patients with RA treated with TNFi; among them, ETN was least likely to cause active TB.

Moreover, a cohort study from Taiwan showed that the 1-year TB risk in RA patients starting TNFi therapy (ETN or ADA) from 2008-2012 was significantly higher than that in non-TNFi controls (incidence rate ratio [IRR], 6.44; 95% CI 4.69-8.33). Both ETN and ADA users, when evaluated separately, had higher TB IR compared with controls. The 1-year TB risk was significantly higher in the ADA cohort than in the ETN cohort (adjusted HR, 3.62; 95% CI 2.17-6.03).[132]

A meta-analysis of long-term extension studies involving patients with chronic, immune-mediated, inflammatory diseases confirmed that TB IR was high with use of TNFi (ETN, IFX, ADA, GOL, and CZP). When analyzed according to disease, the IR in patients with RA with ETN use was lower than with use of TNFi monoclonal antibodies (67.6; 95% CI 12.1-163.9 vs 307.7; 95% CI 184.8-454.9; respectively). High TB IR was also seen with use of non-TNFi TCZ and ABA, but not with RTX, and with the tsDMARD TOF.[133] In phase III and long-term extension studies of TOF for RA, 26 cases of active TB were reported (IRR 0.21; 95% CI 0.14-0.30); 81% of cases occurred in regions with high TB incidence.[63]

Another publication looked at TB IR with non-TNFi targeted therapy for rheumatic diseases. The systematic literature review included phase II and III studies, post-marketing surveillance, long-term extension studies, and registry studies on TCZ, RTX, and ABA for RA (ANK was not included), with a population ranging 231-3881 patients across studies, and showed absent or low risk of TB reactivation with use of these agents (IR range of 0-0.38).[134]

11. In RA patients at increased risk of HBV reactivation, targeted therapies other than RTX are preferred (95% agreement; grade of evidence low).

Patients with RA with an increased risk of HBV reactivation have the option of using targeted therapies such as TNFi (except RTX) do not appear to be linked with high reactivation rates. We deemed the evidence as low quality due to publication bias.

A meta-analysis of cohort studies showed a relatively low pooled prevalence of HBVr in patients with RA treated with TNFi (3.3%; 95% CI 0.7-7.5), although the authors acknowledged significant heterogeneity among studies. The pooled reactivation rate for patients with chronic overt HBV infection (10.7%) was much higher than those with occult infection (2.6%). For all rheumatic and dermatological conditions treated with TNFi, pooled reactivation rates for ETN and ADA were similar; no cases of reactivation were reported in studies with IFX.[87]

HBVr in RA and other chronic inflammatory diseases was primarily reported or evaluated in case reports or small prospective/retrospective studies with use of ETN, IFX, ADA, TCZ, ABA and RTX.[131] A systematic review of such studies using mainly ETN or ADA showed a reactivation rate of 39% among HBsAg+ patients with RA, and 5% in anti-HBc/HBsAg− patients.[135] Other reviews showed an HBVr of 12.3% in HBsAg+ patients and 1.7% in HBsAg-/anti-HBc+ patients with TNFi use for rheumatic diseases.[136,137] These rates may still be relatively low when considered against the rates with RTX: 27%-80% in HBsAg+ patients and 3%-25% in HBsAg-/anti-HBc+ patients.[138,139] HBVr has been observed with ABA and TCZ for RA and other chronic inflammatory diseases in case reports and small retrospective studies, but good serological and virological outcomes can be achieved with antiviral prophylaxis.[141]

12. Modification of targeted therapy should be performed for failure to achieve remission or low disease activity after 6 months (100% agreement; evidence not graded).

No studies directly addressed the question of the optimal time to switch therapy. At our Working Group meetings, it was agreed that if there is no or inadequate response to targeted therapy, and the

treatment causes adverse effects or intolerance, it should be discontinued as soon as possible, and new treatment instituted as soon as it is safe to do so.

First, the question was raised whether targeted therapy was able to induce remission in patients with RA by 6 months. Patients do achieve remission at 6 months, but the proportion is not high: in a Swiss real-world study, at 6 months, about 26% achieved DAS28-defined remission and about 6% achieved remission by Boolean criteria after TNFi treatment.[142]

We also searched the literature for the optimal time it takes for bDMARDs to take effect. For IFX 3 mg/kg plus MTX, most of the patients who responded (about 50% of them, by achieving the Paulus 50% index) did so only after 12 weeks.[143] For ADA 40 mg administered every other week, the eventual 15% of patients who would reach ACR70 took 20 weeks.[144] The regimen of ETN + MTX took 20 weeks to optimally reduce the number of tender and swollen joints.[145] GOL required 28 weeks to achieve optimal ACR20 response, but 36 weeks for ACR50 and ACR70 responses.[146] In the BeST study, patients received MTX 25-30 mg/wk with IFX 3 mg/kg at weeks 0, 2, and 6 and every 8 weeks thereafter, with IFX increased to 6 mg/kg every 8 weeks if the disease was not controlled. The proportion of patients (about 70%) who achieved ACR20 only reached a plateau after 6 months.[147]

A Dutch study of 539 patients assessed the response to TNFi (defined as decrease of DAS28 beyond 1.2) at 3 and 6 months.[148] At 3 months, 44% (233 patients) were considered as responders. Out of the 233, 189 continued receiving the same regimen and at 6 months, 37% of these became responders. The results suggested that lack of response at 3 months did not mean that patients will not respond by 6 months. Therefore, if treatment with a specific targeted agent was switched to another in 3 months, a proportion of patients who would have responded by 6 months would be deprived of the effect of the drug.

Based on the preceding considerations, we concluded that it is reasonable to switch targeted therapy after a trial of 6 months. For some patients with established RA (usually with long disease duration), achieving personal best disease activities might be considered as an alternative target.

It is also reasonable to optimize the dose of csDMARD if it is used together with a bDMARD when the clinical response is not optimal. In a study of 395 MTX- and bDMARD-naive patients, with the primary endpoint of the proportion of patients achieving DAS28—C-reactive protein <3.2 at week 26, it was shown that 60.2% of those receiving MTX 20 mg weekly plus ADA reached the target, compared to 56.5% of those on 10 mg, 44.0% of those on 5 mg weekly and 42.9% of those on 2.5 mg weekly.[149] Regrettably, these findings may not be generalized to other types of patients who have prolonged exposure to DMARDs, or to those receiving bDMARDs besides ADA.

13. In patients with established RA, consideration of tapering or discontinuation of targeted therapy should only be made when the disease is in remission for over 12 months, especially if the patient is receiving concomitant csDMARD (100% agreement; grade of evidence moderate).

A Cochrane review addressed the impact of down-titration (dose reduction or discontinuation) of TNFi on symptoms and adverse events in established RA with low disease activity.[150] Six RCTs and one controlled clinical trial, using ETN or ADA, with durations ranging 24-88 weeks, were eligible for the analysis and provided mainly moderate-quality evidence for down-titration vs continuation.[151,152]

Dose reduction data were available for ETN; pooled results showed no significant differences (statistical or clinical) compared with dose continuation in terms of DAS28 and HAQ measures, although patients receiving reduced doses were less likely to maintain low disease activity. Radiographic outcome was also worse with reduced doses but was not clinically significant. Discontinuation data were available for ETN and ADA use, and pooled results showed inferior outcomes for disease activity, function and radiographic outcome vs continuation.[150] Likewise, another meta-analysis looking at discontinuation of ETN or ADA showed inferior outcomes compared with continuation, but half of the patients were able to maintain low disease activity for 9-12 months after stopping therapy.[158]

Only one trial from the Cochrane review compared disease activity-guided TNFi dose tapering (ADA and ETN) with continuation but reported no statistically significant differences in functional outcomes.[157] Recently, the open-label DRESS RCT showed that disease activity-guided dose reduction (stepwise increase of injection interval every 3 months until disease flare or discontinuation) of ETN or ADA was non-inferior to continuation, based on the proportion of patients with DAS-28 disease flare after 18 months.[159]

The best evidence available for the effect of tapering TNFi while continuing MTX during disease remission came from 2 RCTs with patients who had low disease activity (DAS-28 < 3.2) but were not necessarily in remission. Patients achieved stable low disease activity after initial response even with discontinuation of ADA or reduction of ETN dose while continuing MTX, seen after 78 and 88 weeks, respectively.[155,160]

No study addressed the question on the impact of discontinuing non-TNFi or tsDMARD vs continuing these agents, on RA symptoms and adverse events.

The 2016 update of the EULAR recommendations considered the evidence for tapering of bDMARDs in patients with sustained remission to be level IIb strength B. Predictive factors for who will maintain remission after bDMARD withdrawal will require further research.[7] Our recommendation is that tapering or discontinuation of targeted therapy is feasible when disease is in sustained remission. The remission period of >12 months was retained from our 2015 document because the studies cited at present have at least a 12-month duration. Clinicians should be mindful that our statement was based on mainly moderate-quality evidence from very few studies with heterogeneity.

14. For patients with a past history of treated solid cancer, targeted therapies may be used with caution (95% agreement; grade of evidence very low).

Results of studies on risk of malignancy with TNFi have been mixed: some studies have suggested an increased risk of cancer with biologics for RA, whereas others have not, but have shown instead an increase in risk of skin cancer.[66] We considered the 2015 recommendations of the ACR, that is, for untreated and previously treated skin cancers (melanoma and non-melanoma), csDMARDs are recommended over biologics or TNFi. Moreover, the ACR strongly supported RTX over TNFi for previously treated lymphoproliferative disorder, and conditionally recommended combination csDMARDs over ABA, TCZ or TNFi. Individuals with previously treated solid organ malignancy should receive RA therapy as for a patient without a history of solid organ cancer. All evidence for these recommendations were judged as low quality, but RTX over TNFi was strongly favored because of its current role in treatment of lymphoproliferative disorder. The ACR also noted a suggestion of increased risk for lymphoma with TNFi.[6]

We looked at evidence from cohort studies, focusing on the analysis of patient registry data for TNFi vs combination csDMARD. They showed an increased risk of incident malignancies in the presence of previously treated or untreated melanoma skin cancer and non-melanoma skin cancer with TNFi.[161,162] The risk of incident cancer with previously treated lymphoproliferative disorder was not estimable.[161] Overall, we determined the evidence as very low quality due to imprecision[156,157] and indirectness.[163]

Incident malignancy rates and recurrent malignancy rates did not increase in patients with previously treated solid cancers who received TNFis, when compared with those who received csDMARD for RA, or conventional immunosuppression (non-biologicals) for rheumatic diseases.[161,164,165] The evidence for this was very low to low quality.

During the literature search, no studies were retrieved covering non-TNFi biologics. However, a cohort study published recently showed that risk of cancer among patients with RA starting TNFi, TCZ, ABA, or RTX was the same as that of bDMARD-naive, csDMARD-treated patients. There may be an increased risk for some cancer types (eg, squamous cell carcinoma).[167] In EULAR 2018, a study was presented that examined rates of malignancy (excluding non-melanoma skin cancer) in patients with RA, that found no difference between those newly treated with TCZ compared with those treated with TNFi.[168]

Integrating our findings for cancer risk, we generated a recommendation for the use of targeted therapies, "with caution": the apparent low risk of recurrent malignancy is still a signal for potential harm, and not all patients with prior cancer history may be treated safely with targeted therapies. Clinicians should carefully select patients for whom these may be appropriate.

The optimal time to administer targeted therapy after a diagnosis of prior cancer is unknown. In one of the studies, a majority of subjects had a diagnosis of cancer >10 years before receiving TNFi.[161] The approach to the scenario in which a patient is diagnosed with malignancy while on targeted therapy is also undetermined.

15. For patients undergoing major surgery, we recommend temporary discontinuation of targeted therapy and resumption when wound healing is satisfactory (95% agreement; grade of evidence low).

The question of whether targeted therapies increase the risk of postoperative infections in patients with RA was addressed by two systematic reviews, which analyzed studies on use of TNFi.[169,170] The 1st meta-analysis included eight observational studies and three case-control studies. Overall, the cohorts were comprised of 3681 patients with RA who underwent a major orthopedic surgery (primarily total hip arthroplasty or total knee arthroplasty) with recent pre-operative TNFi exposure (12 days to 3 months), and 4310 patients who also had surgery but had no recent exposure to TNFis. The risk of developing postoperative infection was determined to be higher in the TNFi cohort than in the cohort without TNFi exposure (RR 2.47; 95% CI 1.66-3.68).[169]

Two separate analyses within one systematic review were performed to evaluate the postoperative infection risk with TNFi exposure and the benefit of discontinuing TNFi pre-surgery.[170] Based on 12 studies (overall number of patients: 4975 with TNFi and 61 090 with csDMARDs), risk of postoperative infection was shown to be higher in the TNFi cohort than in the csDMARD cohort (RR 1.81; 95% CI 1.31-2.50). Seven studies were included in the 2nd meta-analysis (501 with TNFi withdrawal and 586 with TNFi continuation), which showed that discontinuing TNFi pre-surgery did not significantly change postoperative infection risk (RR 0.69; 95% CI 0.39-1.21).

The evidence appears to support discontinuing or withholding TNFi to minimize postoperative infection risk, but the benefit of doing so was not demonstrated. Furthermore, we judged the evidence to be of low quality because the study base consisted of retrospective trials; therefore, our current recommendation to suspend targeted treatment pre-surgery is conditional. Our suggestion is compatible with the recommendation of the ACR/American Association of Hip and Knee Surgeons in their 2017 guideline for the perioperative management of antirheumatics in patients with rheumatic diseases who will undergo total hip or knee arthroplasty.[171]

16. For patients with established RA in whom disease cannot otherwise be controlled, TNFi (preferably ETN or CZP) may be continued throughout pregnancy. (95% agreement; grade of evidence low).

Pregnancy in RA can be complicated by both the disease itself and by the effects of RA medication on the mother, the course of pregnancy, and its outcome. Much of the data on the safe use of targeted therapies during pregnancy and lactation were drawn from observational studies and case reports. The multidisciplinary EULAR task force on antirheumatic drugs during pregnancy and lactation performed a systematic literature review from which they derived clinical points for use during pharmacological management of RA in pregnancy.[172]

Among the points to consider regarding targeted therapy use during pregnancy is a recommendation for continued use of TNFi during the 1st trimester. The evidence for this came from cohort studies, case control studies, registry studies, and case reports that showed no increase in rates of miscarriages or congenital malformations vs a control group or background data. ETN and GOL data

were from cohort studies or case series with no control group. The EULAR task force stated that ETN and CZP were options to be used throughout pregnancy because they were known to have low placental transfer.[172]

However, the EULAR task force cited insufficient data for non-TNFi bDMARDs RTX, ANK, TCZ, and ABA; their recommendation was that these should be replaced before conception by other medications and should only be considered when all other pregnancy-compatible agents fail to control RA disease. TOF had only been studied in one case series, and it should be avoided in pregnancy until further data become available.[172]

Evidence is limited to case reports for use of targeted therapy during lactation, and the EULAR recommendations were based only on expert opinion. TNFi should be continued during lactation; IFX, ADA, ETN, and CZP were mentioned as having low transfer through breast milk. Non-TNFi RTX, ANK, ABA, and TCZ had no data but, in theory, may be considered based on their pharmacological properties when no other agents are available. TOF had no data and should be avoided.[172]

4 | DISCUSSION

The availability of targeted therapies for RA has provided rheumatologists and other clinicians the opportunity to improve RA treatment. However, data are still emerging that can guide practitioners: on when to start targeted therapy; in the selection of agent; in monitoring the effects of treatment; and in adjustment or discontinuation of dose. This updated set of APLAR recommendations for treatment of RA provides specific guidance to assist in the care of patients with RA treated with targeted agents.

Notably, data on comparative effectiveness of targeted therapy from head-to-head trials are still limited. Moreover, a proportion of patients have poor response to targeted therapy[173]: one retrospective study in Asia showed that 66% of individuals had an incomplete response to their 1st bDMARD.[174] Questions still remain about the safety of particular targeted therapies, the optimum approach to dose modification, switching and discontinuation, and their appropriate use in specific groups, such as in individuals with cancer and in pregnancy. Further studies on these and related questions should populate the priority research agendas of APLAR, ACR, EULAR and other international rheumatology organizations.

Certain issues around use of targeted agents are especially relevant in the Asia-Pacific. Some infections that are not common in the Western hemisphere, such as TB, are endemic in a few Asian countries. Thus, attention to the data on the use of TNFi and the risk of infection is important for clinicians in our region. Also, screening for, and prevention of, infections through vaccination in the context of targeted therapy for RA should be carefully studied; this action can help optimize use of healthcare resources, as many patients may have limited access to preventive services.

Compounding the issue of patient access to health care is the prohibitive cost of targeted therapies. Their cost, coupled with low rates of insurance coverage across the region, may limit their use to patients who can afford them. It is critical, then, for the clinician to understand the available data on the optimal use of targeted agents in order to select the most cost-effective treatment for their patients. Less costly csDMARDs and biosimilars may be chosen over targeted therapy; therefore, data on their efficacy and safety will need to be constantly monitored and reviewed against the evidence for targeted agents.

With this update focusing on the use of targeted agents, APLAR aimed to address some issues unique to our region. High-quality evidence is still limited, but it is hoped that emerging evidence can be included in future updates of this document. Importantly, there are plans to develop a companion article elaborating on patients' perspectives on use of targeted agents and their feedback on these recommendations; in securing these perspectives, we will use the methodology of the Patient Opinion Real-Time Anonymous Liaison System (PORTAL) project for RA, which elicited patients' values and preferences regarding their treatment through surveys.[175]

5 | CONCLUSION

This update to the 2015 APLAR treatment recommendations for RA reviewed current evidence focusing on the use of targeted agents, to inform clinicians and support them in their clinical management of RA.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors were involved in the conception and design of the manuscript. All authors were involved in formulating the research questions that framed the literature search, as well as in the literature search proper and GRADE assessments. All authors were responsible for drafting of the manuscript and participated in revising it

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