REVIEW ARTICLE

Management of rheumatoid arthritis: 2019 updated consensus recommendations from the Hong Kong Society of Rheumatology

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Abstract

The expanding range of treatment options for rheumatoid arthritis (RA), from conventional synthetic disease-modifying antirheumatic drugs (DMARDs) to biological DMARDs (bDMARDs), biosimilar bDMARDs, and targeted synthetic DMARDs, has improved patient outcomes but increased the complexity of treatment decisions. These updated consensus recommendations from the Hong Kong Society of Rheumatology provide guidance on the management of RA, with a focus on how to integrate newly available DMARDs into clinical practice. The recommendations were developed based on evidence from the literature along with local expert opinion. Early diagnosis of RA and prompt initiation of effective therapy remain crucial and we suggest a treat-to-target approach to guide optimal sequencing of DMARDs in RA patients to achieve tight disease control. Newly available DMARDs are incorporated in the treatment algorithm, resulting in a greater range of second-line treatment options. In the event of treatment failure or intolerance, switching to another DMARD with a similar or different mode of action may be considered. Given the variety of available treatments and the heterogeneity of patients with RA, treatment decisions should be tailored to the individual patient taking into consideration prognostic factors, medical comorbidities, drug safety, cost of treatment, and patient preference.

Keywords Consensus · DMARDs · Guideline · Management · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune, inflammatory disease that may cause progressive joint damage and deformity, leading to functional disability and reduced quality of life [1, 2]. The chronic inflammatory state of RA is also associated with extra-articular problems and increased

mortality [1]. Compared with the age- and gender-matched population, a 68% increase in mortality risk has been reported in patients with RA in Hong Kong [3]. RA may be slightly less prevalent in Hong Kong than in Western countries [4, 5], where it affects approximately 0.5 to 1% of the population [6], but it is still associated with a considerable societal economic burden due to lost productivity and increased use of healthcare resources [7].

Over the last one to two decades, modern therapeutic strategies involving the early diagnosis of RA, the treat-to-target principle, and disease-modifying antirheumatic drugs (DMARDs), which can prevent or reduce progression of structural joint damage and reduce mortality risk, have greatly improved the management of RA [6, 8, 9]. In addition to conventional synthetic DMARDs (csDMARDs), a range of biological DMARDs (bDMARDs) and, more recently, the first biosimilar bDMARDs and targeted synthetic DMARDs (tsDMARDs) are now available for the treatment of RA [6, 10]. While b/tsDMARDs improve outcomes in many RA patients, they are costly and should be used in

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an evidence-based manner that accounts for availability and affordability within the local healthcare system [6, 9, 11].

As a result of rising standards of care and the availability of more therapeutic options, RA treatment is becoming increasingly complex, and recommendations developed by professional societies are increasingly important for providing rheumatologists with evidence-based guidance on best-practice treatment approaches for their patients [9, 10, 12]. Updated recommendations from the European League Against Rheumatism (EULAR) and the Asian Pacific League of Associations for Rheumatology (APLAR) for the management of RA with DMARDs have recently been published [10, 12]. Given the advances in RA management that have been made since our last set of recommendations were published in 2011 [9], we have now updated the Hong Kong Society of Rheumatology (HKSR) recommendations for the management of RA, with a focus on how best to integrate newly available DMARDs into Hong Kong clinical practice.

Methods

Steering committee

Members of the Rheumatoid Arthritis Special Interest Group (RA SIG) formulated a series of statements on RA management relevant to local Hong Kong practice and the healthcare system during several face-to-face meetings. Along with local expert opinions, the recently updated EULAR recommendations [10] were used to guide development of statements related to the use of DMARDs and glucocorticoids (GCs) in RA. In addition, the RA SIG formulated a series of statements related to treatment considerations for special populations, including pregnant women, those with chronic viral hepatitis infection, and patients seronegative for anti-citrullinated protein antibody (ACPA). The appropriate use of musculoskeletal ultrasound (MSUS) in the management of RA was also discussed.

Grading evidence

A system adapted from the Grades of Recommendations Assessment, Development and Evaluation (GRADE) system was used to rate the strength of the recommendation (SoR) and the quality of evidence (QoE) (Table 1) [13]. GRADE methodology gives preference to randomized controlled trials (RCTs) over observational studies as the highest quality source of evidence.

Assessment of recommendation statements

Practicing rheumatologists registered as full members of the HKSR were invited to join a roundtable meeting to discuss and finalize the consensus statements. The attendance rate was 35%. The series of statements was sent to all practicing rheumatologists of the HKSR for voting through several rounds of Delphi exercises. For each statement, rheumatologists voted agree or disagree using an anonymous electronic survey tool; if they voted "disagree," the reason for disagreement was required. The overall response rate was 55% (33 of 60 surveys; 7 surveys undeliverable).

For each statement, consensus was reached if > 80% of participating rheumatologists who responded to the survey voted "agree." If consensus was not reached for any statement, the statement was revised by the expert committee and recirculated for further voting until consensus was reached.

Results

The consensus process resulted in 36 recommendations: 33 statements reached consensus in the first round of voting and 3 statements reached consensus in the second round of voting. The recommendation statements are grouped into relevant categories and summarized in Table 2.

Core principles

The HKSR has included several core principles to serve as a foundation for more specific recommendations for RA management. Although there is no high-quality evidence to specifically support these, they are nevertheless strong recommendations with > 90% support from our rheumatologists.

1. *Rheumatologists are the specialists who should primarily take care of patients with RA.*
   SoR: A; QoE: D
   This acknowledges the importance of specialty care for a complex disease like RA [10]. Rapid assessment of patients by a rheumatologist soon after symptom onset enables rapid diagnosis and initiation of DMARD treatment, and improves outcomes [14–17]. General practitioners should refer patients with suspected RA to a rheumatologist and share their ongoing care with a rheumatologist and other specialists for the management of comorbidities (e.g., interstitial lung disease, inflammatory eye conditions, viral hepatitis, etc.) [10, 18, 19]. Patients in remission or with low and stable disease activity are candidates for shared care arrangements between rheumatologists, including nurse specialists, and primary care practitioners [19–21]. It is important for primary care physicians to have a working knowledge of RA and its treatment [22, 23].

2. *Treatment of RA should be based on a shared decision between the patient and the rheumatologist.*
   SoR: A; QoE: D
   Shared decision-making is important for the success of

Table 1 Grading system used to rate the strength of the recommendations and quality of supporting evidence

Grade	Level	Meaning
Strength of recommendation		
A	Strong	Most well-informed people would want the recommended course of action, and none or only a small proportion would not.
B	Weak	The majority of well-informed people would want the recommended course of action, but a substantial minority would not.
Quality of evidence		
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.

Based on the Grades of Recommendations Assessment, Development (GRADE) system [13]

treat-to-target strategies in RA [24]. Patients should be informed on all aspects of RA and its management, including the risks and benefits of individual treatments, and be involved in the development of a treatment plan to reach an agreed therapeutic target [10, 25]. It is the responsibility of the rheumatologist to raise patients' awareness of their disease and treatment options [26, 27]. A mutually agreed treatment plan between the rheumatologist and patient facilitates treatment adherence [10].

3. *Treatment choices should be individualized and based on a number of factors that include disease activity, prognostic factors, medical comorbidities, safety issues of the medications, cost, and availability of DMARDs.*

   SoR: A; QoE: D

   Given the variety of available treatments and the heterogeneity of patients, management strategies should be tailored to the individual patient. In addition to factors such as disease activity, prognostic factors, medical comorbidities, and safety issues, it is specified that rheumatologists should also consider the cost and availability of newer b/tsDMARDs. Modification of DMARD therapy in terms of drug dosage, frequency of administration, and choice of drugs is needed in various clinical situations that include older age, impairment of renal, liver or cardiac function, other medical comorbidities, concomitant medications, history of intolerance, and complications to DMARDs, as well as other contraindications to a particular class of b/tsDMARDs.

General statements on the treatment strategy for RA

These recommendations cover general decisions that need to be made at the beginning of the management process once the diagnosis of RA has been made. All statements in this category are strong recommendations based on high-quality evidence.

4. *Therapy with DMARDs should be started as soon as the diagnosis of RA is made.*

   SoR: A; QoE: A

   Compared with delayed therapy, the short- and long-term beneficial effects of early DMARD therapy on the progression of radiographic joint damage and other outcomes are now well established [15, 28–32]. Early effective DMARD therapy initiated promptly after diagnosis is therefore important to preserve the structural and functional integrity of the joints [6, 33, 34]. The recommended sequence of DMARD types is included in the next group of recommendations, which address specific aspects of treatment.

5. *Treatment should be targeted at sustained remission or low disease activity (if remission is not achievable).*

   SoR: A; QoE: A

   Several studies have demonstrated that a targeted approach to the management of RA is superior to non-targeted approaches [35–39]. The best treatment goal is clinical remission, but this may be most appropriate in DMARD-naive patients [10, 40–42]. An acceptable alternative treatment target is low disease activity, which may be more appropriate in patients with long-standing disease who have failed previous therapies [10]. It has been cautioned that in certain situations, such as patients whose jobs involve physical labor that may aggravate the signs and symptoms of RA, remission or low disease activity may not be possible, and the treatment target may be to maintain symptom control and work ability [22].

Table 2   HKSR recommendations for the management of RA

Recommendations	SoR	QoE	Agreement (%)
Core principles			
1. Rheumatologists are the specialists who should primarily take care of patients with RA.	A	D	94
2. Treatment of RA should be based on a shared decision between the patient and the rheumatologist.	A	D	97
3. Treatment choices should be individualized and based on a number of factors that include disease activity, prognostic factors, medical comorbidities, safety issues of the medications, cost, and availability of DMARDs.	A	D	100
General statements on the treatment strategy of RA			
4. Therapy with DMARDs should be started as soon as the diagnosis of RA is made.	A	A	100
5. Treatment should be targeted at sustained remission or low disease activity (if remission is not achievable).	A	A	100
6. Objective assessment of disease activity of RA should be obtained to guide treatment decision by means of at least one validated disease activity index (e.g., DAS28, CDAI, SDAI).	A	A	100
Treatment of RA			
7. MTX should be the first-line therapy unless contraindicated.	A	B	97
8. In patients with contraindications or early intolerance to MTX, leflunomide or sulfasalazine may be considered as initial csDMARD therapy.	A	A	94
9. Hydroxychloroquine should not be used as first-line therapy in RA unless in patients with palindromic rheumatism and without poor prognostic factors of RA.	A	B	91
10. Although b/tsDMARDs have been used as first-line therapy in treatment-naive RA in some research studies, this approach is not routinely recommended.	A	B	97
11. Short-term GCs may be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible (preferably to ≤ 7.5 mg/day of prednisolone or equivalent in < 10 weeks).	A	A	97
12. Short-term bridging GCs during csDMARD therapy should ideally be discontinued within 3–6 months.	A	D	94
13. If there is no clinical response to the first csDMARD in 3 months or the treatment target cannot be reached in 6 months, adjustment of DMARD therapy is indicated.	A	C	88
14. When the treatment target cannot be achieved with MTX or other csDMARDs, switching or a combination of csDMARD may be considered in the absence of poor prognostic factors of RA.	A	B	100
15. When the treatment target cannot be achieved with MTX or other csDMARDs, add-on of a b/tsDMARD may be considered in the presence of poor prognostic factors of RA.	A	B	100
16. tsDMARDs (e.g., JAK inhibitors) can be considered in phase 2 of RA treatment; however, the longer safety record of bDMARDs should not be overlooked.	B	A	96
17. Systemic GC as bridging therapy should be avoided when a new b/tsDMARD is initiated because of the increased risk of infection.	A	B	94
Use of b/tsDMARD monotherapy			
18. b/tsDMARDs should be combined with a csDMARD. In patients who cannot use csDMARDs as co-medications, IL-6 inhibitors and JAK inhibitors may have some advantages.	A	A	94
Switching b/tsDMARDs			
19. If a bDMARD has failed, switching to another bDMARD or tsDMARD can be considered.	A	A	97
20. If a first TNF inhibitor has failed, another TNF inhibitor or a b/tsDMARD with another mode of action may be considered.	A	A	97
21. If an IL-6 inhibitor has failed, switching to another IL-6 inhibitor may be considered.	B	D	100
22. If a JAK inhibitor has failed, switching to another JAK inhibitor or other bDMARD may be considered.	B	D	85
Use of MSUS in the management of RA			
23. Use MSUS to evaluate synovitis for diagnosing RA when clinical examination is inconclusive and inconsistent with laboratory tests.	A	B	97
24. Use MSUS to evaluate disease activity when clinical examination is inconclusive and inconsistent with other signs of disease activity (pain or inflammatory markers).	A	A	100
25. MSUS should not be used as routine evaluation of RA disease activity.	A	A	97
Role of biosimilar DMARDs			
26. Approved biosimilars can be considered as an alternative to the bio-originators, particularly in biologic naive patients.	A	A	97

Table 2 (continued)

Recommendations	SoR	QoE	Agreement (%)
27. Switching from bio-originator to biosimilars is acceptable.	B	C	94
Tapering of bDMARD or csDMARD			
28. In sustained remission over 6 months, bDMARDs can be tapered in early RA.	A	B	94
29. In sustained remission, cautious tapering of bDMARDs may be considered in established RA due to an increased risk of flare.	B	B	94
30. After discontinuation of b/tsDMARDs, tapering of csDMARDs can be considered.	B	D	94
Treatment consideration for seronegative RA			
31. Rituximab and abatacept are not preferred in patients with seronegative RA.	A	A	97
Treatment considerations in pregnancy			
32. Use of TNF inhibitors is generally safe during first and second trimesters.	A	C	97
33. Certolizumab and etanercept may be considered during the third trimester due to low placental transfer.	A	C	97
Treatment considerations in patients with chronic HBV and HCV infection			
34. Prophylactic antiviral therapy should be prescribed for patients with chronic (HBsAg+ve) and occult (HBsAg-ve, Anti-HBc+ve, and HBV DNA+ve) HBV infection who require b/tsDMARDs.	A	C	82
35. Prophylactic antiviral therapy should not be prescribed for patients with resolved HBV infection (HBsAg-ve, Anti-HBc+ve but HBV DNA-ve) EXCEPT when treated with B cell depletion therapy.	A	C	91
36. b/tsDMARDs are not contraindicated in patients with chronic HCV infection.	A	D	94

Anti-HBc, antibody against HBV core antigen; *bDMARD*, biological DMARD; *csDMARD*, conventional synthetic DMARD; *DMARD*, disease-modifying antirheumatic drug; *GCs*, glucocorticoids; *HBV*, hepatitis B virus; *HBsAG*, HBV surface antigen; *HCV*, hepatitis C virus; *IL*, interleukin; *JAK*, Janus kinase; *MSUS*, musculoskeletal ultrasound; *MTX*, methotrexate; *RA*, rheumatoid arthritis; *QoE*, quality of evidence; *SoR*, strength of recommendation; *tsDMARD*, targeted synthetic DMARD

6. *Objective assessment of disease activity of RA should be obtained to guide treatment decision by means of at least one validated disease activity index (e.g., DAS28, CDAI, SDAI).*

SoR: A; QoE: A

Validated composite measures, such as the disease activity score (DAS), clinical disease activity index (CDAI), or simplified disease activity index (SDAI), should be used to assess disease activity [10]. However, DAS-based remission, which has been widely used in clinical trials investigating a treat-to-target approach to RA [35, 36, 38], has been criticized as being potentially unreliable and less stringent than the CDAI or SDAI, and is probably better suited as a measure of low disease activity rather than remission [10, 41, 42].

Treatment of RA

The recommendations in this category relate to first-line and subsequent treatment strategies and therefore describe the preferred sequence of DMARDs (Fig. 1).

7. *Methotrexate (MTX) should be the first-line therapy unless contraindicated.*

SoR: A; QoE: B

Short-term, randomized, placebo-controlled trials, long-term prospective studies, and head-to-head trials comparing MTX with other csDMARDs have demonstrated the efficacy and acceptable safety profile of MTX in treatment-naive patients with RA [43, 44]. MTX monotherapy is well established as the first-line standard of care for patients with RA and MTX is considered the "anchor drug" for both monotherapy and combination therapy with other DMARDs (see recommendations 14 and 15 for advice on combination therapy) [6, 10, 22, 45].

8. *In patients with contraindications or early intolerance to MTX, leflunomide or sulfasalazine may be considered as initial csDMARD therapy.*

SoR: A; QoE: A

When required, the csDMARDs leflunomide or sulfasalazine are considered to be the best alternatives to MTX [10]. RCTs have shown the efficacy of these drugs to be superior to placebo and similar to that of MTX, although MTX was used at lower doses than those used currently [10, 46–52].

9. *Hydroxychloroquine should not be used as first-line therapy in RA unless in patients with palindromic rheumatism and without poor prognostic factors of RA.*

SoR: A; QoE: B

There is some evidence that hydroxychloroquine has moderate efficacy in early RA [53, 54] and it is often used as monotherapy in patients with very mild disease [10]. There is also evidence suggesting that hydroxychloroquine may improve the metabolic profile and reduce cardiovascular risk in RA [55–57]. However, in view of its slow onset of action and the availability of more potent csDMARDs [58], we do not recommend hydroxychloroquine for the first-line treatment of RA in patients without contraindications to MTX.

10. *Although b/tsDMARDs have been used as first-line therapy in treatment-naive RA in some research studies, this approach is not routinely recommended.*

   SoR: A; QoE: B

   The results of some recent RCTs have suggested that first-line monotherapy with certain b/tsDMARDs is more effective than MTX monotherapy and may be a viable option for patients with contraindications or intolerance to MTX (see recommendation 18) [59–64]. Importantly however, bridging with high-dose GCs was forbidden in the first 24 weeks of these trials, although low-dose pre-existing GCs were allowed (see recommendation 11) [10]. Moreover, evidence for first-line bDMARDs over first-line MTX plus GCs is inconsistent, with no clear advantages of early bDMARD therapy, other than a possible beneficial effect on long-term radiological outcome [10, 65–70]. Furthermore, evidence suggests that first-line therapy involving bDMARDs could lead to overtreatment of approximately 25% of patients at high cost [6, 71]. There is also evidence to suggest that addition of a bDMARD in patients with suboptimal response to MTX monotherapy ultimately results in a similar response to initial combination therapy of the two agents [59, 72]. Taken together, there is currently insufficient convincing evidence to support a recommendation for the routine use of b/tsDMARDS instead of, or in combination with, MTX as a first-line treatment strategy for RA, and there is no evidence supporting the cost-effectiveness of such an approach [6, 10].

11. *Short-term GCs may be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible (preferably to ≤ 7.5 mg/day of prednisolone or equivalent in < 10 weeks).*

   SoR: A; QoE: A

   The incremental efficacy of GCs when added to csDMARD therapy is well established, and given their rapid anti-inflammatory activity, GCs given orally, intravenously, or intramuscularly can be appropriate bridging therapy until the csDMARD reaches its full effect [6, 68, 73–77]. Intra-articular or intra-tenosynovial GC administration can also be considered in certain circumstances [10, 78]. If daily oral GC dosing is used rather than a single intravenous or intramuscular dose, it should be quickly tapered to a low dose to avoid cumulative toxic effects [6, 79]. According to the treatment protocols of recent RCTs, the dose of prednisone was tapered to 7.5 mg/week in less than 10 weeks [75, 76, 80].

12. *Short-term bridging GCs during csDMARD therapy should ideally be discontinued within 3–6 months.*

   SoR: A, QoE: D

   GCs have been used for up to 6–12 months or longer in several RA treatment strategy studies [36, 37, 39, 81], and there are no RCTs comparing the duration of low-dose GCs as bridging therapy in RA. If GCs cannot be withdrawn within 3–6 months, it has been suggested that csDMARD therapy may have to be considered a failure [10]. Discontinuation of GCs within 3–6 months to avoid side effects is strongly recommended despite the lack of high-quality data on tapering and duration of treatment [81].

13. *If there is no clinical response to the first csDMARD in 3 months or the treatment target cannot be reached in 6 months, adjustment of DMARD therapy is indicated.*

   SoR: A; QoE: C

   In RCTs of RA treatment strategies, protocol-based assessment of disease activity was performed every 3 months to allow further adjustment of csDMARD therapy as needed [35, 37]. No improvement in disease activity after 3 months of treatment made attainment of treatment target at 6 months highly unlikely [10, 82].

14. *When the treatment target cannot be achieved with MTX or other csDMARDs, switching or a combination of csDMARDs may be considered in the absence of poor prognostic factors for RA.*

   SoR: A; QoE: B

   Combination csDMARD therapy was included as an appropriate second-line treatment choice on the basis of the results of RCTs suggesting csDMARD combination therapy has superior efficacy to csDMARD monotherapy and is a more cost-effective option than bDMARDs [66, 83–92]. However, not all trials have shown such benefits [74, 93–96]. Therefore, a combination of csDMARDs should only be considered in patients who do not have poor prognostic factors for RA.

15. *When the treatment target cannot be achieved with MTX or other csDMARDs, adding on a b/tsDMARD may be considered in the presence of poor prognostic factors of RA.*

   SoR: A; QoE: B

   This recommendation relates to the range of currently available b/tsDMARDs for the treatment of RA: the tumor necrosis factor (TNF) inhibitors adalimumab, certolizumab, etanercept, golimumab, and infliximab; the costimulation inhibitor abatacept; the interleukin

(IL)-6 receptor inhibitors tocilizumab and sarilumab; the anti-B cell agent rituximab; and the Janus kinase (JAK) inhibitors (tsDMARDs) baricitinib and tofacitinib. RCTs have established that combination therapy with a b/tsDMARD and a csDMARD is more effective than csDMARD monotherapy [11, 93]. Although patients with poor prognostic factors were included in such studies, there are no subgroup analyses comparing outcomes in patients with and without poor prognostic factors. Overall, current evidence does not suggest superiority of csDMARD combination over certain bDMARDs in MTX failures in early RA, although bDMARDs offer better protection against radiological damage [66, 84, 85, 87, 89, 91, 92]. The choice between adding b/tsDMARDs and a combination of csDMARDs according to the presence or absence of poor prognostic factors of RA is based on clinical decision [10]. As there is a paucity of head-to-head comparative RCTs, we do not include a preference of b/tsDMARDs after MTX or csDMARD failures. Generally, bDMARDs have a longer track record for safety than tsDMARDs.

16. *tsDMARDs (e.g., JAK inhibitors) can be considered in step 2 of RA treatment; however, the longer safety record of bDMARDs should not be overlooked.*

SoR: B; QoE: A

Addition of a bDMARD or a tsDMARD to treatment is an effective and recommended treatment strategy in patients with an insufficient response to csDMARD therapy alone (see recommendation 15 above) [10]. There is, however, much more clinical experience with bDMARDs than with tsDMARDs, so in the absence of long-term safety data for tsDMARDs [93], bDMARDs may be preferred [6, 9, 10]. There is no preference for TNF inhibitor or non-TNF inhibitor bDMARDs [10]. The use of these agents is at the discretion of attending rheumatologists, who should consider costs, patient characteristics/comorbidities, contraindications to each bDMARD, and patient preference based on route and frequency of administration [9, 97].

17. *Systemic GC as bridging therapy should be avoided when a new b/tsDMARD is initiated because of the increased risk of infection.*

SoR: A; QoE: B

In contrast to csDMARDs, b/tsDMARDs have a rapid onset of action [10]. Several large observational cohort studies have shown that GCs are an independent risk factor for serious infection and related mortality in patients with RA receiving bDMARDs [98–100]. Therefore, bridging GCs should be reserved for csDMARD therapy only until the effect of the drugs is maximized (see recommendation 11) [10].

Use of b/tsDMARD monotherapy

18. *b/tsDMARDs should be combined with a csDMARD. In patients who cannot use csDMARDs as co-medications, IL-6 inhibitors and JAK inhibitors may have some advantages.*

SoR: A; QoE: A

The recommendation to use combination therapy reflects consistent RCT evidence that, relative to monotherapy, all b/tsDMARDs offer better efficacy when combined with a csDMARD [10, 11, 93]. A number of RCTs have demonstrated superiority of tocilizumab, tofacitinib, and baricitinib monotherapy over MTX monotherapy [59–64]. There is, however, no evidence that TNF inhibitor bDMARDs are clinically superior to MTX as monotherapy [10, 69]. As a result, IL-6 inhibitor or JAK inhibitor monotherapy may be preferred in patients who cannot use csDMARDs because of intolerance or contraindication [10]. Otherwise, b/tsDMARDs should be added to csDMARDs as combination therapy (see recommendations 10 and 15) [10].

Switching b/tsDMARDs

19. *If a bDMARD has failed, switching to another bDMARD or tsDMARD can be considered.*

SoR: A; QoE: A

This recommendation is based on meta-analyses showing that switching to another b/tsDMARD is effective in patients in whom previous bDMARD therapy failed [101, 102]. Prospective studies provide support for the use of a second bDMARD (abatacept, rituximab, or another TNF inhibitor) in patients previously unsuccessfully treated with a TNF inhibitor bDMARD [103, 104].

20. *If a first TNF inhibitor has failed, another TNF inhibitor or a b/tsDMARD with another mode of action may be considered.*

SoR: A; QoE: A

Although it may be expected that an agent with a different mode of action is needed in non-responders [6], RCTs show that use of another TNF inhibitor is effective in producing a clinical response [105–107]. Non-TNF inhibitor bDMARDs have also been shown to be effective in such patients [10, 101, 103–105, 108].

21. *If an IL-6 inhibitor has failed, switching to another IL-6 inhibitor may be considered.*

SoR: B; QoE: D

There is currently limited evidence to support in-class switching between IL-6 inhibitors [10, 109]. There is an abstract stating that a relevant proportion of tocilizumab non-responders showed clinical
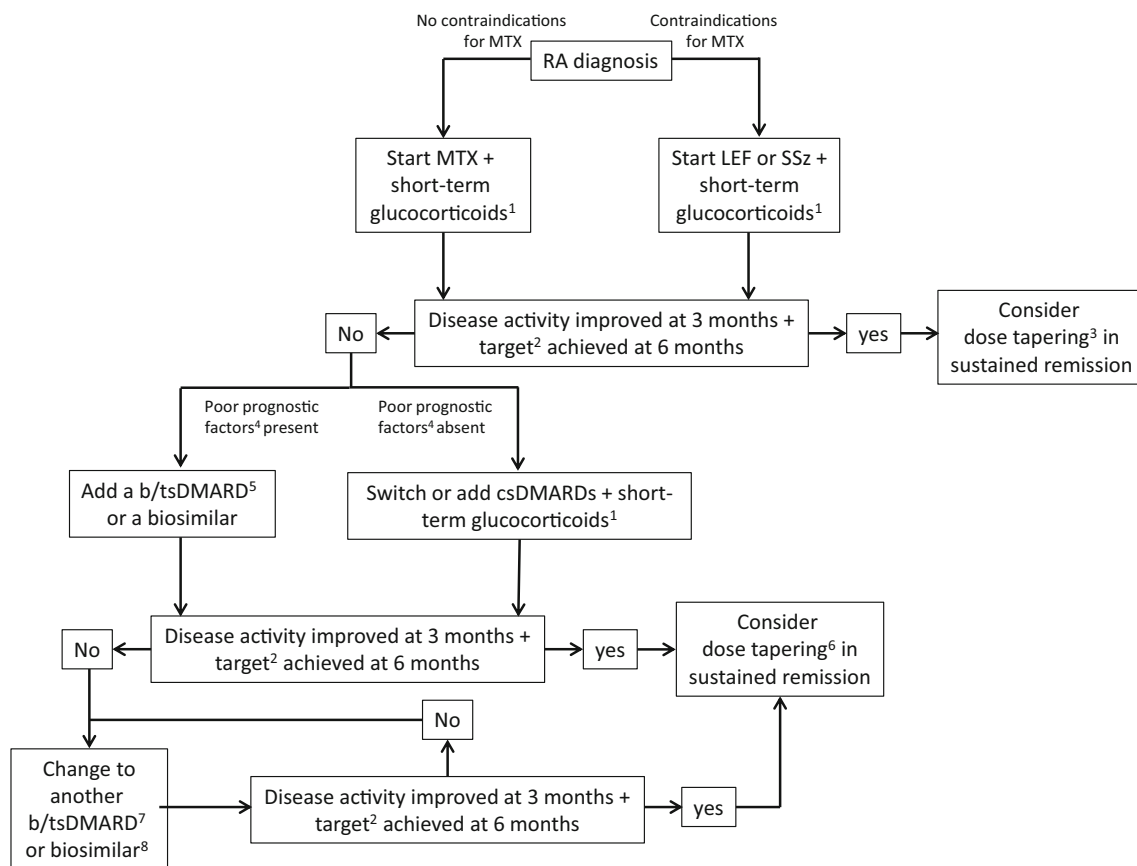
Fig. 1 Algorithm summarizing the 2019 HKSR recommendations for the treatment of patients with RA. *ACPA*, anticitrullinated protein antibody; *bDMARD*, biological DMARD; *csDMARD*, conventional synthetic DMARD; *DMARD*, disease-modifying antirheumatic drug; *IL*, interleukin; *LEF*, leflunomide; *MTX*, methotrexate; *RA* rheumatoid arthritis; *RF*, rheumatoid factor; *SSz*, sulfasalazine; *TNF*, tumour necrosis factor; *tsDMARD*, targeted synthetic DMARD. [1]Use glucocorticoids as bridging therapy with csDMARDs until the csDMARD reaches its full effect; ideally discontinue glucocorticoids within 3–6 months. [2]The treatment target should be remission or low disease activity (if remission is not achievable). [3]Generally dose reduction without complete withdrawal. [4]Poor prognostic factors: moderate to high disease activity; high acute phase reactant levels; high swollen joint counts; presence of RF and/or ACPA, especially at high levels; presence of early erosions; failure of ≥ 2 csDMARDs. [5]Current practice would be to start with a bDMARD rather than a tsDMARD because of the longer safety record with bDMARDs; in patients who cannot use concomitant csDMARDs, IL-6 inhibitors and tsDMARDs (JAK-inhibitors) may have some advantages. [6]Dose reduction or interval increase can be performed safely with low risk of flare, particularly in patients with early RA, but stopping is associated with high flare rates. [7]This may be a bDMARD with the same or another mode of action, but if a second TNF-inhibitor fails, patients should receive an agent with another mechanism of action. [8]A biosimilar of a bio-originator DMARD should not be used if there has been an insufficient response to the bio-originator (or another biosimilar of the same molecule) or vice versa

improvement after switching to sarilumab despite low immunogenicity with tocilizumab [110]. There is no significant difference in adverse effects between tocilizumab and sarilumab use [111].

22. *If a JAK inhibitor has failed, switching to another JAK inhibitor or other bDMARD may be considered.*

    SoR: B; QoE: D

    JAK inhibitors have been studied in large RCTs of csDMARD non-responders and bDMARD non-responders. However, there is a paucity of studies on switching from JAK inhibitor non-responders to a second JAK inhibitor or to bDMARDs. This area is worth exploring as there is an increasing trend to use JAK inhibitors in step 2 of RA treatment.

Use of MSUS in the management of RA

23. *Use MSUS to evaluate synovitis for diagnosing RA when clinical examination is inconclusive and inconsistent with laboratory tests.*

    SoR: A; QoE: B

    Gray-scale MSUS and power Doppler are validated for the identification of synovitis in RA. The combined gray-scale and power Doppler are validated for histological synovitis [112–114]. Observational studies have shown MSUS to be more effective than clinical examination for the detection of synovitis [114–118]. When there is diagnostic doubt, MSUS has been recommended to improve the certainty of a diagnosis of RA above

clinical criteria alone due to its effectiveness in detecting subclinical synovitis [119, 120].

24. *Use MSUS to evaluate disease activity when clinical examination is inconclusive and inconsistent with other signs of disease activity (pain or inflammatory markers).*

    SoR: A; QoE: A

    There is no reliable evidence to justify routine use of MSUS in the assessment of disease activity in addition to composite disease activity scores [121–123]. However, when there is inconsistency between clinical examination and disease activity, it may be unclear if the patient has subclinical inflammatory synovitis or a more widespread pain syndrome, which may not be inflammatory. As treatment is different, it is important to differentiate these accurately by MSUS.

25. *MSUS should not be used as a routine evaluation of RA disease activity.*

    SoR: A; QoE: A

    Compared to clinical examination, ultrasound examination is a sensitive tool to detect residual synovial hypertrophy and power Doppler signal. Applying ultrasound may reclassify patients from clinical remission to low disease activity. However, there is insufficient evidence to support MSUS as a cost-effective component of routine disease monitoring during treat-to-target therapy [121–123].

Role of biosimilar DMARDs

26. *Approved biosimilars can be considered as an alternative to the bio-originators, particularly in biologic naive patients.*

    SoR: A; QoE: A

    Before each biosimilar is approved, regulatory agencies, such as the European Medicines Agency (EMA) and US Food and Drug Administration (FDA), require a pharmacokinetic/pharmacodynamic study in humans, and at least one RCT to demonstrate equivalent efficacy and immunogenicity and comparable safety of the biosimilar to its bio-originator. Compared with their respective bio-originator bDMARDs, equivalent efficacy and safety of several biosimilars targeting TNF have been observed in bDMARD-naive patients with RA in small-scale RCTs [124–128]. Biosimilars can be used as an alternative when cost is a consideration.

27. *Switching from bio-originator to biosimilars is acceptable.*

    SoR: B; QoE: C

    Observational extension studies of RCTs of bio-originator versus biosimilar products, in which RA patients initially treated with the bio-originator were switched to the biosimilar, have demonstrated no loss of

efficacy or increase in the rate of adverse events after the switch [129–134]. Patients with RA were included in a RCT demonstrating that switching from bio-originator infliximab to biosimilar was non-inferior to continued treatment with the bio-originator in patients with immune-mediated inflammatory diseases, but the study was not powered to demonstrate non-inferiority of the switch for separate indications [135]. Real-world registry data also support the practice of switching patients with stable disease activity from bio-originator to biosimilar bDMARDs [136]. Although adequate evidence exists to support a switch from a bio-originator bDMARD to its biosimilar, there is currently no evidence to support switching between two biosimilars or between a bio-originator and its biosimilar on multiple occasions [137].

Tapering of bDMARD or csDMARD

28. *In sustained remission over 6 months, bDMARDs can be tapered in early RA.*

    SoR: A; QoE: B

    The feasibility of bDMARD tapering has been demonstrated in RCTs in patients with early RA who attained remission or low disease activity while receiving bDMARD therapy, and were randomized to continue full-dose bDMARD therapy or to a dose reduction strategy [72, 138, 139]. Analyses of subsets of patients from RCTs, who reached remission after randomization to receive bDMARD therapy and then underwent tapering of bDMARD, have also helped to establish the role of bDMARD tapering in early RA [67, 68, 140–143]. Collectively, the evidence suggests that patients with early RA in sustained remission (i.e., DAS28 < 2.6 for 6–12 months) during therapy with MTX and a bDMARD are the best candidates for bDMARD tapering (50% dose reduction or discontinuation), and backbone csDMARD therapy should be continued. Continued careful monitoring is essential during and after tapering as flares can occur. Currently, most of the evidence supporting this recommendation relates to TNF inhibitor bDMARDs.

29. *In sustained remission, cautious tapering of bDMARDs may be considered in established RA due to an increased risk of flare.*

    SoR: B; QoE: B

    RCTs have been conducted in patients with established RA who were in remission or had low disease activity while receiving bDMARD therapy and were then randomized to continue full-dose bDMARD therapy or to a dose reduction strategy [144–148]. Compared with studies in patients with early RA (see recommendation 28), the results of these RCTs and

prospective uncontrolled studies of bDMARD tapering in patients with established RA [149–158] show that tapering bDMARDs is feasible only in a relatively small subset of patients in sustained remission [159]. Several studies have shown that the detection of power Doppler signal on MSUS is predictive of a greater risk of flare after bDMARD tapering in patients with established RA previously in sustained DAS28 remission [160–162]. A combination of clinical and imaging remission could therefore potentially help to identify patients who are most likely to tolerate bDMARD tapering without flare, but further studies are required to confirm the cost-effectiveness of such an approach [123, 159].

30. *After discontinuation of b/tsDMARDs, tapering of csDMARDs can be considered.*

SoR: B; QoE: D

Most recent studies have focused on tapering bDMARDs only [163, 164] and evidence of csDMARD tapering is relatively weak. Two landmark RCTs conducted over two decades ago addressed the possibility of tapering csDMARDs in RA [165, 166]. Tapering of csDMARDs has also been recently investigated in patients with early RA and sustained response, who had been treated in a treat-to-target manner after initial randomization to triple csDMARD therapy or MTX monotherapy [163]. It is generally thought that csDMARD tapering should entail cautious dose reduction without complete withdrawal [10, 12].

Treatment consideration for seronegative RA

31. *Rituximab and abatacept are not preferred in patients with seronegative RA.*

SoR: A; QoE: A

Both rituximab and abatacept have been shown to be most beneficial in patients with positive ACPA [167, 168].

Treatment considerations in pregnancy

32. *Use of TNF inhibitors is generally safe during first and second trimesters.*

SoR: A; QoE: C

Available data indicate that TNF inhibitors, which are classified as pregnancy category B (no documented human toxicity) by the US FDA, do not increase the risk of miscarriage or congenital malformation [169, 170]. Transport of immunoglobulin (IgG) proteins across the placenta increases steadily after the first trimester of pregnancy, and neonatal exposure to TNF inhibitor bDMARDs would be expected to be highest in infants of mothers exposed in

the third trimester (see recommendation 33) [169]. Compared with the TNF inhibitor bDMARDs, rituximab, tocilizumab, and abatacept have comparatively limited documentation of safety in pregnancy and should be replaced by other medications before conception [169]. These drugs should be used during pregnancy only when no other pregnancy-compatible drug can effectively control RA [169]. Since tsDMARDs have insufficient documentation for use in pregnancy, these should be avoided until further evidence is available [169].

33. *Certolizumab and etanercept may be considered during the third trimester due to low placental transfer.*

SoR: A; QoE: C

There is significant placental transfer of IgG during the third trimester, and as IgG clearance is relatively slow in neonates, prolonged exposure to TNF inhibitors during pregnancy may potentially increase the risk of neonatal infection [169, 171]. Among the TNF inhibitor bDMARDs, placental transfer of certolizumab and etanercept is relatively low, so these agents are preferred for use in the third trimester of pregnancy [169].

Treatment considerations in patients with chronic hepatitis B virus and hepatitis C virus infection

34. *Prophylactic antiviral therapy should be prescribed for patients with chronic (HBsAg+ve) and occult (HBsAg-ve, Anti-HBc+ve, and HBV DNA+ve) HBV infection who require b/tsDMARDs.*

SoR: A; QoE: C

Clinical experience and case series show that the risk of hepatitis B virus (HBV) reactivation with b/tsDMARDs is substantially reduced when infected patients receive appropriate prophylactic antiviral therapy [45, 172]. In Asia, where HBV infection is endemic, screening for HBV should be conducted in all patients scheduled for b/tsDMARD therapy [22, 172]. For HBsAg+ve patients, prophylactic antiviral therapy should be started at least 1 week before the use of b/tsDMARDs [172]. There is a lack of evidence regarding the first-line choice of prophylactic antiviral drug, but either entecavir or tenofovir would be appropriate in patients with chronic HBV infection [172].

35. *Prophylactic antiviral therapy should not be prescribed for patients with resolved hepatitis B infection (HBsAg-ve, Anti-HBc+ve but HBV DNA-ve) EXCEPT when treated with B cell depletion therapy.*

SoR: A; QoE: C

Case series show that for patients with resolved

HBV infection treated with b/tsDMARDs, the risk of reactivation with b/tsDMARD therapy is very low [172]. Routine use of prophylactic antiviral therapy would therefore not be a cost-effective approach in these patients, but patients should be closely monitored for reactivation [172]. Antiviral prophylaxis may however be advisable in patients with resolved HBV infection scheduled for treatment with rituximab, which can induce profound B cell depletion resulting in secondary immunosuppression [172].

36. *b/tsDMARDs are not contraindicated in patients with chronic HCV infection.*

SoR: A; QoE: D

Small case series suggest that the use of TNF inhibitors does not affect viral load or cause reactivation of hepatitis C virus (HCV) [172–177]. However, there is a lack of safety data of tsDMARDs in patients with HCV infection. TNF inhibitor bDMARDs have the longest safety record; therefore, they are the preferred bDMARDs in patients with RA and chronic HCV. These patients should be warned of the risk of HCV reactivation and be monitored by hepatologists.

Discussion

Recommendations for the use of the newly available tsDMARDs and biosimilar DMARDS are an important feature of this updated consensus. Early diagnosis of RA and prompt initiation of DMARD therapy according to the treat-to-target approach are crucial. Patients presenting with symptoms suggestive of RA should be referred to a rheumatologist for evaluation early before irreversible joint damage occurs [6, 10]. Early RA is characterized by synovitis [6], but it may be difficult to detect subclinical synovitis during physical examination [178]. ACPA and MSUS are valuable tools to aid early diagnosis of RA [179–181].

The treatment target of RA should be sustained remission or low disease activity when remission cannot be achieved. Frequent monitoring of disease activity (ideally every 3 months) and prompt adjustment of treatment if the target is not reached are the foundations of an effective treat-to-target approach [6]. A ≥ 50% clinical improvement in a validated composite disease activity measure is desirable within 3 months of a new treatment and the target should be achieved within 6 months [10, 82].

In line with our 2011 recommendations for first-line DMARD treatment of RA [5], the general consensus is still that patients should receive MTX monotherapy [10, 12, 45]. Despite the increasing evidence of the b/tsDMARDs in RA [59, 60, 62–68, 70, 72, 182], there remains insufficient

evidence to support a recommendation for b/tsDMARDs as first-line therapy. We reiterate our previous general recommendation to use GC bridging therapy during csDMARD therapy [5], but we now also specify a low-dose target (i.e., ≤ 7.5 mg/day of prednisolone within 10 weeks of starting a csDMARD) and that GCs should ideally be discontinued within 3–6 months. Such practices should help to minimize GC use and reduce their adverse effects.

While similar in principle to our 2011 recommendations for stepping up of DMARDs [5], our updated recommendations incorporate newly available tsDMARDs and biosimilar DMARDs in the treatment algorithm. When there is insufficient response to first-line csDMARD therapy, patients should be stratified according to prognostic factors. Patients without poor prognostic factors have the option of switching to another csDMARD as monotherapy, or receiving csDMARD combination therapy, whereas the addition of a b/tsDMARD to MTX should be considered in patients with poor prognostic factors. Although we do not provide specific statements on the risk of infection during b/tsDMARD therapy, any ongoing GC bridging therapy should be discontinued before starting a b/tsDMARD. It is prudent to protect against the most common vaccine-preventable infections in patients with RA, including *Pneumococcus*, influenza, HBV, human papilloma virus, and herpes zoster [12, 45]. If the first b/tsDMARD fails, patients should be switched to another b/tsDMARD with the same or a different mode of action to the initial b/tsDMARD. In the event that two b/tsDMARDs with the same mode of action fail (i.e., two TNF inhibitor bDMARDs), a b/tsDMARD with a different mode of action should be considered [10].

While we specify that monotherapy with IL-6 inhibitors or JAK inhibitors may be preferable to other bDMARDs in patients who cannot tolerate csDMARDs, and that TNF inhibitor bDMARDs are the only b/tsDMARDs with sufficient safety data to justify their use during pregnancy, there is no hierarchical positioning for the use of any type of b/tsDMARD in combination with a csDMARD. As the efficacy of b/tsDMARDs (TNF inhibitor bDMARDs, non-TNF inhibitor bDMARDs, and JAK inhibitors) does not differ, the initial choice of drugs should be based on patient preference, tolerability, and cost [10, 12, 69].

Although bDMARDs may be preferred to tsDMARDs for their longer track record [10], the latter have the potential to gain at least an equal footing to bDMARDs within the RA treatment algorithm when more long-term tsDMARD safety data become available.

In the event of sustained remission (> 6 months) during combined csDMARD/bDMARD therapy, bDMARD tapering is feasible in a subset of patients—especially patients with early RA [159, 183]. The risk of flare may be lowered if the bDMARD dose is reduced rather than discontinued [164]. We therefore recommend a relatively cautious approach to tapering in patients with established RA, ideally without

discontinuation of bDMARD therapy, because of an increased risk of flare. Patients who experience a disease flare after discontinuation of bDMARD therapy could regain remission with the resumption of the original bDMARD [9, 159].

In comparison to the EULAR recommendations, ours have incorporated the treatment consideration for special patient groups such as seronegative RA, pregnant patients, and those with chronic hepatitis B and C infection. The clinical application of musculoskeletal ultrasound, the use of biosimilars, and the switching between bio-originators and biosimilars are also included. Similar to other parts of the world, the health care system of Hong Kong is facing challenges that include rising costs, increasing demand for medical service, and more expensive technologies, as well as an aging population. The b/tsDMARDs are reimbursed by our Government in less effluent patients. Our updated consensus recommendations may serve as a guidance to the hospital administration for adjusting the subsidy scheme of the b/tsDMARDs in RA. We will continue to update and modify our recommendations periodically based on novel evidence in the literature.

Compliance with ethical standards

Disclosures None.

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