Rheumatology International (2019) 39:1483–1497
https://doi.org/10.1007/s00296-019-04372-y

Rheumatology
INTERNATIONAL

RECOMMENDATIONS

Kuwait association of rheumatology 2018 treatment recommendations for patients with rheumatoid arthritis

Hebah Alhajeri[1] · Fatemah Abutiban[2] · Wasl Al-Adsani[1] · Adel Al-Awadhi[3] · Ali Aldei[4] · Ahmad AlEnizi[2] · Naser Alhadhood[5] · Adeeba Al-Herz[4] · Waleed Alkandari[5] · Ahmad Dehrab[6] · Aqeel A. Muhanna Ghanem[1] · Eman Hasan[4] · Sawsan Hayat[1] · Khulood Saleh[5] · Hoda Tarakmeh[1] · Yaser Ali[1]

Received: 3 May 2019 / Accepted: 4 July 2019 / Published online: 15 July 2019

Abstract

The Kuwait Association of Rheumatology (KAR) aimed to develop a set of recommendations for the treatment of patients with rheumatoid arthritis (RA), tailored to the unique patient population and healthcare system of Kuwait. Each recommendation was developed based on expert opinion and evaluation of clinical practice guidelines from other international and national rheumatology societies. Online surveys were conducted to collate feedback on each KAR member's level of agreement (LoA) with definitions of disease-/treatment-related terms used and the draft recommendations. Definitions/recommendations achieving a pre-defined cut-off value of ≥ 70% agreement were accepted for inclusion. Remaining statements were discussed and revised at a face-to-face meeting, with further modifications until consensus was reached. A final online survey was used to collect feedback on each KAR member's LoA with the final set of recommendation statements on a scale of 0 (complete disagreement) to 10 (complete agreement). Group consensus was achieved on 66 recommendation statements, including 3 overarching principles addressing the pharmacological treatment and management of RA. Recommendations focused on treatment of early RA, established RA, patients with high-risk comorbidities, women during pregnancy and breastfeeding, and screening and treatment of opportunistic infections. The KAR 2018 Treatment Recommendations for RA reported here are based on a synthesis of other national/international guidelines, supporting literature, and expert consensus considering the Kuwaiti healthcare system and RA patient population. These recommendations aim to inform the clinical decisions of rheumatologists treating patients in Kuwait, and to promote best practices, enhance alignment and improve the treatment experience for patients.

Keywords DMARDs (biologic) · DMARDs (synthetic) · Tumor necrosis factor-alpha · Anti-TNF · Early rheumatoid arthritis · Rheumatoid arthritis · Pregnancy · Infections · Treatment

Introduction

Rheumatoid arthritis (RA) is a common, chronic, and systemic autoimmune disease, with an estimated prevalence of ~0.25−1% globally [1, 2]. Epidemiological data for RA in the Middle East are very limited, but prevalence estimates range from ~0.16% in North Africa and the Middle East to ~1% in Kuwait [2, 3]. RA disease is associated with pain, fatigue, disability, and comorbidities, which can adversely impact patients' health-related quality of life and work productivity [4, 5].

Early diagnosis and effective treatment of patients with RA is required to minimise long-term joint damage and disability [6–8]. There are an increasing number of disease-modifying anti-rheumatic drug (DMARD) therapies available,

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00296-019-04372-y) contains supplementary material, which is available to authorized users.

✉ Hebah Alhajeri
hebah.alhajeri@gmail.com

1 Mubarak Al-Kabeer Hospital, Jabriya, Kuwait

2 Al Jahra Hospital, Al Jahra, Kuwait

3 Department of Medicine, Kuwait University, Kuwait City, Kuwait

4 Al Amiri Hospital, Kuwait City, Kuwait

5 Farwaniya Hospital, Al Farwaniya, Kuwait

6 Adan Hospital, Hadiya, Kuwait

which can alter disease trajectory by slowing or preventing radiographic progression [9, 10]. These DMARDs are broadly classified into three main categories [11]: conventional synthetic DMARDs (csDMARDs), which include methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine; biological DMARDs (bDMARDs) [12], including tumor necrosis factor inhibitors (TNFi), such as adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab; and non-TNFi biologics, such as the T-cell co-stimulation inhibitor, abatacept, the anti-B-cell agent, rituximab, the interleukin-6 (IL-6) receptor-blocking monoclonal antibody, tocilizumab, and the IL-1 inhibitor, anakinra. Targeted synthetic DMARDs (tsDMARDs) inhibiting Janus kinase (JAK) have also been shown to be effective in modifying RA disease [12]. Nevertheless, the therapeutic management of RA continues to evolve with the approval of an increasing number of biosimilars and new treatments that target specific inflammatory mediators [12, 13].

As literature on the efficacy and safety of RA treatments increases, the development of clinical treatment recommendations can be used to synthesize and translate this information to inform treatment decisions made by healthcare professionals (HCPs). By considering the needs of different patient subgroups, HCPs can tailor their approach to managing individual patients with RA.

The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have published comprehensive recommendations for the management of RA [14–18], which inform and influence clinical practice internationally. At a national/regional level, the Canadian Rheumatology Association (CRA), British Society for Rheumatology (BSR), British Health Professionals in Rheumatology (BHPR), and Asia Pacific League of Associations for Rheumatology (APLAR) have developed their own sets of treatment recommendations for patients with RA [19–21], which adapt international recommendations, taking their respective patients' profiles, clinical practice settings, healthcare systems, and the views of decision makers into account.

While published international guidelines provide valuable advice for the management of RA patients in Kuwait, local HCPs and decision makers would benefit from published treatment recommendations tailored to their unique patient population and healthcare system. In Kuwait, 70% of the population are expatriates [22], and navigating the healthcare system is different for Kuwaiti and non-Kuwaiti patients. For Kuwaiti patients, biologic treatments are provided within a week of being prescribed and are free at the point of use, with costs fully covered by the Ministry of Health (MoH). In contrast, non-Kuwaiti patients must follow a strict and long protocol to be approved for biologic treatment, the cost of which is covered partially by the Kuwait Patients Helping Fund Society charity (not the MoH). The introduction of RA treatment recommendations that are specific to patients in a Kuwaiti practice setting should help to address inequalities among Kuwaiti and non-Kuwaiti patients in terms of access to biologics, lower disease activity, and better physical function [3]. Furthermore, there is a need to provide HCPs in Kuwait with internationally aligned recommendations for screening and treating patients at risk of chronic infections such as tuberculosis (TB), viral hepatitis B (HBV), and viral hepatitis C (HCV). This is especially important for the large expatriate population in Kuwait, many of whom are from countries where these opportunistic infections are endemic [23, 24].

Methods

Expert panel

The recommendations presented here were jointly developed by a panel of 15 experts from the Kuwait Association of Rheumatology (KAR), which aims to advance the knowledge of physicians treating patients with rheumatic diseases and to standardize their clinical practice (Supplementary Table 1). All rheumatology experts were invited to participate on the basis of their seniority and experience of medical practice in Kuwait, and were considered to be representative of rheumatology practitioners across Kuwait. The panel was supported by an expert infectious disease physician with several years of experience in treating infectious diseases, plus experience of medical practice in Kuwait.

All participants contributing to the development of these recommendations provided a full list of disclosures (Supplementary Table 1).

Development of evidence-based recommendations

To inform the development of the recommendations, pragmatic literature reviews were conducted by members of the expert panel. This focused on international guidelines for the treatment for RA, treatment of RA during pregnancy and breastfeeding, treatment in patients with cancer, and on the screening, prevention and management of infections in patients undergoing treatment for RA (see Supplementary Materials for further details).

RA disease and treatment definitions and RA treatment recommendations were drafted by two members of KAR. The scope was pre-agreed by the panel based on their collective understanding and experience of the needs of patients in Kuwait.

Many of the recommendations were selected or adapted from those previously published by ACR [14, 15], EULAR [16–18], CRA [19], and jointly by the BSR and BHPR [21], taking into consideration the healthcare system and medical

practice in Kuwait, the quality of published evidence relating to the relative benefits and harms of the treatment options under consideration, the differences in access to treatments by Kuwaiti citizens versus foreign nationals, and the KAR's insight regarding the profile of patients with RA in Kuwait and their experience of patients' preferences in clinical practice. Cost-effectiveness of the treatments was not considered. Each recommendation was formulated to be either in favour of or against an intervention, and some were subject to specific conditions.

Collating expert feedback on the draft recommendations statements

All experts were invited to complete two online surveys using Google Forms, in which they were asked to indicate their level of agreement (LoA) with each draft definition and recommendation on a 5-point Likert scale (strongly agree/agree/neutral/disagree/strongly disagree). Respondents were also given the opportunity to provide a rationale for their LoA.

The first survey (distributed by email on 3-Apr-2018) collected feedback on the definitions and recommendations relating to the treatment of early RA and established RA (defined in Supplementary Table 2), patients with high-risk comorbidities, and of patients with RA during pregnancy and breastfeeding. The second survey (distributed by email on 10-May-2018) collected feedback on definitions and recommendations relating to the screening, prevention and management of infections in patients with RA.

Reaching a consensus on each definition and recommendation statement

All 15 KAR rheumatologists were invited to attend a 1-day face-to-face meeting on 21-Apr-2018, where the results of pragmatic literature reviews, and anonymized responses to the first survey were presented. Definitions and recommendations achieving a pre-defined cutoff of $\geq 70\%$ agreement (strongly agree/agree) from the survey participants were accepted for inclusion in the final set of recommendations without revision. Statements where $< 70\%$ of participants strongly agreed/agreed were debated; considering the rationale and evidence-base, and the experts' experiences of patients' preferences in clinical practice. Each statement was then amended to implement the proposed suggestions until consensus had been reached, i.e., no experts had any further comments.

The infectious disease physician reviewed anonymized feedback for any draft definitions and recommendations relating to infections that received $< 70\%$ agreement among respondents. Based on the results for each definition/recommendation, the infectious disease physician either revised the respective text or provided the expert panel with a written response to provide further evidence or a clarification of rationale for the statement.

Final online survey

The final definitions/recommendations were incorporated into an online survey hosted on SurveyMonkey®, distributed to the expert panel by email on 21-Jun-2018. Anonymized LoA scores for each statement, on a scale of 0 (complete disagreement) to 10 (complete agreement), were collated and mean scores are presented here. The switch from a Likert scale to a continuous LoA scale for the final online survey was pre-agreed at the beginning of the consensus process and enabled greater granularity of the strength of expert agreement with all final recommendations statements.

Independent review of the treatment recommendations

An independent rheumatology expert was invited by email on 20-Dec-2018 to review the final treatment recommendations. The independent expert was selected by the expert panel on the basis of their experience in developing local clinical practice recommendations for RA in the UK and good knowledge of medical practice for rheumatology patients in Kuwait. No changes were made to the recommendations, but some points of clarification were added to the explanatory text within this publication.

Results/recommendations

A list of abbreviations used and a glossary of the expert-agreed disease- and treatment-specific terms used in the recommendations is provided (Supplementary Tables 2 and 3). An abbreviated guideline summary of the final recommendations can be found in the Supplementary Appendix. These recommendations are made based on the medications licensed for RA in Kuwait; physicians outside of Kuwait consulting these recommendations should check which medications are licensed in their region. The KAR advises users of these recommendations that this document does not supersede the summary of product characteristics document for any medications mentioned. The summary of product characteristics for all medications prescribed or taken should be consulted for information on the risks, side effects, and need for monitoring.

Recommendations for the treatment of RA in Kuwait

Many of the recommendations for the treatment of RA in Kuwait are adopted or adapted from other national/international guidelines [14–21]. Where unchanged, the

experts agreed with the evidence-base and rationale underpinning the original recommendation and felt it was relevant for patients in Kuwait. For each recommendation that has either been adapted or developed independently, the rationale and evidence-base is provided. All recommendations and associated mean LoA scores are presented in Tables 1, 2, 3, 4.

All 15 rheumatologists responded to the final online survey to indicate their LoA with each KAR treatment recommendation for RA. Overall, there was a high LoA among the survey participants across all treatment recommendations; all mean LoA scores fell between 8.0 and 10.

General principles

There was a high LoA among the expert panel for the three general principles for the treatment of patients with RA, as presented in Table 1. General principle #1 recommended a goal of remission, and was adapted from a CRA recommendation [19] using the goal of low disease activity (LDA; DAS28 < 3.2) when remission is not possible. The aim was to provide clarity that this refers to a state of LDA excluding remission, since in clinical practice achieving full remission can take a very long time, thereby making LDA a more practical target. The adapted recommendation does not address patient-reported outcomes, because these are not routinely captured in Kuwaiti clinical practice.

General principle #2 was adapted from overarching principle B in the EULAR 2016 recommendations for the management of RA [17], since the experts agreed that treatment decision based on disease activity, the presence of poor prognostic factors, comorbidities, and safety is a "central and self-evident rule to any therapeutic approach." The experts agreed that treatment decisions should be based on the presence of poor prognostic factors (as defined in the EULAR 2016 recommendations [17]; Supplementary Table 2), rather than "patient factors, such as progression of structural damage," to reflect how disease progression is evaluated in Kuwait. Use of regular X-rays to assess structural damage progression is not currently routine practice for all rheumatologists in Kuwait.

General principle #3 was taken without amendment from the EULAR 2016 recommendations [17]. The KAR experts agreed that specialty care by rheumatologists for a complex disease such as RA is advantageous for patients, given rheumatologists' experience with the therapeutic interventions used, and their awareness of and experience with comorbidities. The experts also agreed that the use of "primarily" was appropriate and needed to factor in multidisciplinary care, e.g., comorbidities requiring consultation of other specialists.

Treatment of patients with early RA

The KAR developed ten recommendations for treatment of patients with early RA (defined as RA with disease/symptoms of less than 6 month duration), which are provided in Table 1 and summarized in Fig. 1. There was a high LoA among the expert panel across all early RA recommendations (range of mean LoA scores: 9.13–9.93).

Recommendation #5 on assessing poor prognostic factors is an adapted CRA recommendation; the CRA's definition of poor prognostic factors has been replaced with EULAR's broader definition of poor prognostic factors (moderate [after csDMARD therapy]-to-high disease activity according to composite measures, high acute phase reactant levels, high swollen joint counts, presence of rheumatoid factor and/or ACPA [especially at high levels], combinations of the aforementioned, presence of early erosions, or failure of 2 or more csDMARDs).

Recommendation #6 on the use of DMARD monotherapy over double/triple therapy was adapted from the ACR treatment recommendations for DMARD-naïve patients [15]. The conditional part of the statement was excluded as the experts felt that the recommendation was relevant for all patients. Despite more rapid benefits of combination therapy, DMARD monotherapy reflects current practice for many rheumatologists in Kuwait and was considered by the expert panel to be an efficacious, safe, and cost-effective option for patients with low disease activity [26–28]. Combination therapy with csDMARDs was recommended for patients with poor prognostic factors, moderate-to-high disease activity, and those with an inadequate response to monotherapy (Recommendation #10) [19].

Recommendation #9 on methotrexate dosing was adapted from a CRA 2012 recommendation [19] and recommends a maximum dose of 20 mg (rather than 25 mg) as absorption and bioavailability of a methotrexate dose > 20 mg per week is considered to be poor unless administered as a split dose or subcutaneously [25, 29, 30].

Recommendation #12 lists multiple treatment options for patients with persistent moderate-to-high disease activity despite csDMARD monotherapy. This provides the treating physician with an opportunity to make shared decisions with the patient after informing them of the mode of administration and the risk of adverse reactions associated with each treatment option.

Treatment of patients with established RA

The KAR developed eigth recommendations for the treatment of patients with established RA, which are provided in Table 1 and summarized in Fig. 1. There was a high LoA among the expert panel across all of the established RA recommendations (range of mean LoA scores: 9.27–10).

Table 1 General principles and treatment recommendations for patients with early and established RA

#	The KAR 2018 treatment recommendations for patients with early and established RA	Level of agreement
General principles		
1	The goal of treatment is remission, and when remission is not possible, low disease activity (DAS28 < 3.2)[a] while controlling symptoms, halting damage, and preventing disability	9.93
2	Treatment decisions should be made based on disease activity, the presence of poor prognostic factors, comorbidities and safety issues	10.00
3	Rheumatologists are the specialists who should primarily care for patients with RA	10.00
Early RA		
4	Therapy with DMARDs should be started as soon as the diagnosis of RA is made	9.93
5	The presence of poor prognostic factors in RA should be assessed at baseline and considered when making treatment decisions	9.93
6	If disease activity is low, use DMARD monotherapy over double or triple therapy	9.73
7	Methotrexate should be the first csDMARD to be used in patients with early RA, unless contraindicated	9.73
8	A complete blood count, liver and renal biochemistry, a chest radiograph, and screening for HBV and HCV should be ordered prior to initiating methotrexate therapy	9.80
9	Dosing of methotrexate should be individualized to the patient. Oral methotrexate should be started and titrated to a usual maximum dose of 20 mg per week by rapid dose escalation. In patients with an inadequate response or intolerance to oral methotrexate, subcutaneous administration should be considered	9.13
10	Combination therapy with csDMARDs should be considered, particularly in patients with poor prognostic factors, moderate-to-high disease activity, and those who have an inadequate response to monotherapy	9.60
11	In patients with a contraindication to methotrexate (or early intolerance to methotrexate), leflunomide or sulphasalazine should be considered as part of the first treatment strategy	9.53
12	In patients with persistent moderate-to-high disease activity despite csDMARD monotherapy (with or without glucocorticoids), use combination csDMARD therapy, a TNFi or non-TNFi biologic, or JAK inhibitors	9.87
13	If patients experience disease flares, add short-term glucocorticoids at the lowest possible dose and for the shortest possible duration, to the treatment strategy	9.80
Established RA		
14	csDMARD/biologic therapy should be adjusted every 3–4 months, as long as the goal has not been achieved	9.73
15	Ordering radiographs of the hands and feet every 12 months is recommended in patients with recent-onset disease. Radiographs can be performed at longer intervals in patients with established disease	9.40
16	A change in therapy should be considered in patients with radiographic progression despite an adequate clinical response	9.33
17	Glucocorticoids (oral, intramuscular, or intraarticular) can be added to csDMARD therapy as part of the initial treatment strategy and may be an option for managing disease flares	9.93
18	Biologics and JAK inhibitors are recommended for patients experiencing an inadequate response to csDMARDs. In exceptional circumstances involving patients with csDMARD contraindications or high disease activity and poor prognostic factors, biologics and JAK inhibitors may be an option after failure of csDMARD monotherapy, or in csDMARD-naive patients	9.93
19	In patients experiencing treatment failure with 1 TNFi, due to lack of efficacy or toxicity, the following options are recommended: a) Switch to another TNFi agent b) Add methotrexate (or other csDMARD) if the TNFi agent was used as a monotherapy c) Switch to a non-TNFi biologic d) Switch to a JAK inhibitor	10.00
20	In patients experiencing treatment failure with 2 TNFi biologics, the following options are recommended: a) Switch to a non-TNFi biologic b) Switch to a JAK inhibitor	9.87
21	If a patient achieves sustained remission for at least 1 year (without glucocorticoid use), a reduction in biologic and/or csDMARD therapy can be attempted with caution	9.27

[a]Or a CDAI score of ≤ 10.0, The above recommendations for the treatment of RA in Kuwait were adopted or adapted from other national/international guidelines (primarily [19], plus [15–17])

Table 2 Laboratory monitoring for DMARDs and treatment of RA in patients with high-risk comorbidities

#	The KAR 2018 recommendations for laboratory monitoring for DMARDs and treatment of RA in patients with high-risk comorbidities	Level of agreement
22	For patients receiving csDMARD therapy, check their complete blood count and renal function tests, ALT, and AST levels every 2 weeks until the patient has received a stable dose for 6 consecutive weeks, and then repeat the laboratory tests on a monthly basis for 3 months[a]	8.60
23	In patients with congestive heart failure, use combination csDMARD therapy or a non-TNFi biologic treatment, or JAK inhibitors, over TNFi biologic treatment	9.67
24	In patients with HBV infection receiving effective antiviral treatment, follow the recommendations made for patients without HBV infection	9.47
25	In patients with HCV infection, collaboration between the treating rheumatologist and a gastroenterologist and/or a hepatologist is recommended to discuss appropriate individualized treatment for the patient based on their comorbidities, reason(s) for not treating the HCV infection, and the need to minimize immunosuppression	9.87
26	In patients with HCV infection receiving effective antiviral treatment, follow the recommendations made for patients without HCV infection	9.67
27	In patients with HCV infection not receiving or not requiring antiviral treatment, use csDMARD therapy over bDMARD and tsDMARD treatment. Treating the patient with csDMARDs other than methotrexate or leflunomide, such as sulfasalazine or hydroxychloroquine, should be considered	9.87
28	In patients with serious infections, use combination csDMARD therapy or abatacept over TNFi biologic treatment	9.47
Malignancy		
29	In patients with previously treated or untreated skin cancer (melanoma or non-melanoma), use csDMARD therapy over treatment with biologics or JAK inhibitors	9.13
30	In patients previously treated for lymphoproliferative disease, use rituximab over TNFi biologic treatment	9.87
31	In patients successfully treated for a solid malignancy 5 or more years ago, follow the recommendations made for patients without this condition	9.87

[a]Possible extension of the repeat laboratory tests beyond 3 months is an option, and is dependent on current practice for the treating physician. The above recommendations, with the exception of #22 and #25, were adopted or adapted from Ref. [15]

Recommendation #15 was adapted from the CRA 2012 recommendation to revise the use of radiographs every 6–12 months in patients with recent onset disease [19] to once every 12 months, to avoid unnecessary radiation exposure.

For recommendation #18 on biologics and JAK inhibitors, the experts agreed with the rationale and evidence-base underpinning the CRA 2012 recommendation on TNFi therapy [19], but also extended this recommendation to the use of non-TNFi biologics and JAK inhibitors based on recent long-term safety and efficacy data for tofacitinib and baricitinib [31, 32]. EULAR also expanded this recommendation to bDMARDs and JAK inhibitors in their 2016 update of treatment recommendations for RA [17].

Treatment options after failure with 1 TNFi are presented in recommendation #19. TNFi should preferentially be used with concomitant methotrexate, unless contraindicated. In patients who become intolerant to methotrexate at a high dose, if a lower dose is tolerated, its use in addition to a TNFi (or other bDMARD) is preferred [33]. The experts agreed with the rationale and evidence-base underpinning this recommendation made by the CRA regarding failure of 1 TNFi therapy [19], but also recommended the option of switching to a JAK inhibitor if the TNFi was used as a monotherapy, based on recent efficacy and safety data [31, 32, 34]. The wording of the CRA's original recommendation has been adapted to refer to "serious adverse events" rather than "toxicity" to better reflect what physicians in Kuwait would consider TNFi failure.

Recommendation #20 is based on the rationale and evidence-base that patients failing 2 TNFi treatments are unlikely to respond to a third [35]. The EULAR 2016 recommendation states that "If a bDMARD or tsDMARD has failed, treatment with another bDMARD or tsDMARD should be considered; if 1 TNF-inhibitor therapy has failed, patients may receive another TNF-inhibitor or an agent with another mode of action". However, the EULAR recommendations also note the lack of evidence to support: use of a second JAK/IL-6 inhibitor after a patient has failed a treatment that targets the same inflammatory mediator, or use of TNFi as an effective and safe option after bDMARDs with other modes of action have failed [16].

The experts make recommendation #21 on therapy reduction based on recent studies which have concluded that, despite risk of a flare in disease activity, tapering biologic and/or csDMARD therapy in patients with RA who have achieved sustained remission can be successful and safe [36, 37].

Table 3 Screening and treatment of infections in patients with RA, and treatment of RA in patients with infections

#	The KAR 2018 recommendations for the screening and treatment of infections in patients with RA, and treatment of RA in patients with infections	Level of agreement
Tuberculosis infection		
32	Prior to initiation of bDMARDs or tsDMARDs, all patients should be screened for LTBI	9.80
33	Prior to initiation of bDMARDs or tsDMARDs, in immunocompetent patients, screen for LTBI with an IGRA, i.e., either QFT-GIT, or T-Spot	9.93
34	Prior to initiation of bDMARDs or tsDMARDs, in immunocompromised patients, screen for LTBI using a dual-screening strategy, i.e., any 2 of the following: QFT-GIT; T-Spot; TST - IGRA (QTF-GIT or T-Spot) are preferred for patients who have received the BCG vaccine - If the 1 initial screening test is positive, there is no need to perform dual-screening - If the 1 initial screening test is negative or indeterminant, the dual-screening strategy is recommended - If both IGRA tests are indeterminant, 2-step TST (performing a second TST if the initial TST is negative) is recommended - Use of the online TST/IGRA Interpreter (version 3.0), available at http://www.tstin3d.com, is recommended to assist TST and IGRA result interpretation	8.27
35	Prior to initiation of bDMARDs or tsDMARDs, consider obtaining a baseline chest X-ray for all patients	N/A[a]
36	Prior to initiation of bDMARDs or tsDMARDs, if a patient tests positive with either IGRA or TST, obtain a chest X-ray - If the chest X-ray is negative, the healthcare provider may initiate treatment for LTBI - If the chest X-ray is positive or suspicious, the patient should undergo evaluation for active TB In patients diagnosed as having LTBI or active TB, consider referral to a specialist for the recommended treatment	9.33
37	Patients receiving treatment with bDMARDs or tsDMARDs with a suspicious chest X-ray or signs and symptoms of active TB infection should undergo evaluation for active TB	10.00
38	In patients with suspected LTBI with isoniazid-susceptible TB, the primary treatment regimen recommended is isoniazid 5 mg/kg q.d. (up to a maximum 300 mg q.d.) for 9 months	8.73
39	Alternative treatment regimens for patients with suspected LTBI, which may be considered, are: a) Rifampin 600 mg taken p.o. q.d. for 4 months. b) Isoniazid 15 mg/kg (up to a maximum 900 mg) + Rifapentine 900 mg (if weight > 50 kg) q.w. x 12 doses (pyridoxine 50 mg p.o. with each dose); c) In patients unable to tolerate or comply with 9 months' isoniazid treatment, isoniazid 300 mg p.o. q.d. for 6 months has some efficacy	N/A[a]
40	In patients with suspected LTBI with isoniazid-resistant TB or adverse reaction to isoniazid, treatment with rifampicin 600 mg p.o. q.d. for 4 months is recommended	9.20
41	In patients diagnosed with LTBI, treatment with bDMARDs or tsDMARDs can be initiated or resumed after 1 month of treatment with anti-TB medications	9.60
42	Annual screening for LTBI is recommended in patients receiving treatment with bDMARDs or tsDMARDs for RA (Fig. 2) - In patients with no history of LTBI or active TB treatment, annual dual-screening is recommended using any 2 of the following: QTF-GIF, T-Spot or TST. For those with indeterminant test results, consider repeating the IGRA test in 1-3 weeks and/or performing a 2-step TST - Patients who test positive for IGRA or TST at baseline (prior to initiating treatment) often remain positive for these tests, even after successful treatment of LTBI, and repeat testing is not recommended. These patients need monitoring for clinical signs and symptoms of recurrent TB disease, including annual chest X-ray - Obtaining a routine annual chest X-ray for patients receiving RA treatment should be considered	8.00
Viral hepatitis B infection		
43	Prior to initiation of DMARD treatment, all patients should be screened for HBV (Fig. 2)	9.87
44	Screening for HBV should include all 3 serological markers of HBV exposure and immunity (HBcAb, HBsAg and HBsAb), and baseline serum HBV-DNA assessment to rule out occult viremia in any patient with HBcAb positivity (particularly in those lacking HBsAb) (Fig. 2)	9.53
45	For a patient with natural immunity to HBV from prior exposure (i.e., HBcAb positive, normal liver function tests, and HBsAb positive and HBsAg negative), RA treatment recommendations are the same as those for unexposed patients, as long as the patient's viral load is monitored every 6–12 months	9.53
46	For patients with chronic HBV who are untreated, referral for hepatology evaluation is appropriate prior to initiating immunosuppressive therapy	9.87
Viral hepatitis C infection		
47	Prior to initiation of DMARD treatment, all patients with known risk factors for HCV infection should be screened for HCV	9.73
48	Close monitoring of serum aminotransferases (ALT and AST) and HCV RNA should be considered in patients with HCV who are receiving TNFi treatment	9.87

[a]Recommendations revised following the final level of agreement vote, during manuscript development. The majority of the recommendations are adopted or adapted from [15]. Recommendations #38–40 are adopted or adapted from [63]

Table 4 Treatment of RA during pregnancy and breastfeeding

#	The KAR 2018 recommendations for the treatment of RA during pregnancy and breastfeeding	Level of agreement
General principles		
49	All women with RA should receive pre-pregnancy counseling and adjustment of therapy should be considered before a planned pregnancy	10.00
50	Treatment options should be discussed with the mother to ensure an informed decision is made with respect to the balance of ceasing/continuing medication and the risk of adverse outcomes for mother and baby as a result of poor disease control	10.00
csDMARDs		
51	Methotrexate at any dose should be avoided in pregnancy and stopped 3 months in advance of conception	N/A[a]
52	In the case of accidental pregnancy on methotrexate, the drug should be stopped immediately, folate supplementation (5 mg q.d.) started, and a careful evaluation of the fetus carried out by a physician who is an expert in this field	10.00
53	In the case of accidental pregnancy on leflunomide, the drug should be stopped immediately, folate supplementation (5 mg q.d.) started, plus cholestyramine washout given until plasma levels of the drug is undetectable	9.67
54	Sulphasalazine with folate supplementation (5 mg q.d.) is compatible throughout pregnancy and breastfeeding	9.80
55	Hydroxychloroquine remains the antimalarial of choice in women planning a pregnancy with RA in need of treatment and should be continued during pregnancy. In addition, hydroxychloroquine is compatible with breastfeeding	9.93
bDMARDs and tsDMARDs		
56	bDMARDs (rituximab, anakinra, tocilizumab, abatacept, tofacitinib, baricitinib) have limited documentation on safe use in pregnancy and should be replaced by other medication before conception	9.80
57	Rituximab should be stopped 6 months before conception, but unintentional exposure early in the first trimester is unlikely to be harmful to the fetus. In addition, rituximab should not be used in a breastfeeding mother	9.73
58	Infliximab may be continued until 16 weeks' of pregnancy and etanercept and adalimumab may be continued until the end of the second trimester of pregnancy	9.73
59	Etanercept and adalimumab should be avoided in the third trimester and infliximab stopped at 16 weeks. If these drugs are continued later in pregnancy to treat active disease, then live vaccines should be avoided in the infant until 7 months of age	9.87
60	Certolizumab pegol is compatible with all 3 trimesters of pregnancy and has reduced placental transfer compared with other TNFi biologic treatment	10.00
Lactation and DMARDs		
61	Anti-inflammatory drugs compatible with breastfeeding should be considered for continuation during lactation. This applies to prednisone, immunoglobulin, non-selective COX inhibitors and celecoxib (adapted for anti-inflammatory drugs used in Kuwaiti medical practice)	8.73
62	csDMARDs compatible with breastfeeding should be considered for continuation during lactation. This applies to hydroxychloroquine, chloroquine, sulphasalazine, and cyclosporin (adapted for csDMARDs used in Kuwaiti medical practice)	9.87
63	Methotrexate and leflunomide are not recommended in a breastfeeding mother	10.00
64	csDMARDs and tsDMARDs with no or limited data on breast feeding should be avoided in lactating women. This applies to methotrexate, cyclophosphamide, leflunomide, tofacitinib and baricitinib (adapted for csDMARDs and tsDMARDs used in Kuwaiti medical practice)	9.93
65	Continuation of TNFi biologic treatment (infliximab, adalimumab, etanercept and certolizumab pegol) should be considered compatible with breastfeeding	9.33
66	bDMARDs with no data on breastfeeding, such as rituximab, anakinra, tocilizumab and abatacept, should be avoided during lactation if other therapy is available to control the disease (adapted for bDMARDs used in Kuwaiti medical practice)	9.80

[a]Recommendations revised following the final level of agreement vote, during manuscript development. The above recommendations, with the exception of general principles #49 and #50, were adopted or adapted from [18] and [21]

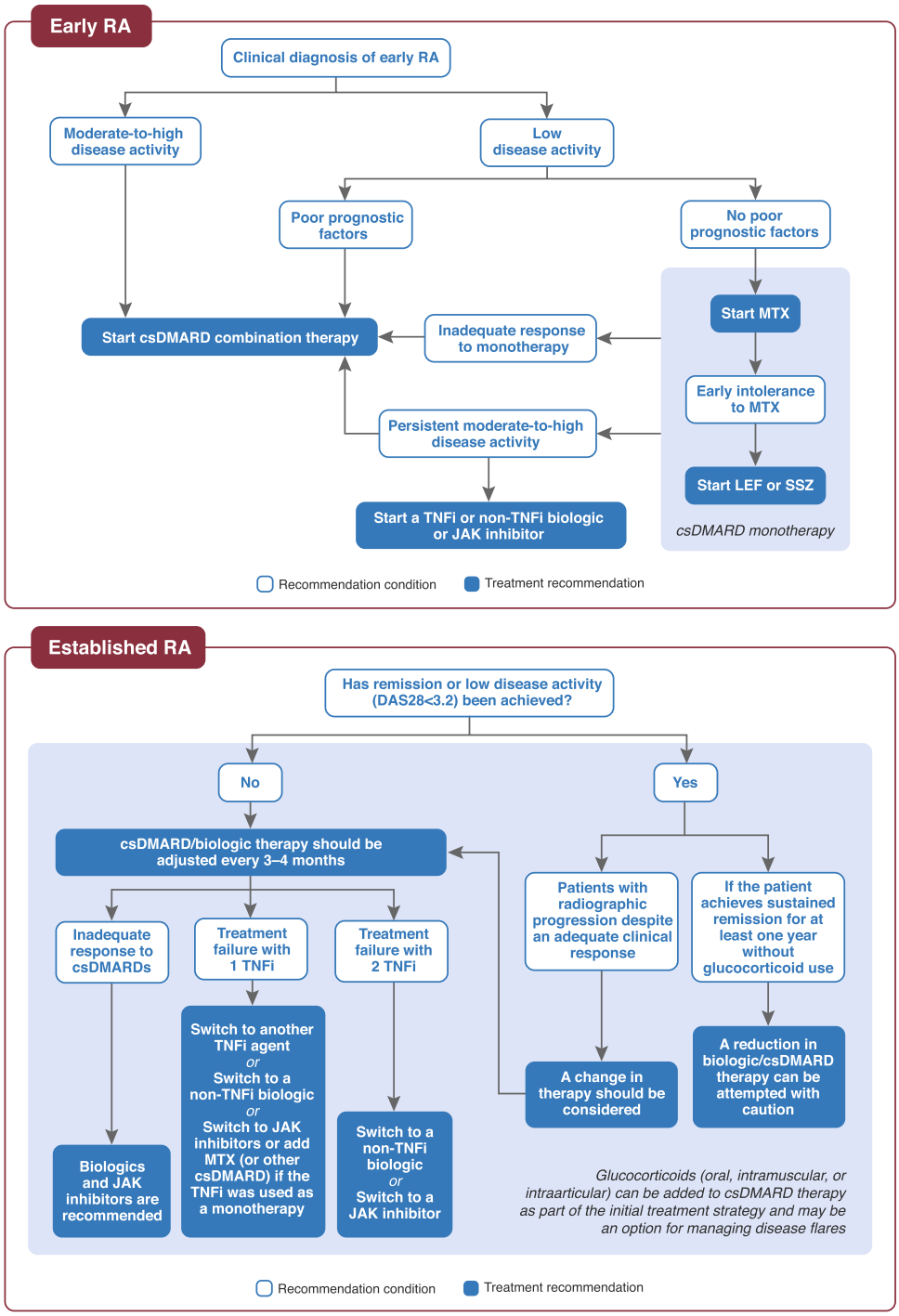

Fig. 1 Recommended algorithms for treatment of early RA and established RA. *csDMARD* conventional synthetic disease-modifying anti-rheumatic drug, *DAS28* disease activity score 28-joint count, *JAK* Janus kinase, *LEF* leflunomide, *MTX* methotrexate, *SSZ* sulphasalazine, *TNFi* tumor necrosis factor inhibitors

Laboratory monitoring for DMARDs and treatment of RA in patients with high-risk comorbidities

A total of seven recommendations were developed regarding laboratory monitoring for DMARDs and treatment of RA in patients with high-risk comorbidities (see Table 2). There was a high LoA among the expert panel with all seven recommendations (range of mean LoA scores: 8.60–9.87).

The experts made recommendation #22 for laboratory monitoring of DMARDs based on their routine clinical practice, and recommendation #25 for collaboration as gastroenterologists/hepatologists may be more informed on the potential risk of adverse events from medications taken for comorbidities and infections. Together with the rheumatologist, they can use their knowledge of potential adverse drug reactions and interactions to make treatment

decisions for patients with RA to minimize the risk of immunosuppression.

Recommendation #28 is based on an ACR 2016 recommendation for patients with previous serious infections [15], since TNFi are known to increase the risk of serious infection (life-threatening or requiring intravenous antibiotics or hospitalization), and the risk of infections in patients treated with csDMARDs and abatacept is considered to be lower [38, 39].

Recommendation #31 is also based on an ACR 2016 recommendation [12]. A timeframe was included, because many treatment guidelines and experts recommend restricted use of immunosuppressive treatments for at least 5 years following a diagnosis of cancer [14, 40–44].

Screening and treatment of infections in patients with RA

The experts developed 17 recommendations for screening and treatment of infections in patients with RA (see Table 3 and Fig. 2). Overall, there was a high LoA among the expert panel for these recommendations (range of mean LoA scores: 8.00–10).

Tuberculosis Infection

Based on the assumption that all patients in the Kuwait population will have received BCG vaccination, a dual-screening strategy (i.e., any two of the following: QFT-GIT; T-Spot; TST) is required (recommendation #34; LoA: 8.27). IGRA are preferred in patients who have been vaccinated, because immunized patients may generate false TST-positive test results for several years after their vaccination; however, there may be an anergic response to the initial IGRA and implementing a dual-screening approach reduces the likelihood of a false negative outcome [45, 46]. Since all patients initiating DMARD therapy in Kuwait are considered to be at high risk of TB infection, it is anticipated that obtaining a baseline chest X-ray for patients (recommendation #35) will continue as standard practice.

The experts considered that Kuwaiti patients are at sufficient risk of tuberculosis (TB) infection [47] to recommend annual screening for LTBI in patients being treated for RA (recommendation #42; LoA: 8.00), in line with the evidence-based recommendation made by ACR in 2012 [14] and the 2016 update [15].

Viral hepatitis B infection

The experts recommended screening for HBV in all patients with RA prior to initiating DMARD treatment (recommendation #43; LoA: 9.87), since the immunosuppressive properties of some DMARDs can stimulate replication of HBV and precipitate severe flares of HBV infection [48–51].

Recommendation #44 (LoA: 9.53) for the screening of three serological markers of HBV is based on recommendations from the Centre for Disease Control to screen for all three markers in immunocompromised patients [52] and because HBV reactivation can occur in both HBsAg-positive and HBsAg-negative/HBcAb-positive patients with detectable HBV-DNA (occult HBV infection) during TNFi therapy [53]. Recommendation #46 (LoA: 9.87) regarding referral for hepatology evaluation suggests that a hepatologist decides whether the patient should be treated for HBV, or closely monitored for HBV reactivation, before immunosuppressive DMARDs treatments for RA are initiated [54, 55].

Viral hepatitis C infection

Recommendation #47 (LoA: 9.73) was made to identify those patients who should be treated with an HCV direct-acting antiviral agent and to avoid exposing patients with HCV infection to hepatotoxic immunosuppressive medications.

Recommendation #48 (LoA: 9.87) for the close monitoring (every 3 months) of serum aminotransferases and HCV RNA levels was deemed necessary for detecting HCV reactivation and liver damage [56–58]. Physicians should stop treatment with immunosuppressive TNFi treatment for RA in patients with evidence of either.

Treatment of RA during pregnancy and breastfeeding

Most of the 18 recommendations made by KAR regarding the treatment of RA during pregnancy and breastfeeding (see Table 4) are aligned with recommendations from EULAR, and the BSR/BHPR committee in 2016 [18, 21]. Overall, there was a high LoA among the expert panel for these recommendations (range of mean LoA scores: 8.73–10).

General Principles for the treatment of RA during pregnancy and breastfeeding

There was complete agreement among the expert panel with the KAR's general principles for the treatment of RA during pregnancy and breastfeeding. Recommendation #49 (LoA of 10.00) was made to limit the safety and teratogenicity risks associated with RA treatments.

In addition, recommendation #50 (LoA: 10.00) on the discussion of treatment options was made to encourage treating physicians to provide women with information on the risks of maintaining or discontinuing treatment for RA during pregnancy and breastfeeding, so that patients can make an informed, shared decision.

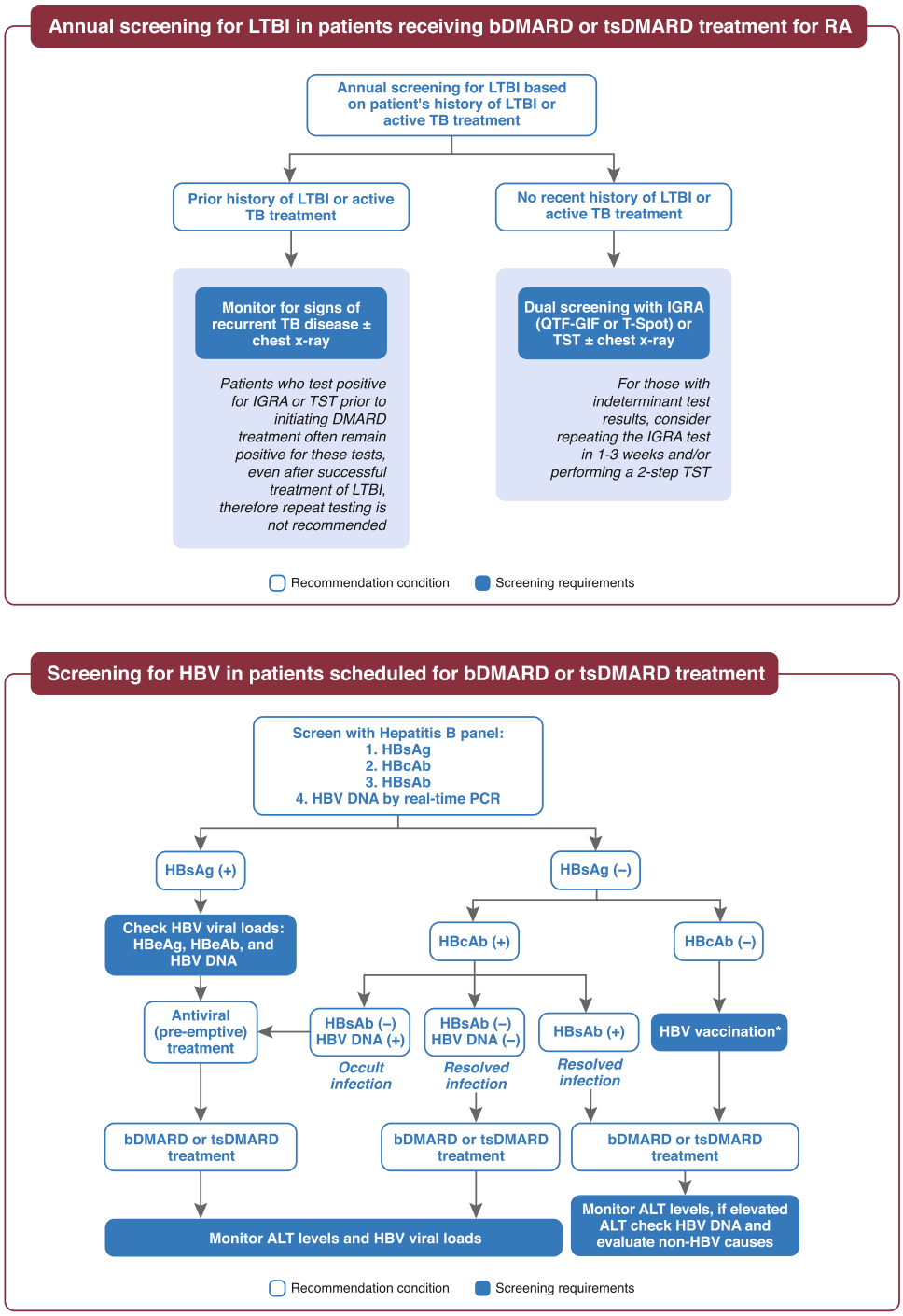

Fig. 2 Recommended algorithms for annual screening for latent tuberculosis infection in patients with RA and for testing viral hepatitis B reactivation in patients with RA prior to initiating DMARD treatment. The figure for HBV screening is adapted from Lan et al. [53]. *ALT* alanine aminotransferase, *anti-TNF* anti-tumor necrosis factor, *bDMARD* biological disease-modifying anti-rheumatic drug, *DNA* deoxyribonucleic acid, *HBcAb* antibody against HBV core antigen, *HBeAb* antibody against HBV envelope antigen, *HBeAg* HBV envelope antigen, *HBsAb* antibody against HBV surface antigen, *HBsAg* HBV surface antigen, *HBV* hepatitis B virus, *IGRA* interferon gamma release assay, *LTBI* latent tuberculosis infection, *PCR* polymerase chain reaction, *RA* rheumatoid arthritis, *TB* tuberculosis, *tsDMARD* targeted synthetic disease-modifying anti-rheumatic drug, *T-Spot* T-SPOT®.TB test, *TST* Mantoux tuberculin skin test, *QTF-GIF* Quantiferon®-TB gold in-tube test. *In patients with HBsAb titre below the immunoprotective level

csDMARDs and pregnancy

Recommendation #53 (LoA: 9.67) on immediate cessation of leflunomide during accidental pregnancy is in line with that made by the drug manufacturer, which is based on evidence of birth defects in animal models when leflunomide is taken during pregnancy [59].

bDMARDs and tsDMARDs

The recommendations regarding bDMARDs and tsDMARDs during pregnancy and breastfeeding, and lactation and DMARDs presented in Table 4 are aligned with EULAR recommendations [18], and adapted according to DMARDs licensed and available for use in Kuwait.

Discussion

These KAR 2018 treatment recommendations for RA represent the first guidelines designed specifically for treating patients with RA in Kuwait. The panel of experts consulted other national/international treatment guidelines for RA, conducted a pragmatic literature review, and drew upon their extensive experience of treating patients with RA in Kuwait, to develop these national treatment recommendations. The recommendations focus on the specific areas of early RA, established RA, patients with high-risk comorbidities, patients with RA during pregnancy and breastfeeding, and the screening and treatment of infections in patients with RA.

To inform the development of the treatment recommendations, KAR conducted a comprehensive review of other national/international treatment recommendations for RA and a pragmatic review of relevant, recently published literature. However, KAR did not independently evaluate the evidence-base underpinning the recommendations adopted from these other national/international treatment recommendations.

The KAR recommendations reported here have been tailored to the specific healthcare system and demographic patient profile for Kuwait. First, the recommendations have been adapted to include all pharmacological treatments for RA licensed for use in Kuwait, including JAK inhibitors; the safety and efficacy data for which have been published recently [12, 13, 60]. Second, there is a need for improved screening tools in Kuwait for chronic infections such as TB, HBV, and HCV. These recommendations address this unmet need by recommending a specific, internationally aligned pathway, for screening and treating these opportunistic infections in patients being treated for RA; 70% of the population in Kuwait are expatriates, a substantial proportion of whom are from countries where these chronic infections are endemic, such as India, Bangladesh, and the Philippines [23, 24, 61].

During the development of these recommendations, KAR carefully considered the difference in access to biologics between Kuwaiti and foreign national patients in Kuwait [62]. This difference in access to biologics may pose a barrier to the implementation of some recommendations regarding treatment with biologics. To implement recommendations regarding the screening and treatment of infections in RA, rheumatologists may require infectious disease training. The timing and cost-effectiveness of this were not taken into consideration during recommendation development, which may limit the implementation of these recommendations in clinical practice. A 'Patient Passport' to provide physicians with the patient's vaccination and screening history, and tools to screen the patient before initiating DMARD treatment, would help those without access to infectious disease training. However, it may be challenging to implement this as standard practice across both the public and private healthcare sectors of Kuwait.

The use of these recommendations for patients with RA will help to promote best practices and alignment in clinical decision making among rheumatologists in Kuwait, ultimately improving patients' treatment experience. Targeted analysis of KRRD data to evaluate the prevalence of comorbidities, chronic infections, and cancer among patient in Kuwait with RA, and examination of the impact of the recommended treatment algorithms on the proportion of patients achieving remission, will help inform future updates of these recommendations.

Conclusions

The KAR 2018 treatment recommendations for RA reported here are based on a synthesis and careful compilation and adaptation of other national/international guidelines, supporting medical literature, and expert consensus considering the Kuwaiti healthcare system and RA patient profile. These recommendations aim to inform the clinical decisions of rheumatologists treating patients in Kuwait, and to promote best practices, enhance alignment, and improve the treatment experience for patients.

Acknowledgements The authors thank Peter C. Taylor, MA, PhD, FRCP, FRCPE, for his independent review of the KAR 2018 Recommendations for RA. The authors also acknowledge Hinal Tanna, PhD, and Debbie Nixon, DPhil from Costello Medical, Cambridge, UK, for facilitating the recommendations meeting and surveys, and for medical writing and editorial assistance in preparing this manuscript for publication, based on the authors' input and direction.

Author contributions HA, FA, WAA, AAA, AA, AAE, NA, AAH, WA, AD, AAMG, EH, SH, KS, HT, and YA contributed to the conception, design, acquisition or analysis, and interpretation of the data. All authors approved the final version to be published after critically revising the manuscript for important intellectual content.

Funding The KAR received unrestricted funds for the development of the KAR 2018 treatment recommendations for patients with RA from Eli Lilly, NewBridge Pharmaceuticals, Roche, and Pfizer.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

References

1. Gibofsky A (2012) Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. Am J Manag Care 18(13 Suppl):S295–S302
2. Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T et al (2014) The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 73(7):1316–1322. https://doi.org/10.1136/annrheumdis-2013-204627
3. Al-Herz A, Al-Awadhi A, Saleh K, Al-Kandari W, Hasan E, Ghanem A et al (2016) A comparison of rheumatoid arthritis patients in Kuwait with other populations: results from the KRRD registry. Br J Med Med Res 14:1–11. https://doi.org/10.9734/BJMMR/2016/24673
4. van Vilsteren M, Boot CRL, Knol DL, van Schaardenburg D, Voskuyl AE, Steenbeek R et al (2015) Productivity at work and quality of life in patients with rheumatoid arthritis. BMC Musculoskelet Disord 16:107. https://doi.org/10.1186/s12891-015-0562-x
5. Gerhold K, Richter A, Schneider M, Bergerhausen H-J, Demary W, Liebhaber A et al (2015) Health-related quality of life in patients with long-standing rheumatoid arthritis in the era of biologics: data from the German biologics register RABBIT. Rheumatology 54(10):1858–1866. https://doi.org/10.1093/rheumatology/kev194
6. Finckh A, Liang MH, van Herckenrode CM, de Pablo P (2006) Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: a meta-analysis. Arthritis Rheum 55(6):864–872. https://doi.org/10.1002/art.22353
7. Goekoop-Ruiterman YM, de Vries-Bouwstra JK, Allaart CF et al (2007) Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med 146(6):406–415. https://doi.org/10.7326/0003-4819-146-6-200703200-00005
8. Aletaha D, Smolen JS (2018) Diagnosis and management of rheumatoid arthritis: a review. JAMA 320(13):1360–1372. https://doi.org/10.1001/jama.2018.13103
9. Pincus T, Ferraccioli G, Sokka T, Larsen A, Rau R, Kushner I et al (2002) Evidence from clinical trials and long-term observational studies that disease-modifying anti-rheumatic drugs slow radiographic progression in rheumatoid arthritis: updating a 1983 review. Rheumatology 41(12):1346–1356. https://doi.org/10.1093/rheumatology/41.12.1346
10. Combe B, Lula S, Boone C, Durez P (2018) Effects of biologic disease-modifying anti-rheumatic drugs on the radiographic progression of rheumatoid arthritis: a systematic literature review. Clin Exp Rheumatol 36(4):658–667
11. Smolen JS, van der Heijde D, Machold KP, Aletaha D, Landewé R (2014) Proposal for a new nomenclature of disease-modifying antirheumatic drugs. Ann Rheum Dis 73(1):3–5. https://doi.org/10.1136/annrheumdis-2013-204317
12. Rein P, Mueller RB (2017) Treatment with biologicals in rheumatoid arthritis: an overview. Rheumatol Ther 4(2):247–261. https://doi.org/10.1007/s40744-017-0073-3
13. Cohen S, Kay J (2017) Biosimilars: implications for rheumatoid arthritis therapy. Curr Opin Rheumatol 29(3):260–268. https://doi.org/10.1097/bor.0000000000000379
14. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM et al (2012) 2012 Update of the 2008 American College of Rheumatology (ACR) recommendations for the use of disease-modifying anti-rheumatic drugs and biologics in the treatment of rheumatoid arthritis (RA). Arthritis Care Res 64(5):625–639. https://doi.org/10.1002/acr.21641
15. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC et al (2016) 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 68(1):1–26. https://doi.org/10.1002/art.39480
16. Combe B, Landewé R, Daien CI, Hua C, Aletaha D, Alvaro-Gracia JM et al (2017) 2016 Update of the EULAR recommendations for the management of early arthritis. Ann Rheum Dis 76(6):948–959. https://doi.org/10.1136/annrheumdis-2016-210602
17. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M et al (2017) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 76(6):960–977. https://doi.org/10.1136/annrheumdis-2016-210715
18. Gotestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C et al (2016) The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis 75(5):795–810. https://doi.org/10.1136/annrheumdis-2015-208840
19. Bykerk VP, Akhavan P, Hazlewood GS, Schieir O, Dooley A, Haraoui B et al (2012) Canadian Rheumatology Association recommendations for pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs. J Rheumatol 39(8):1559–1582. https://doi.org/10.3899/jrheum.110207
20. Lau CS, Chia F, Harrison A, Hsieh TY, Jain R, Jung SM et al (2015) APLAR rheumatoid arthritis treatment recommendations. Int J Rheum Dis 18(7):685–713. https://doi.org/10.1111/1756-185x.12754
21. Flint J, Panchal S, Hurrell A, van de Venne M, Gayed M, Schreiber K et al (2016) BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology 55(9):1693–1697. https://doi.org/10.1093/rheumatology/kev404
22. World Population Review (2018) Kuwait population 2018. https://Worldpopulationreview.Com/Countries/Kuwait-Population/. Accessed 10 Jan 2019
23. The Public Authority for Civil Information (2015) Kuwait stat app for statistical services. Statistical Services System. https://www.paci.gov.kw/stat/default.aspx. Accessed 23 Oct 2018
24. World Health Organization (2018) Global tuberculosis report 2018. https://www.who.int/tb/publications/global_report/en/. Accessed 23 Oct 2018
25. Bannwarth B, Pehourcq F, Schaeverbeke T, Dehais J (1996) Clinical pharmacokinetics of low-dose pulse methotrexate in rheumatoid arthritis. Clin Pharmacokinet 30(3):194–210
26. de Jong PH, Hazes JM, Barendregt PJ, Huisman M, van Zeben D, van der Lubbe PA et al (2012) Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: first results of the tREACH trial. Ann Rheum Dis 72(1):72–78. https://doi.org/10.1136/annrheumdis-2011-201162
27. Benucci M, Saviola G, Manfredi M, Sarzi-Puttini P, Atzeni F (2011) Cost effectiveness analysis of disease-modifying antirheumatic drugs in rheumatoid arthritis: a systematic review literature. Int J Rheumatol 2011:845496. https://doi.org/10.1155/2011/845496
28. Choy E, Aletaha D, Behrens F, Finckh A, Gomez-Reino J, Gottenberg JE et al (2017) Monotherapy with biologic disease-modifying anti-rheumatic drugs in rheumatoid arthritis. Rheumatology 56(5):689–697. https://doi.org/10.1093/rheumatology/kew271
29. Hoekstra M, Haagsma C, Neef C, Proost J, Knuif A, van de Laar M (2004) Bioavailability of higher dose methotrexate comparing oral and subcutaneous administration in patients with rheumatoid arthritis. J Rheumatol 31(4):645–648
30. Goodman SM, Cronstein BN, Bykerk VP (2015) Outcomes related to methotrexate dose and route of administration in

patients with rheumatoid arthritis: a systematic literature review. Clin Exp Rheumatol 33(2):272–278
31. Cohen SB, Tanaka Y, Mariette X, Curtis JR, Lee EB, Nash P et al (2017) Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. Ann Rheum Dis 76(7):1253–62. https://doi.org/10.1136/annrheumdis-2016-210457
32. Keystone EC, Genovese MC, Schlichting DE, de la Torre I, Beattie SD, Rooney TP et al (2018) Safety and efficacy of baricitinib through 128 weeks in an open-label, long-term extension study in patients with rheumatoid arthritis. J Rheumatol 45(1):14–21. https://doi.org/10.3899/jrheum.161161
33. Burmester G-R, Kivitz AJ, Kupper H, Arulmani U, Florentinus S, Goss SL et al (2015) Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised concerto trial. Ann Rheum Dis 74(6):1037–1044. https://doi.org/10.1136/annrheumdis-2013-204769
34. Martinez-Feito A, Plasencia-Rodriguez C, Navarro-Compan V, Hernandez-Breijo B, Gonzalez MA, Monjo I et al (2019) The effect of methotrexate versus other disease-modifying antirheumatic drugs on serum drug levels and clinical response in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors. Clin Rheumatol 38(3):949–954. https://doi.org/10.1007/s10067-018-4355-0
35. Karlsson JA, Kristensen LE, Kapetanovic MC, Gülfe A, Saxne T, Geborek P (2008) Treatment response to a second or third TNF-inhibitor in RA: results from the South Swedish Arthritis Treatment Group Register. Rheumatology 47(4):507–513. https://doi.org/10.1093/rheumatology/ken034
36. Schett G, Emery P, Tanaka Y, Burmester G, Pisetsky DS, Naredo E et al (2016) Tapering biologic and conventional DMARD therapy in rheumatoid arthritis: current evidence and future directions. Ann Rheum Dis 75(8):1428–1437. https://doi.org/10.1136/annrheumdis-2016-209201
37. van der Woude D, Young A, Jayakumar K, Mertens BJ, Toes RE, van der Heijde D et al (2009) Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: results from two large early arthritis cohorts. Arthritis Rheum 60(8):2262–2271. https://doi.org/10.1002/art.24661
38. Salliot C, Dougados M, Gossec L (2009) Risk of serious infections during rituximab, abatacept and anakinra therapies for rheumatoid arthritis: meta-analyses of randomized placebo-controlled trials. Ann Rheum Dis 68(1):25–32. https://doi.org/10.1136/ard.2007.083188
39. Yun H, Xie F, Delzell E, Levitan EB, Chen L, Lewis JD et al (2016) Comparative risk of hospitalized infection associated with biologic agents in rheumatoid arthritis patients enrolled in Medicare. Arthritis Rheumatol 68(1):56–66. https://doi.org/10.1002/art.39399
40. Bernheim O, Colombel JF, Ullman TA, Laharie D, Beaugerie L, Itzkowitz SH (2013) The management of immunosuppression in patients with inflammatory bowel disease and cancer. Gut 62(11):1523–1528. https://doi.org/10.1136/gutjnl-2013-305300
41. Laharie D (2014) Previous cancer and/or lymphoma in patients with refractory IBD–Pro: anti-TNF or immunosuppressive treatment. Dig Dis (Basel, Switzerland) 32(Suppl 1):116–21. https://doi.org/10.1159/000367861
42. Mantzaris GJ (2014) Previous cancer and/or lymphoma in patients with refractory IBD–Con: anti-TNF or conventional immunosuppressive treatment. Digestive Diseases (Basel, Switzerland) 32(Suppl 1):122–127. https://doi.org/10.1159/000367862
43. Elandt K, Aletaha D (2011) Treating rheumatic patients with a malignancy. Arthritis Res Ther 13(3):223. https://doi.org/10.1186/ar3352
44. Bombardier C, Hazlewood GS, Akhavan P, Schieir O, Dooley A, Haraoui B et al (2012) Canadian Rheumatology Association recommendations for the pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs: Part II Safety. J Rheumatol 39(8):1583–1602. https://doi.org/10.3899/jrheum.120165
45. Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K (2010) Updated guidelines for using interferon gamma release assays to detect mycobacterium tuberculosis infection—United States, 2010. MMWR recommendations and reports: morbidity and mortality weekly report 59(RR-5):1-25
46. Winthrop KL, Weinblatt ME, Daley CL (2012) You can't always get what you want, but if you try sometimes (with two tests—TST and IGRA—for tuberculosis) you get what you need. Ann Rheum Dis 71(11):1757–1760. https://doi.org/10.1136/annrheumdis-2012-201979
47. Akhtar S, Mohammad HG (2008) Seasonality in pulmonary tuberculosis among migrant workers entering Kuwait. BMC Infect Dis 8:3. https://doi.org/10.1186/1471-2334-8-3
48. Lubel JS, Testro AG, Angus PW (2007) Hepatitis B virus reactivation following immunosuppressive therapy: guidelines for prevention and management. Intern Med J 37(10):705–712. https://doi.org/10.1111/j.1445-5994.2007.01479.x
49. Lok ASF, Ward JW, Perrillo RP, McMahon BJ, Liang TJ (2012) Reactivation of hepatitis B during immunosuppressive therapy: potentially fatal yet preventable. Ann Intern Med 156(10):743–745. https://doi.org/10.1059/0003-4819-156-10-201205150-00013
50. Yang CH, Wu TS, Chiu CT (2007) Chronic hepatitis B reactivation: a word of caution regarding the use of systemic glucocorticosteroid therapy. Br J Dermatol 157(3):587–590. https://doi.org/10.1111/j.1365-2133.2007.08058.x
51. Burton MJ, Curtis JR, Yang S, Chen L, Singh JA, Mikuls TR et al (2015) Safety of biologic and non-biologic disease-modifying antirheumatic drug therapy in veterans with rheumatoid arthritis and hepatitis B virus infection: a retrospective cohort study. Arthritis Res Ther 17(1):136. https://doi.org/10.1186/s13075-015-0628-z
52. Weinbaum CM, Mast EE, Ward JW (2009) Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. Hepatology 49(Suppl 5):S35–S44. https://doi.org/10.1002/hep.22882
53. Lan JL, Chen YM, Hsieh TY, Chen YH, Hsieh CW, Chen DY et al (2011) Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor alpha therapy. Ann Rheum Dis 70(10):1719–1725. https://doi.org/10.1136/ard.2010.148783
54. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT (2015) American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 148(1):215–219. https://doi.org/10.1053/j.gastro.2014.10.039
55. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM et al (2018) Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 67(4):1560–1599. https://doi.org/10.1002/hep.29800
56. Zechini B, Pasquazzi C, Aceti A (2004) Correlation of serum aminotransferases with HCV RNA levels and histological findings in patients with chronic hepatitis C: the role of serum aspartate transaminase in the evaluation of disease progression. Eur J Gastroenterol Hepatol 16(9):891–896
57. Pompili M, Biolato M, Miele L, Grieco A (2013) Tumor necrosis factor-alpha inhibitors and chronic hepatitis C: a comprehensive literature review. World J Gastroenterol 19(44):7867–7873. https://doi.org/10.3748/wjg.v19.i44.7867

58. Karadağ Ö, Kaşifoğlu T, Özer B, Kaymakoğlu S, Kuş Y, İnanç M et al (2016) Viral hepatitis screening guideline before biological drug use in rheumatic patients. Eur J Rheumatol 3(1):25–28. https://doi.org/10.5152/eurjrheum.2015.150072
59. Krause ML, Amin S, Makol A (2014) Use of DMARDs and biologics during pregnancy and lactation in rheumatoid arthritis: what the rheumatologist needs to know. Ther Adv Musculoskelet Dis 6(5):169–184. https://doi.org/10.1177/1759720X14551568
60. Choy EHS, Miceli-Richard C, González-Gay MA, Sinigaglia L, Schlichting DE, Meszaros G et al (2019) The effect of JAK1/JAK2 inhibition in rheumatoid arthritis: efficacy and safety of baricitinib. Clin Exp Rheumatol 37(4):694–670
61. Ameen R, Sanad N, Al-Shemmari S, Siddique I, Chowdhury RI, Al-Hamdan S et al (2005) Prevalence of viral markers among first-time Arab blood donors in Kuwait. Transfusion 45(12):1973–1980. https://doi.org/10.1111/j.1537-2995.2005.00635.x
62. Al-Herz ASK, Al-Awadhi A, Al-Kandari W, Hasan E, Ghanem A, Ali Y et al (2018) Easy accessibility of biologics and its impact on disease activity and quality of life in Kuwaiti patients with rheumatoid arthritis [Abstract]. Arthritis Rheumatol 70(Suppl 9):624
63. Norton BL, Holland DP (2012) Current management options for latent tuberculosis: a review. Infect Drug Resist 5:163–173. https://doi.org/10.2147/idr.s29180