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Egyptian guidelines for the treatment of Rheumatoid Arthritis — 2022 update

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Abstract

Background: Busy rheumatologists, and busy patients as well as policy makers, require accurate, succinct, transparent, easily digested summaries of evidence and recommendations for management. Our objective was to develop an up-to-date evidence-based, consensus, clinical practice guidelines for treat-to-target management of rheumatoid arthritis in adults.

Results: Ninety-four (94.7%) of the expert committee completed the 2-round e-Delphi surveys. A total of 33 recommendation items, addressing the main rheumatoid arthritis (RA) domains, were identified. The level of agreement (rate 7–9), for the statements which reached consensus, ranged from 85 to 100%. Consensus was achieved on the wording of all the clinical practice guidelines identified by the scientific committee. A management algorithm for the management of rheumatoid arthritis have been developed.

Conclusion: These updated recommendations reflect the most recent evidence for the management of RA. It also outlines the multidisciplinary team role in enhancing the RA patients' care. The recommendations offer strategies to achieve optimum treat-to-target outcomes. However, standards of care are defined based on the clinical data obtained for individual patients and are prone to modification. High-quality, broad scope evidence-based clinical practice guidelines offer a path for bridging the gap between best practice, policy, local settings and patients' choice.

Keywords: Rheumatoid arthritis, DMARDs, Biologic therapy, Treatment guidelines, Treat to target

Introduction

Since the publication of the original Egyptian recommendations for treatment of rheumatoid arthritis (RA) [1], a chronic inflammatory disease that causes joint pain, swelling, stiffness and impaired function, there has been a dramatic expansion of the available treatment options for the disease. At the same time, healthcare professionals and researchers are attaining new experiences and knowledge about the efficacy as well as safety of those treatment modalities which warrant further consideration of the recommended management algorithm. In concordance, novel measures of imaging modalities and patient educational tools [2] give the patients more information, allowing them to be more informed and involved in the shared decision-making process.

Although the main target of these guidelines is primarily rheumatologists and aims to make informed decisions about patients' management, they are also valuable for people living with RA as well as health policymakers. In 2020, the Egyptian health authorities have launched a nationwide Universal Health Insurance System, aiming to ensure that all Egyptians have comprehensive health care for all family members in the 'New Republic' [3]. Setting

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up guidelines for management plays a vital role in the patients' management process. The Egyptian Academy of Rheumatology launched the clinical, evidence-based guidelines (CEG) initiative protocol which was accepted by the local ethical committee. The overarching principle was to produce an up-to-date evidence-based consensus, clinical practice recommendations for treat-to-target management of the different rheumatic disorders. Therefore, an update to the earlier published recommendations for management of rheumatoid arthritis patients was required, including a critical analysis and evaluation of the more recent literature.

Methods

Design

A multistep process strategy was adopted to develop the RA evidence-based, consensus management recommendations. The CEG guideline development process protocol was the standard based on which study design was formulated. The consensus was achieved based on the current scientific evidence and clinical knowledge. The aim was to determine the extent to which experts agree about a particular issue, with the ultimate goal of providing a unified expert opinion. The manuscript followed the guidelines for reporting systematic reviews and meta-analyses [4].

Study teams

Core team

To supervise, coordinate, and assist with developing the scope of the project and initial clinical questions, nominating the expert panel and drafting the manuscript. The core team also shared in identifying the project's scope and the PICOT key questions addressed for this update.

Key questions used to develop the guideline

This management recommendations were centred on a sequence of organized key clinical questions that outline the targeted patients, the intervention, investigation, the comparison(s) used, the outcomes used to measure efficacy, effectiveness, or risk as well as time (PICOT) [5]. The evidence to respond to the key questions was gathered according to the following phases: the clinical questions formulation, configuring the questions, check for the evidence, critical analysis and assortment of evidence, results presentation, and guideline statements. These questions, shown in Table 1, formed the foundation of the systematic review search and subsequently the clinical standards for patients' care.

Literature review team

Led by an experienced literature review consultant, the review team reviewed full-text publications and rated the quality of evidence. Literature was also searched for best practice recommendations for joint imaging. This search for best practice evidence was based on the specific core items and domains included in the clinical research questions addressing the different aspects of RA management. An expert in methodology helped in conducting the literature review.

Data sources

To acquire best practice evidence for clinical recommendations development, the PubMed/ MEDLINE, Embase and Cochrane databases were searched. Based on the

Table 1 Levels of evidence

Level of evidence	
1a	SR (with homogeneity*) of RCTs
1b	Individual RCT (with narrow confidence interval)
1c	All or none
2a	SR (with homogeneity*) of cohort studies
2b	Individual cohort study (including low-quality RCT, e.g. < 80% follow-up)
2c	'Outcomes' research; ecological studies
3a	SR (with homogeneity*) of case-control studies
3b	Individual case-control study
4	Case series (and poor-quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal or based on physiology, bench research, or 'first principles'
Grades of recommendation	
A	Consistent level 1 studies
B	Consistent levels 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from levels 2 or 3 studies
D	Level 5 evidence or troubling, inconsistent, or inconclusive studies of any level

SR Systematic review, *RCT* Randomized controlled trial

outcomes of the systematic review and their own clinical experience, the committee compiled a comprehensive list of proposals for the management of RA. The quality and level of evidence [6, 7] were also identified for each category according to the Oxford Centre for Evidence-based Medicine (CEBM) system [7].

Study selection

The boundaries of the systematic review were set according to the inclusion and exclusion criteria aiming at identifying the relevant studies.

Inclusion criteria

Eligibility criteria were based on the PICO approach, study design, and date.

Inclusion criteria included the following:

(a) Manuscripts published as guidelines
(b) Guidelines providing endorsements on RA general management of RA
(c) Guidelines including a range of different medical therapies
(d) Guidelines published from January 2010 to May 2022
(e) Guidelines published in English
(f) Systematic reviews, randomized controlled trials (RCTs), uncontrolled trials, observational studies including cohort, case control and cross-sectional studies or those where economic evaluation was made

The included publications should include the identification criteria of classification, evidence and recommendations. Also, the formal process for developing the management recommendations (Delphi exercise, panel conference) should be delineated.

Exclusion criteria

The exclusion criteria included the following: (a) when there were different versions of the guidelines from the same health authority available, only the most recent one was included. (b) Editorials, commentaries, conference abstracts, and non-evidence-based narrative/personal reviews, manuscripts lacking of English version, were excluded.

Expert panel

Those who will be appointed by the core team. The participants should have the professional knowledge, training, and experience in the field of RA, with active participation in scientific research in this field, years of expertise of the involved experts ranged from 12 to 44 years.

Target audience

The guideline will be of particular interest to healthcare professionals who treat and manage patients with RA, mainly the rheumatologists. The guideline should also provide a helpful resource to general practitioners, physiotherapists, dieticians, and pharmacists as well as patients and those in the National Health Service who are in charge of commissioning the care for RA patients.

Delphi

The Delphi technique is a well-established approach to gather expert-based verdicts to aiming at using them to identify a consensus. Its methodology is based on a series of several 'rounds' of questionnaires directed to experts committee [8].

Consensus process

Two Delphi rounds were completed to achieve consensus regarding the rheumatoid arthritis treat-to-target (T2T) management approach. In round 1, each participant was invited to rank 13 key clinical research questions. In round 2, the participants received individualized survey including 33 statements across forming the main items to consider in the T2T strategy of RA.

Voting process

Live voting was delivered in two online rounds limited within a pre-specified time. All the task force participants were asked to contribute and were pre-informed of the start-end times of each voting round. Every participant received a unique access link, and anonymous votes were collected and processed. Responses were evaluated and analysed independently. Comments raised by the participants on the different statements regarding its 're-phrasing, potential ambiguity, unidentified overlaps' were gathered after each round and evaluated by the core team.

Rating

The members of the expert panel were asked to rate each statement in the range of 1–9 where 1 indicates 'complete disagreement' and 9 indicate 'complete agreement'. Generally, responses can be stratified such as follows: 1–3: represent disagreement, 4–6: represent uncertainty, and 7–9: represent agreement. Voters were advised that it was not mandatory to vote on all statements, and that they may refrain from ranking any statement if it falls outside their area of speciality. An 'uncertainty' vote represents 'inconvenience about the accuracy of the recommendation'. All statements were open for the entry of comments. The members

were urged to leave comments, particularly wherever they vote a disagreement. Ranks of each item were recorded and mean and standard deviation calculated and entered anonymously into a database.

Definition of consensus

Before data analyses, it was determined that statements require 80% agreement in order to ignore or accept a statement. A total of 80% was selected as a proper cutoff point based on the study carried out by Lynn [11] who concluded that an 80% consensus reflect content validity of the statement. Achieving 80% agreement (scores 7–9) would, consequently, qualify the statements to become a recommendation in this guideline. Similarly, 80% disagreement (scores 1–3) means that this statement will be omitted [8–10]. If the rate came in the uncertainty score (4–6), this specific statement should be revised in view of the comments. If after the second round of votes, all votes on a statement fell into the agreement bracket (7–9), the levels of agreement on the statement of recommendation were defined as 'high' [12].

Developing the clinical care standards framework

Based on the outcomes of the Delphi process, a structured template was established to facilitate standardized identification of the variable treatment recommendation constituents. For each constituent, the format in which the recommendations/information to be delivered has been identified.

Chronogram of Delphi rounds

The first round took place between 20 and 24 November 2021 (5 days). The aspects identified as ignore or need amendment have been identified in view of the first Delphi round outcomes. Statements that needed reconsideration were revised in view of the participants' comments and included in the second round. The second round took place on the 29th of November 2021 (5 days after the first round) and lasted for 8 days (until the 6th of December 2021).

Ethical aspects

This study was performed in accordance with the Helsinki Declaration. The Clinical, Evidence-based, Guidelines (CEG) initiative protocol was approved the local ethical committee: ethical approval code: 34842/8/21, ethical board Tanta University. Written ethics approval from the experts sharing in this work was deemed unnecessary according to national regulations.

Results

Literature research and evidence selection

By using a search strategy, we identified 9895 possibly relevant studies during the research selection phase. A total of 9663 were excluded: 1068 duplicates and 8595 by title and abstract screening (studies did not examine population or intervention of interest, did not match study design of interest, or did not report outcome measures of interest). As a result, 232 studies were selected for full article evaluation. Due to the fact that 198 research did not provide evidence that matched the PICOT strategy, only 34 studies were considered in this study (Fig. 1). The level of evidence and grades of recommendations were mentioned in Table 1.

Expert panel characteristics:

The Delphi form was sent to expert panel ($n = 19$), of whom 18 (94.7%) completed in the two rounds. The participants were from governorates and health centres throughout Egypt: Ain Shams University ($n = 6$, 33.33 %), Cairo University ($n = 2$, 11.11%), Tanta University ($n = 2$, 11.11%), Benha University ($n = 2$, 11.11%), Fayoum University ($n = 1$, 5.55%), Zagazig University ($n = 1$, 5.55%), Assiut University ($n = 1$, 5.55%), Minia University ($n = 1$, 5.55%), and Mansoura University ($n = 1$, 5.55%), in addition to ($n = 1$, 5.55%) international expert from the UK.

Table 2 showed general considerations and treat-to-target strategy for RA management, while Table 3 showed disease monitoring and remission parameters.

Delphi round 1

This round was dedicated to the key clinical questions, which included 13 items (Table 4) including the following:

- Overarching principles about RA diagnosis and assessment, disease remission, and low disease activity
- How to monitor RA?
- The target(s) of treatment (how to treat to target?)
- Patient communication and shared decision-making, RA management, and drug tapering in RA management
- How to personalize the patient care?
- The non-pharmacological management in RA and the role of self-management in the treatment of RA

The experts' panel responded 94.7% (18/19) in round 1. The participant who did not share in round-1 Delphi was excluded from round 2. All domains and questions

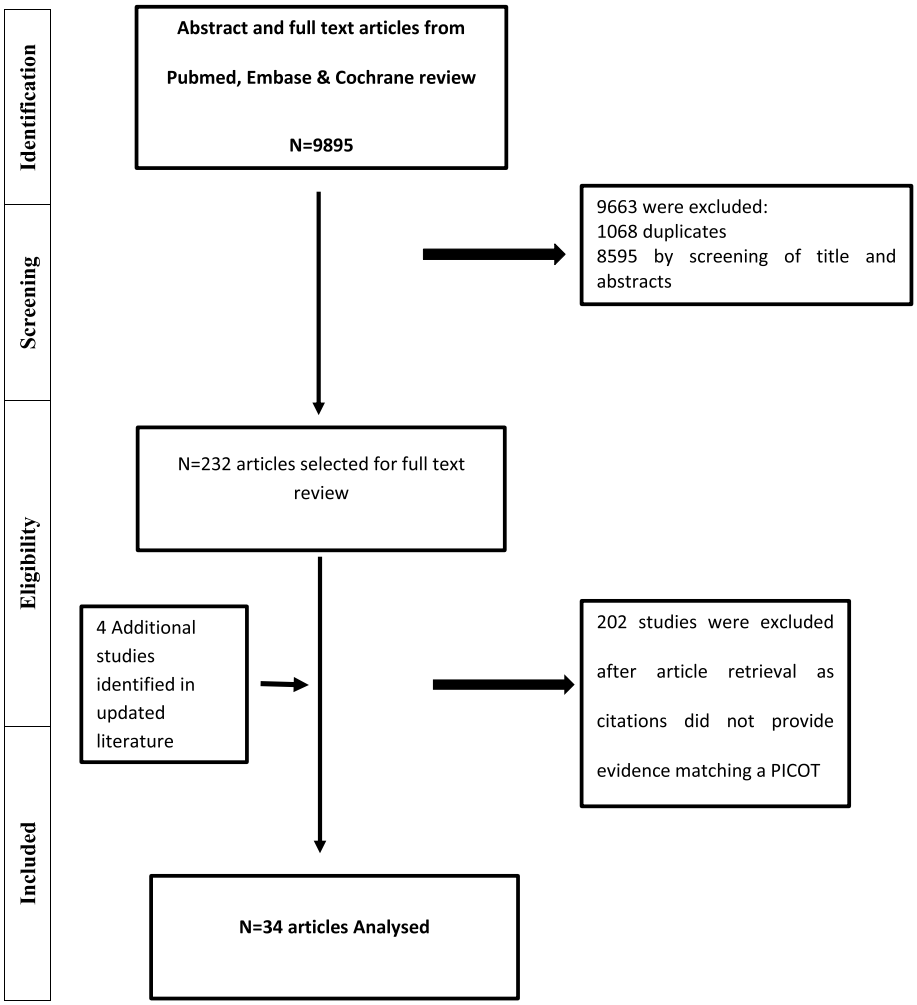

Fig. 1 Flow chart for the systematic review process. PICOT, patient/population, intervention, comparison, outcomes, and time

were agreed upon (with 80% of respondents strongly agreeing or agreeing), and no questions were retired.

Delphi round 2

Based on the literature research, a list of 33 recommended suggestions was generated using the input from round 1. The response rate for round 2 was 100% from the experts' panel (18/18). Wording modifications were suggested for 9 statements. The statements were modified and amended. For all statements, the consensus was reached (as $\geq$ 80% of respondents strongly agreed or agreed).

Based on those results, this document was written, containing the answers to the key clinical questions which entail recommendations for the management of RA (Table 5).

Algorithm of these recommendations was demonstrated in Fig. 2; personalized care was demonstrated in Fig. 3.

Types of DMARDs used are as follows:

Synthetic DMARDs

- (csDMARDs): Conventional here implies that they have entered the treatment armament for RA in a conventional historic way that involved fortuitous and empiric findings of disease-modifying efficacy (e.g. methotrexate, leflunomide, sulfasalazine, hydroxychloroquine).
- Targeted synthetic DMARDs: Chemical (oral) drugs that are developed by modelling them to interact with specific, well-defined molecules or known structures, particularly aiming to inhibit their active sites, e.g. baricitinib, tofacitinib, and upadacitinib.

Table 2 Overarching principles and treat-to-target strategy

Standard	Statement	Mean rate ± SD	% of agreement	Level of agreement
General considerations	1. RA patients should be looked after by rheumatologists 2. RA diagnosis is mainly clinical depending on the evaluation of an expert rheumatologist (some aiding tools such as musculoskeletal ultrasound (MSUS) could aid in the diagnosis and disease assessment). The classification criteria are for classifying the disease not for diagnosis 3. Continuous assessment of RA patient regarding (prognostic factors, disease activity, and severity & functional status) is important for optimum management decision 4. Ultrasound can be used in routine monitoring of disease activity, adjustment of the DMARD dose, or guided local injection in adults with RA 5. Treatment should be started as soon as the diagnosis of RA is made 6. Treatment should be individualized to meet the patient requirement 7. Treatment of patients with RA should be based on a shared decision between the patient and the rheumatologist 8. When choosing a treatment plans, consider the patient's motivation, comorbidities, functional ability, structural damage development (as determined by imaging or sonography), and disease activity level 9. Early in the treatment course, rheumatologist should frequently monitor the active disease (every 1–3 months) and then get less frequent (every 3–6 months) 10. Clinical and ultrasound disease activity should be assessed regularly 11. Within 3 months of treatment, at least a 50% improvement in disease activity should be reached and the target within 6 months 12. Adequate response to treatment at 6 months is considered if DAS-28 score improved by 1.2 13. Treatment should be continuously adjusted until achieving the target 14. Once the treatment target has been achieved, it should be sustained. Continuous monitoring should be carried out to ensure maintenance of the target 15. Regular assessment of comorbidities is essential in the management strategy	8.27 ± 1.7	100	H
Treat-to-target strategy	1. Treat-to-target strategies: sustained clinical remission (as defined by the American College of Rheumatology-(ACR)-EULAR Boolean or index criteria) or low disease activity is advised to be adopted 2. Controlling signs and symptoms, avoiding structural damage, comorbid conditions, drug toxicity, and optimizing function, growth and development, quality of life, and social engagement are the main objectives of treating RA patients 3. Whenever feasible, it is desirable to adopt the least expensive kind of treatment 4. Before cDMARD therapy, all the patients should be screed for full blood count, liver and kidney functions, and hepatitis C and hepatitis B status. Baseline chest X-ray is also advised. Before commencing biologic therapy, all the patients should have the above-mentioned tests as well as test for latent tuberculosis (T-spot/IGRA test) 5. MTX should be part of the first treatment strategy 6. Treat to target involves monitoring disease activity often and modifying the therapy as necessary to meet treatment objectives	8.55 ± 0.61	100	H

Table 2 (continued)

Standard	Statement	Mean rate ± SD	% of agreement	Level of agreement
	7. Disease SUSTAINED remission is the main goal for treating RA patients (clinical, ultrasonographic, and functional) 8. Another goal is to achieve minimal (or low) disease activity, which is measured by clinical, ultrasonographic, and functional measures, especially in individuals with refractory, chronic diseases 9. For those who have a higher risk of radiological advancement, think about making remission the aim rather than minimal disease activity (the presence of anti-CCP antibodies or erosions on X-ray at baseline assessment) 10. Until the goal of remission or low disease activity is achieved, measure C-reactive protein (CRP) and disease activity (using a composite score such the DAS-28) monthly in a specialist care programme for persons with active RA 11. Difficult to treat/refractory arthritis cases should be identified, assessed for the underlying causes, and managed on individual bases			

MSUS Musculoskeletal ultrasound, *RA* Rheumatoid arthritis, *DMARDs* Disease-modifying antirheumatic drugs, *DAS* Disease activity score, *MTX* Methotrexate

Biological DMARDs: Drugs which made using biotechnology. They are genetically engineered to act like natural proteins in the immune system.

- Biological originator DMARDs (TNFi: adalimumab, etanercept, certolizumab, golimumab, infliximab; IL-6Ri: tocilizumab, sarilumab; Costimulation-i: abatacept; anti-B cell (CD20): rituximab)
- Biosimilar DMARDs(currently for: adalimumab, etanercept, infliximab, rituximab)

Communication, shared decision-making, self-management, and education

1. Explain the risks and benefits of treatment options to adults with RA in ways that can be easily understood. Throughout the course of their disease, offer them the opportunity to talk about and agree all aspects of their care and respect the decisions they make.

2. Implement shared decision-making in the management process. Offer verbal and written information to adults with RA as follows:

- Improve their understanding of the condition and its management.
- Counter any misconceptions they may have.

3. Adults with RA who wish to know more about their disease and its management should be offered the opportunity to take part in existing educational activities, including self-management programmes.

Discussion

This updated guidelines for rheumatoid arthritis management include recommendations on referral, diagnosis, investigations, and treatment. It aims to improve quality of life and prevent joint damage by ensuring that people with rheumatoid arthritis receive the appropriate treatment protocols adopting a treat-to-target strategy. The guidelines summarize the current medical knowledge, weight the benefits and harms of diagnostic procedures and treatments, and give specific recommendations based on this information and on experts' experience.

The developed guidelines are in general in agreement with the most recently published guidelines for the management of rheumatoid arthritis [13–16]. In addition to the quality presented, the developed guidelines not only addressed on the pharmacotherapy of rheumatoid arthritis but also consider the 'non-pharmacologic' approaches (such as quality of life, patient education, lifestyle advice, as well as self-management) offering a broad scope. This comes in contrast to the 2021-ACR [14] guidelines which focussed only on medication therapies to treat rheumatoid arthritis. The guidelines also endorse the use of short-term glucocorticoids when initiating or changing conventional DMARDs (this can be in the form of variable dose regimens and routes of administration). The steroid should not be used as long-term therapy but should be tapered and stopped as swiftly as clinically possible. This is in agreement with the EULAR guidelines [15] and in relative agreement with the ACR 2021 guidelines [14] which reported very low to moderate evidence assigned to the use of glucocorticoids, particularly for patients

Table 3 Disease monitoring and remission parameters

Standard	Statement	Mean rate ± SD	% of agreement	Level of agreement
Disease remission	• Clinical remission: DAS-28: < 2.6 • Ultrasound remission • Functional good outcome: remission or minimal disease activity Health Assessment Questionnaire (HAQ, 0–3) < 0.5	8.5 ± 0.78	94.4%	H
Low disease activity	• Clinical: DAS-28 between 2.6 and 3.2 • Ultrasound: grade 1 in power Doppler ultrasonography (PDUS) • Functional good outcome: remission or low disease activity Health Assessment Questionnaire (HAQ, 0–3) < 0.5	8.5 ± 0.78	94.4%	H
Monitoring:	Patients with active RA should be closely monitored on a regular basis, whether they are starting treatment or have seen a flare-up of their disease activity. As a result, it is possible to increase the dosage of disease-modifying antirheumatic drugs (DMARDs), determine whether short-term glucocorticoid bridging therapy is necessary, determine how well patients are handling their medication regimen, monitor side effects, offer support, and promote adherence. The best method for keeping track of and controlling active illness status is disease activity During the disease course, while monitoring RA patients as follows: A) Ensure that all adults with RA have the following: 1. Rapid access to specialist care for flares (hot clinic) 2. Information about when and how to access specialist care 3. Ongoing drug monitoring B) Monitoring should be frequent in active disease or after initiation of DMARD therapy (whether conventional, biologic, or synthetic), every 1–3 months. If there is no improvement by, at most, 3 months, after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted. After achieving treatment target (remission or low disease activity), consider a review appointment to take place every 3–6 months to ensure that the target has been maintained C. Offer all adults with RA, including those who have achieved the treatment target, an annual review to the following: ○ Assess disease activity and damage and measure functional ability ○ Check for the development of comorbidities, such as hypertension, ischemic heart disease, osteoporosis, and depression ○ Assess symptoms that suggest complications, such as vasculitis and disease of the cervical spine, lung, or eyes ○ Organize appropriate cross referral within the multidisciplinary team ○ Assess the need for referral for surgery ○ Assess the effect the disease is having on a person's life ○ Assess the comorbidity status	8.72 ± 0.46	100%	H

HAQ Health assessment questionnaire, *PDUS* Power Doppler ultrasound, *RA* Rheumatoid arthritis, *cDMARDs* Conventional disease-modifying antirheumatic drugs, *DAS* Disease activity score

taking glucocorticoids to remain at target. Furthermore, this guidelines recommended that for those patients who do not achieve the target after taking the first conventional DMARD for 3 months, and in the absence of poor prognostic factors, the use of another conventional DMARDs, either as mono- or combination therapy, is advised rather than using biologic therapy. By 6 months of conventional DMARDs therapy, biologic therapy can be added for those patients whose disease activity is high or moderate and have poor prognostic factors.

Judgments about evidence and recommendations are complex; therefore, formulation of guidelines should be based on clear questions. Principally, any question addressing clinical management has four components: patients, an intervention, a comparison, and the outcomes of interest [17]. Grading the quality of evidence and the strength of recommendations is vital for this purpose. In this work, we implemented the Oxford Centre for Evidence-based Medicine (CEBM) system [7], which is in agreement with the EULAR guidelines for rheumatoid arthritis [15]. In contrast, the ACR adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [18]. While the Oxford levels of evidence include 10 categories (Table 1), GRADE uses four levels for quality of evidence: high, moderate, low, and very low. These levels

Table 4 Key clinical questions used to develop the guideline

1. What are the general considerations about RA diagnosis and assessment?
2. What is the meaning of disease remission and low disease activity?
3. How to monitor RA?
4. What is the target of treatment (how to treat to target?)
5. What is the role of patient communication and shared decision in standard care?
6. How to use the csDMARDs in RA management?
7. How to use the bDMARDs and tsDMARDs in RA management?
8. How to switch between RA therapies?
9. When and how to taper drug in RA management?
10. How to personalize the patient care?
11. What is the non-pharmacological management in RA?
12. What is the role of self-management in the treatment of RA?
13. When to refer to surgery in RA patients?

SR Systematic review, *RCT* Randomised controlled trial, *cDMARD* Conventional disease-modifying antirheumatic drug, *csDMARDs* Conventional synthetic disease-modifying antirheumatic drugs, *bDMARDs* Biologic disease modifying antirheumatic drugs, *boDMARDs* Bio-originator disease modified antirheumatic drugs, *bsDMARDs* Bio-similar disease-modifying antirheumatic drugs, *tsDMARDs* Target synthetic disease-modifying antirheumatic drugs

imply a gradient of confidence in estimates of treatment effect and thus a gradient in the consequent strength of inference [19]. While GRADE provides a systematic and transparent approach to assessing the certainty of evidence and strength of recommendations, it is important to acknowledge that using GRADE will commonly involve some subjective judgments, and assessments may vary between individuals [20, 21]. This is supported by the finding that inter-rater agreement for GRADE assessments by different, untrained individuals is limited [22, 23].

Guidelines help clinicians translate best evidence into best practice [24]. However, it is important to highlight that adherence to treatment recommendations will not guarantee a successful outcome in every patient in each clinical scenario. The ultimate assessment should be carried out by a rheumatologist responsible for the clinical decision-making and considering the individual patient medical status, priorities, favourite options, and values. Recommendations within this guideline are based on the best clinical evidence. Clinical practice guidelines aim to provide a frame on how to enhance the suitability and quality of care, to improve the interventions' cost-effectiveness, to act as a tool for education, and to categorise relevant research pathways. Based on the level of evidence and strength of the recommendations, the recommendations are intended to help inform clinical decision-making [25]. This agrees with the outcomes of this work highlighted in the algorithm that there is no isolated target for the management of RA, but they are multiple pathways leading at the end to the desired goal.

In our work, we consider disease-sustained remission is the main goal for treating RA patients (clinical, ultrasonographic, and functional), while the EULAR 2019 updated recommendations [15] consider only clinical remission is the main therapeutic target for patients with RA. Also, we put clear cutoff point of starting biologic therapy. Also, we added clear and more detailed points on drug tapering, personalized medicine, and non-pharmacological management of RA.

The key strengths of this work are linked to the diversity as well as the experience of the contributors, the high levels of the achieved consensus, and the wide-ranging agreement with the most recently available management recommendations. Also, the methodology adopted the PICOT strategy, the patient-reported outcomes, and the treat-to-target outcome as the main foundations of this study.

Limitations of the guideline

One particular challenge with the current published guidelines is the limited comparative evidence to inform selection of therapies. Therefore, for the purpose of this work, indirect comparisons among trials/therapies were used. Though this guideline represents the best data available at the time of preparing this report, caution should be exercised in rendering the data; future studies may mandate alteration of the conclusions or recommendations included in this work. As health care is not universally uniform, it may be needed or even preferable to depart from the stated recommendations to set up a tailored management programme tailored to specific patients with particular circumstances. Just as adherence to guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

In conclusion, clinical guidelines have been upheld as an essential part of quality medical practice. This work was developed aiming at offering updated, concise, patient-focused, evidence-based, expert recommendations for the management of RA. As data continue to endorse best practices in management, implementation of this guideline in standard practice will ideally lead to improved quality of care for people with RA. The broad representation of the consensus panel would have a role in disseminating of the results of this work to such a large number of local rheumatologists, with consequent high chances of increased uptake and implementation of the guidelines.

Table 5 RA recommendations

Standard	Statement	Mean rate ± SD	% of agreement	Level of agreement
	1. Start the first line of treatment strategy with conventional disease-modifying antirheumatic drug (cDMARD) monotherapy using methotrexate (15–25 mg/week) as soon as possible and ideally within 3 months of onset of persistent symptoms. For patient who cannot tolerate oral methotrexate, subcutaneous or intramuscular methotrexate can be prescribed. To choose the preferred method of methotrexate administration, it is advisable to use shared decision-making (oral vs subcutaneous vs intramuscular). To evaluate the patient's reaction to treatment, methotrexate should be given for 8 to 12 weeks (LOE:1a GOR: A) - In patient who could not tolerate MTX, try some steps to alleviate the side effects before switching to another DMARDs (such as increasing folic acid dose, splitting oral MTX dose over 24 h, or switching between oral and parenteral routes of MTX administration **2.** When MTX is contraindicated, or patient could not tolerate it, consider treatment with leflunomide (20 mg/day) or sulfasalazine (2 g/day) as first line of treatment strategy. Consider hydroxychloroquine (200–400 mg) for first-line treatment as an alternative to oral methotrexate and leflunomide or sulfasalazine for mild or palindromic disease (LOE:1a GOR:A) **3.** Offer additional (combined) cDMARDs (oral methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine), in combination, in a step-up strategy when the treatment target (remission or low disease activity) has not been achieved after 3 months despite dose escalation **4.** Significant improvement (DAS-28 $\geq$ 1.2) using cDMARDAs should be achieved by 3 months. If no significant improvement has been achieved, by 3 months, adding another DMARD to MTX or using a different combination DMARD therapy is advised (DMARDs doses should be optimized to the maximum tolerable licensed levels) (LOE: 1aGOR: A) **5.** DMARD combination therapy means double or triple traditional/conventional DMARD therapy **6.** Double DMARD therapy means: MTX + SSZ, MTX + HCQ, SSZ + HCQ, or MTX + LEF **7.** Triple DMARD therapy means: MTX or LEF + SSZ + HCQ	8.66 ± 0.59	100%	H
	8. Glucocorticoids: short-term glucocorticoids should be considered when initiating or changing csDMARDs; the dose and route of administration may vary: orally at doses up to 7.5 mg/day, orally at 30 mg starting dose, as a single intramuscular injection of 120 mg methylprednisolone, or as a single 250 mg intravenous pulse therapy of methylprednisolone. Oral steroid therapy should be tapered as rapidly as clinically feasible, within 3 months from treatment start. Long-term use of GC, especially at doses above 5 mg/day, should be avoided because of the many potential risks In adults with established RA, only continue long-term treatment with glucocorticoids when as follows: ○ The long-term complications of glucocorticoid therapy have been fully discussed, and all other treatment options (including biological and targeted synthetic DMARDs) have been offered **9.** Symptom control ○ Consider oral nonsteroidal anti-inflammatory drugs (either traditional NSAIDs and COX-2 selective inhibitors), when control of pain or stiffness is inadequate. Consider the patient's risk factors, such as age and pregnancy, as well as the possibility of gastrointestinal, liver, and cardio-renal toxicity ○ When treating symptoms of RA with oral NSAIDs: ■ Offer the lowest effective dose for the shortest possible time ■ Offer a proton-pump inhibitor (PPI) ■ Review risk factors for adverse events regularly	8.55 ± 0.61	100%	H
	10. If the treatment target is not achieved after 6 months of DMARD combination therapy, addition of a bDMARD should be considered with or without MTX (LOE: 2a. GOR:B) **11.** Only a specialist rheumatology team with experience in the administration of these drugs should initiate biological therapy and monitor treatment response and side effects	8.61 ± 0.5	100%	H

Table 5 (continued)

Standard	Statement	Mean rate ± SD	% of agreement	Level of agreement
	12. The cutoff point of starting biologic therapy is high disease activity: DAS-28 > 5.1 or if DAS-28 > 4.2 and associated with 3 or more poor prognostic factors (significantly elevated acute phase reactant levels, *high swollen joint count (> 4), the presence of significantly positive (high titres) rheumatoid factor or anti-CCP, the presence of early erosions (radiographic or sonographic, functional disability (HAQ or equivalent) score > 2, US Doppler activity ≥ 2 in ≥ 3 joints)* (LOE: 3bGOR: B) **13.** First-line biologic therapy: Use TNF-inhibitors (adalimumab, etanercept, infliximab, certolizumab pegol, or golimumb) or IL-6 inhibitor (tocilizomab) as first-line bDMARD. cDMARD should be added to the biologic therapy. Alternatively, synthetic DMARD (tofacitinib, baricitinib, upadacitinib) can be considered (LOE: 2a. GOR: B)	8.66 ± 0.69	100%	H
	14. TNF inhibitors had been given a slight preference over other biologics due to availability of long-term registry data worldwide **15.** Significant improvement using bDMARDAs should be achieved by 3 months, and the target should be achieved by 6 months. Treatment with TNF inhibitors should be continued only if there is an adequate response at 6 months following initiation of therapy. An adequate response is defined as an improvement in DAS-28 of 1.2 points or more **16.** After initial response, treatment should be monitored no less frequently than 6 monthly intervals with assessment of DAS-28 (LOE:4 GOR: C) **17.** If the patient has an inadequate initial response (primary failure), prescription of an alternative TNF-α inhibitor is not advised. Switch out of therapeutic class considering a drug with other working mechanism is advised **18.** An alternative TNF-α inhibitor may be considered for patients in whom treatment is withdrawn due to an adverse event before the initial 6-month assessment of efficacy, provided the risks and benefits have been fully discussed with the patient and documented (LOE:3b GOR: C) **19.** In case of secondary failure to anti-TNF agent (patients who respond to the therapy after an induction regimen but subsequently lose response during maintenance treatment), initially verify if the symptoms are due to active disease and confirm compliance. If verified, therapeutic drug monitoring is advised. In case of low drug levels with high antibodies, adding a csDMARD is advised; alternative is switching to another anti-TNF. However, if there is adequate drug level, no antibodies, it is advisable to switch out of the therapeutic class. If subtherapeutic drug levels, without antibodies, it is advisable to do dose escalation or add a csDMARD (LOE:3b GOR: C)	8.77 ± 0.42	100%	H
	20. If a first-line bDMARD has failed, a short course of low-dose corticosteroids can be considered, in addition to optimizing the csDMARD dose **21.** Escalation of dose of the TNF-α inhibitors above their licensed starting dose is not recommended **22.** If a second TNF inhibitor fails, patients should receive an agent with another mode of action **23.** Treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose, and product price per dose). This may need to be varied in individual cases due to differences in the mode of administration and treatment schedules	8.77 ± 0.42	100%	H
	24. A bsDMARD of any of the reference boDMARDs should not be used if the respective boDMARD (or another bsDMARD of the same molecule) has failed to induce sufficient efficacy or vice versa **25.** Use of the TNF-α inhibitors for the treatment of severe, active, and progressive RA in adults not previously treated with methotrexate or other csDMARDs is not recommended (LOE:2b GOR: C) **26.** When switching from an anti-TNF drug (originator) to a biosimilar of that originator, one has to take into consideration that antidrug antibodies against the originator will cross-react with the biosimilar, causing treatment failure (LOE:4 GOR: C) **27.** If target not achieved after 6 months, treatment changes to the following: ■ A non-TNFi bDMARD [(tocilizumab or sarilumab, a human anti-IL-6 receptor antibody), rituximab (mainly for RA patients who has positive rheumatoid factor/*Anti-CCP), Abatacept*)] with/without csDMARD **OR** ■ Targeted synthetic DMARDs tsDMARDs)as tofacitinib, baricitinib or upadacitinib) with/without csDMARD as third-line bDMARDs until reach remission	8.38 ± 0.69	100%	H

Table 5 (continued)

Standard	Statement	Mean rate ± SD	% of agreement	Level of agreement
	28. bDMARDs (and tsDMARDs) should primarily be prescribed in combination with csDMARDs, such as methotrexate or leflunomide, leaving the option of monotherapy, with a preference for certain drugs (IL-6 pathway inhibitors and tsDMARDs), as an exception in case of intolerance or contraindication to all csDMARDs. (LOE:3b GOR: B) **29.** It is not advisable to routinely test for antidrug antibodies and drug levels in clinical practice. Measuring serum drug level and levels of anti-drug antibodies are only advisable in cases of secondary failure, since a good clinical response would not lead to cessation of therapy even in the presence of antidrug antibodies, or low drug levels, and vice versa. Furthermore, the use of MTX, even at low doses (7.5–10 mg/week or more) reduces the incidence of antidrug antibodies (LOE:4 GOR: C)	8.55 ± 1.99	94.4%	H
	30. Drug tapering: (LOE:3b GOR: C) • For individuals who have maintained their treatment target (remission or low disease activity) for at least a year without the use of glucocorticoids, think carefully about lowering dosages or quitting medications altogether as part of a step-down strategy. If the treatment aim is no longer fulfilled, return right away to the prior DMARD regimen • If the patient has been taking biologic therapy and sustained remission, tapering bDMARD can be done, while the patient continue the conventional DMARDs therapy and with close monitoring of the disease activity. Return promptly to the previous bDMARD regimen if the treatment target is no longer met	8.66 ± 0.49	100%	H
	31. Personalized care: (LOE:4 GOR: C) • Patients who develop *elevated liver enzymes*: double fold elevation; reduce MTX & LEF to half dose. If reach threefold, stop MTX and LEF • Patients with HBV infection should receive antiviral treatment before starting bDMARDs with close monitoring after starting biological therapy • In hypertensive patients, be careful regarding salt and water retention property of leflunomide. Baseline measurement of blood pressure is recommended with adjustment of blood pressure therapy if required • In patients with NYHA class 3 or 4 heart failure, non-TNF inhibitor bDMARD or tsDMARD are recommended over TNF inhibitors • Patients complicated with interstitial lung disease: MTX associated with corticosteroid is recommended as first-line therapy. IL-6 inhibitors should be considered as 1st line in bDMARDs then rituximab; while abatacept is the first choice in patients with nontuberculous mycobacterial lung disease • In patients with history of lymphoproliferative disorder, rituximab is preferable over other bDMARDs • tsDMARDs are better to be avoided in patients with high risk for cardiovascular problems or venous thromboembolism	8.44 ± 0.78	94.4%	H
	1. **Non-pharmacological management** (LOE:4 GOR: C) • Physiotherapy Adults with RA should have access to specialist physiatrist, with periodic review as follows: ○ Improve general fitness and encourage regular exercise ○ Learn exercises for enhancing joint flexibility, muscle strength, and managing other functional impairments ○ Learn about the short-term pain relief provided by methods such as transcutaneous electrical nerve stimulators (TENS), and wax baths • Occupational therapy Adults with RA should have access to specialist occupational therapy, with periodic review, if they have the following: ○ Difficulties with any of their everyday activities ○ Problems with hand function • Hand exercise programmes Due to the shortage of occupational therapists in Egypt, we recommend rheumatologists /physiatrist to take care with this aspect of therapy Consider a tailored strengthening and stretching hand exercise programme for adults with RA with pain and dysfunction of the hands or wrists if as follows: ○ They are not on a drug regimen for RA. ○ They have been on a stable drug regimen for RA for at least 3 months. The tailored hand exercise programme for adults with RA should be delivered by a practitioner with training and skills in this area • Podiatry ○ All adults with RA and foot problems should have access to a podiatrist for assessment and periodic review of their foot health needs	8.22 ± 1.11	94.4%	H

Table 5 (continued)

Standard	Statement	Mean rate ± SD	% of agreement	Level of agreement
	○ Functional insoles and therapeutic footwear should be available for all adults with RA if indicated. Due to the shortage of podiatrists in EGYPT, we recommend physiatrist to take care with this aspect of therapy • Psychological interventions ○ Offer psychological interventions to help adults with RA cope with their condition, such as relaxation, stress management, and cognitive coping techniques • Diet and complementary therapies ○ Explain to adults with RA who want to experiment with their food that there is not a lot of proof that will help their arthritis. ○ However, they might be inspired to adhere to the tenets of the Mediterranean diet (more bread, fruit, vegetables, and fish, less meat, and replace butter and cheese with products based on vegetable and plant oils) ○ Explain to individuals with RA who want to explore complementary therapies that while some may help with symptoms in the short term, there is little to no evidence to support their effectiveness over the long term. ○ If an adult with RA decides to try complementary therapies, advise them 1. These approaches should not replace conventional treatment 2. This should not prejudice the attitudes of members of the multidisciplinary team or affect the care offered			
	2. Timing and referral for surgery (LOE: 3b. GOR:C) A. Offer to refer adults with RA for an early specialist surgical opinion if any of the following do not respond to optimal nonsurgical management ○ Persistent pain due to joint damage or other identifiable soft tissue cause ○ Worsening joint function Progressive deformity ○ Persistent localized synovitis not responding to conservative systemic and/or local management B. Offer to refer adults with any of the following complications for a specialist surgical opinion before damage or deformity becomes irreversible ○ Imminent or actual tendon rupture ○ Nerve compression (for example carpal tunnel syndrome & cervical cord myelopathy) ○ Stress fracture C. When surgery is offered to adults with RA, explain that the main expected benefits are as follows: ○ Pain relief ○ Improvement, or prevention of further deterioration, of joint function ○ Prevention of deformity D. Adults with RA who have suspected or confirmed septic arthritis should get immediate combination medical and surgical therapy (especially in a prosthetic joint) E. If an adult with RA develops any symptoms or signs that suggest cervical myelopathy • Request an urgent MRI scan • Refer for a specialist surgical opinion F. Do not let concerns about the long-term durability of prosthetic joints influence decisions to offer joint replacements to younger adults with RA	8.41 ± 1.12	94.4%	H

MSUS Musculoskeletal ultrasound, *RA* Rheumatoid arthritis, *csDMARDs* Conventional synthetic disease-modifying antirheumatic drugs, *bDMARDs* Biologic disease modif antirheumatic drugs, *boDMARDs* Bio-originator disease-modifying antirheumatic drugs, *bsDMARDs* Bio-similar disease modified antirheumatic drugs, *tsDMARDs* Target synthetic disease modified antirheumatic drugs, *DAS* Disease activity score, *MTX* Methotrexate, *LEF* Leflunomide, *HCQ* Hydroxychloroquine, *SSZ* sulfasalazine, *TENS* Transcutaneous electrical nerve stimulators

The developed guidelines and recommendations are envisioned to offer general guidance for commonly met clinical scenarios. The recommendations do not command the care for individual patients. Adherence to the recommendations stated in this guideline should be considered as voluntary, with the ultimate decision to apply them to be decided by the treating healthcare professional in view of the specific patient's individual

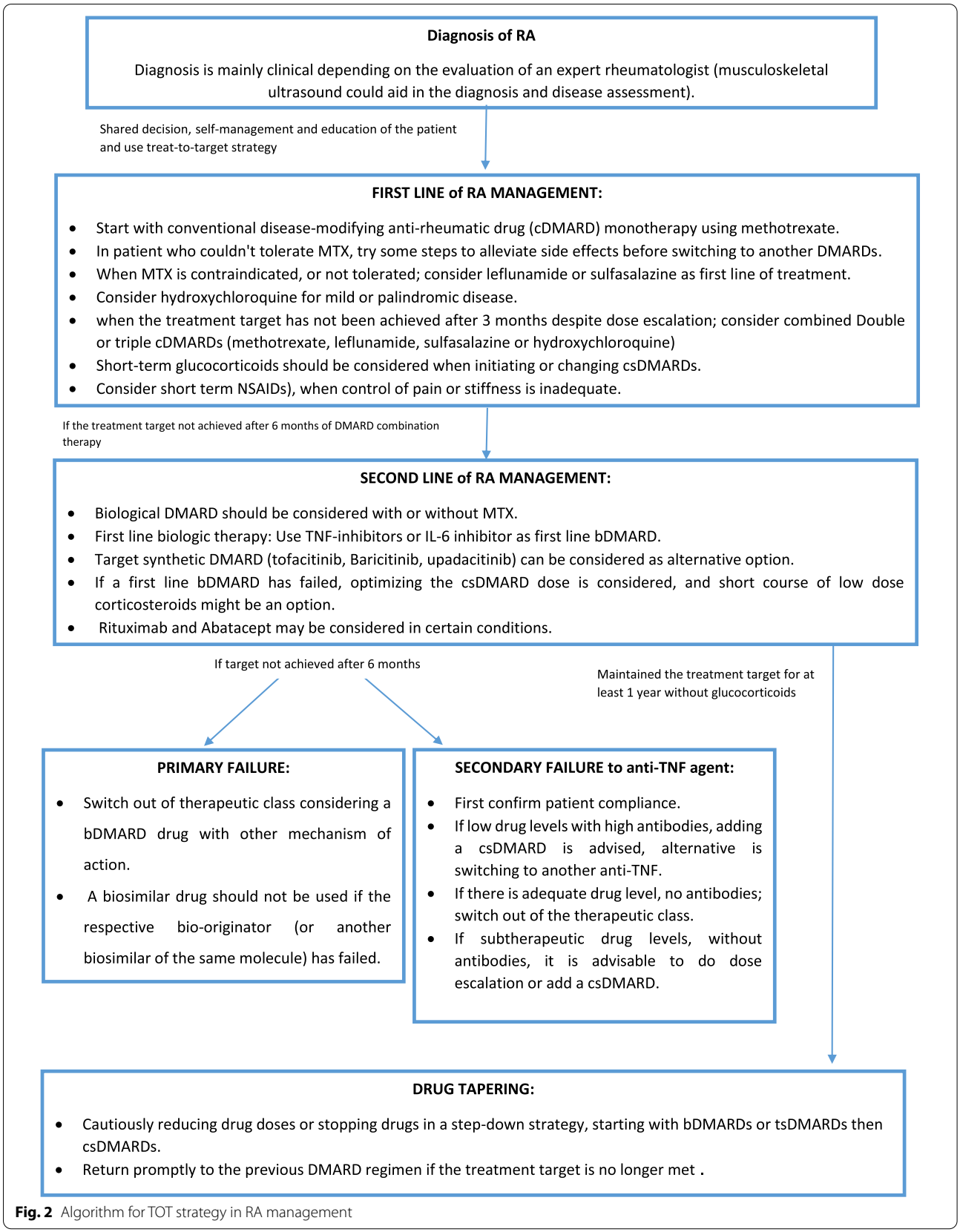

Fig. 2 Algorithm for TOT strategy in RA management

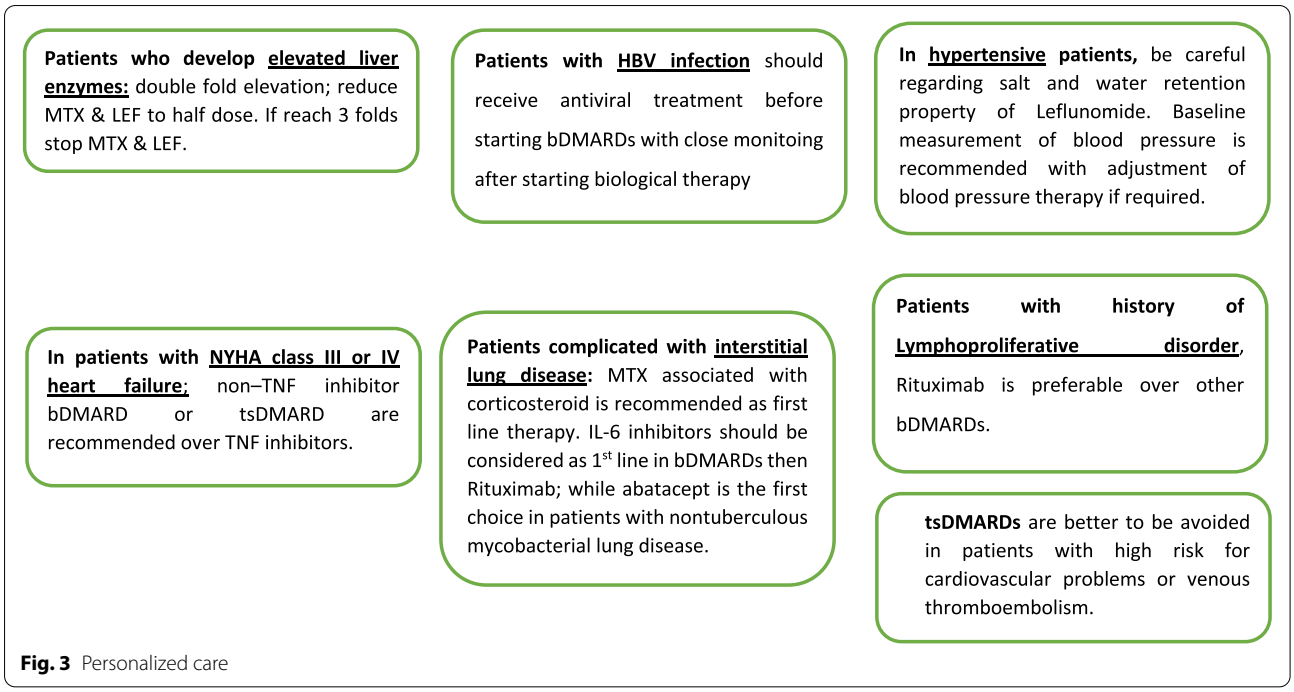

Fig. 3 Personalized care

condition and comorbidities. Guidelines and recommendations are projected to endorse useful or desirable outcomes but do not guarantee any specific outcome. The guidelines do not recommend any commercial products or services. The guidelines are meant to help in the decision-making process but do not convey all uncertainties of patient care.

Abbreviations

ACR: American College of Rheumatology; bDMARDs: Biologic disease-modifying antirheumatic drugs; boDMARDs: Bio-originator disease-modifying antirheumatic drugs; bsDMARDs: Biosimilar disease-modifying antirheumatic drugs; cDMARDs: Conventional disease-modifying antirheumatic drugs; CEBM: Centre for evidence-based medicine; CEG: The Clinical, Evidence-based, Guidelines; DAS: Disease activity score; DMARDs: Disease-modifying antirheumatic drugs; EULAR: European Alliance of Associations for Rheumatology; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HAQ: Health assessment questionnaire; HCQ: Hydroxychloroquine; LEF: Leflunomide; MSUS: Musculoskeletal ultrasound; MTX: Methotrexate; PDUS: Power Doppler ultrasound; PICOT: Patient, intervention, comparison, outcome and time; RA: Rheumatoid arthritis; RCT: Randomized controlled trial; SR: Systematic review; SSZ: Sulfasalazine; TENS: Transcutaneous electrical nerve stimulators; tsDMARDs: Target synthetic disease-modifying antirheumatic drugs; T2T: Treat to target.

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Authors' contributions

Conceptualization and design, YEM and MHA; acquisition of data, YEM and MHA; formal analysis, MEG; investigation, NG and MM; methodology, all authors; writing — original draft, YEM, MHA, and ST; final approval of the version to be submitted, all authors. The authors read and approved the final manuscript.

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Availability of data and materials

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Declarations

Ethics approval and consent to participate

This study was performed in accordance with the Helsinki Declaration. This was a multistep process which followed the 'Clinical, Evidence-based, Guidelines' (CEG) initiative protocol (ethical approval code: 34842/8/21, ethical board Tanta University) aiming at setting up an actionable clinical gold standard for treat-to-target management of rheumatic and bone diseases.

Consent for publication

Not applicable

Competing interests

The authors declare that Mona Mansour is editor in chief. Mohammed Hassan Abu-Zaid, Salwa Galal, and Rehab Ali are associate editors in the Egyptian Rheumatology and Rehabilitation. Mohammed Mortada, Yasser El Miedany, Naglaa Gadallah, and Waleed Hassan are from editorial board of the journal. The other authors declare that they have no competing interests.

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