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ORIGINAL ARTICLE

Recommendations for the management of rheumatoid arthritis in the Eastern Mediterranean region: an adolopment of the 2015 American College of Rheumatology guidelines

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Abstract

Clinical practice guidelines can assist rheumatologists in the proper prescription of newer treatment for rheumatoid arthritis (RA). The objective of this paper is to report on the recommendations for the management of patients with RA in the Eastern Mediterranean region. We adapted the 2015 American College of Rheumatology guidelines in two separate waves. We used the adolopment methodology, and followed the 18 steps of the "Guidelines 2.0" comprehensive checklist for guideline development. For each question, we updated the original guidelines' evidence synthesis, and we developed an Evidence Profile (EP) and an Evidence to Decision (EtD) table. In the first wave, we adoloped eight out of the 15 original questions on early RA. The strength changed for five of these recommendations from strong to conditional, due to one or more of the following factors: cost, impact on health equities, the balance of benefits, and harms and acceptability. In the second wave, we adoloped eight out of the original 44 questions on established RA. The strength changed for two of these recommendations from strong to conditional, in both cases due to cost, impact on health equities, balance of benefits and harms, and acceptability. The panel also developed a good practice recommendation. We successfully adoloped 16 recommendations for the management of early and established RA in the Eastern Mediterranean region. The process proved feasible and sensitive to contextual factors.

Keywords Adoloped · Guidelines · Management · Recommendations · Rheumatoid arthritis

Highlights
- One good practice recommendation for healthcare professionals to provide patients with the needed education regarding progression and treatment options for rheumatoid arthritis.
- Eight graded recommendations for the management of early rheumatoid arthritis.
- Eight graded recommendations for the management of established rheumatoid arthritis.

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Abbreviations

ACR	American college of rheumatology
AE	Adverse events
DMARD	Disease-modifying antirheumatic drugs
GRADE	Grading of Recommendations Assessment, Development and Evaluation
MTX	Methotrexate
RA	Rheumatoid arthritis
TNF	Tumor necrosis factor
TNFi	Tumor necrosis factor alpha inhibitor

Introduction

Rheumatoid arthritis (RA) is an inflammatory joint disease that causes pain, swelling, and disability in advanced stages

[1–4]. It is ranked 42nd following malaria in contributing to global disability [5]. Its prevalence is 3/1000, with women affected more than men [5, 6]. In the Middle-East, the prevalence of RA is around 0.16% [5].

The management of RA aims to decrease symptoms, improve quality of life, and prevent disease progression [7]. The choice of treatment depends upon disease activity, prognostic factors, and patients' responsiveness to previous lines of treatment [8, 9] with several effective options available. Guidelines are helpful to guide physicians, patients, and payers to choose the appropriate management plan.

De novo development of guidelines is time consuming and requires large financial and human resources. Also, adopting published guidelines developed for another setting is not desirable, given the importance of contextual factors in developing recommendations. Adaptation of guidelines addresses the above challenges, as it requires less resources and time and considers contextual factors in the process of adaptation.

The objective of this manuscript is to report on the adapted recommendations for the management of RA in the EMR (See Supplementary material for the Executive Summary).

Methodology

We adapted these guidelines in two waves in 2016 and 2017 using the GRADE approach.

We have previously reported the methodology used for this project [10] in relation to the following: (1) groups and roles; (2) selecting guideline topics; (3) identifying and training guideline panelists; (4) prioritizing questions and outcomes; (5) identifying, updating, or conducting systematic reviews; (6) preparing GRADE evidence tables and EtD frameworks; (7) formulating and grading strength of recommendations; (8) using the GRADEpro-GDT software (www.gradepro.org).

Briefly, we followed the adolopment methodology [11], an efficient model for guideline production based on adoption, adaptation, and development of recommendations utilizing the GRADE Evidence to Decision (EtD) frameworks [12, 13]. To implement this methodology, we followed the 18 steps of the GIN-McMaster guideline development tool (hei.mcmaster.ca/guidecheck.html) based on the "Guidelines 2.0" comprehensive checklist for guideline development [14]. The target end-users of the recommendations were rheumatologists in the EMR managing patients with RA.

The adaptation was based on the "2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis," as the source guidelines [15]. Through a formal prioritization process, we selected a limited number of recommendations to adapt in each of the two waves. We also used a formal process to select patient important outcomes relevant to the selected questions.

For each question, the guideline coordination team updated the 2014 evidence review conducted for the source guidelines. This included searches for both systematic reviews and primary studies relevant to the selected questions (see Appendix d for search strategies). We assessed identified systematic reviews for relevance (directness), quality (risk of bias) using AMSTAR, and up-to-datedness. When necessary, we updated the original meta-analysis. We ran additional searches relating to values and preferences and resource use, the latter being restricted to the EMR.

The guideline coordination team then developed an Evidence Profile (EP) [16, 17] and an EtD table following the GRADE approach [12, 13, 18]. For each of the two waves, the guideline panel met in person to discuss and adapt the recommendations.

The panel rated the certainty of evidence supporting each recommendation according to the GRADE methodology, as "high," "moderate," "low," or "very low" [19, 20] (Table 1). The panel graded the strength of each recommendation as either strong or conditional (also known as or called weak) [21] (Table 2). The factors considered when grading the strength of recommendation were as follows: priority of the problem, benefits and harms of the option, certainty of the evidence, values and preferences, resource use, feasibility, acceptability, and equity.

During their second meeting, the panelists developed a good practice statement, which represents a recommendation that "guideline panels feel is important but that, in the judgment of the GRADE working group, is not appropriate for formal ratings of quality of evidence" [20].

Results

Through a formal prioritization process, we selected eight out of the 15 original questions on early RA to adapt in wave 1 (Table 3), and eight out of the original 44 questions on established RA to adapt in wave 2 (Table 4). In addition, the panel developed one good practice statement [20].

Good practice statement

In patients with RA, the panel recommends that healthcare practitioners provide patients with the needed education about the nature of disease, its progression, the various types of medications, and their expected benefits and harms. (See Table 5 for the good practice statement checklist) [20].

Table 1 Certainty of evidence

Certainty of evidence	Explanation
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Early RA recommendations

Results of the general search for wave 1

The search for systematic reviews of effectiveness yielded 772 papers published after the date of the search conducted for the ACR guidelines. Only two were relevant to the project [22, 23]. The systematic search for primary studies of effectiveness yielded 2051 papers, out of which five were eligible [24–28] (Appendix e).

Table 2 Interpretation of strong and conditional (weak) recommendations

Implications	Strong recommendation	Conditional (weak) recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations.	Policymaking will require substantial debate and involvement of various stakeholders.

We identified 16 papers addressing patients' values and preferences. None were specific to the EMR. Based on the review of these papers, the panelists judged that there is probably no uncertainty or variability in how much people value the main outcomes: pain, function, and avoiding adverse effects, across all guideline questions. This judgment was later reflected in the EtD tables (Appendix f). We could not find any studies on resource use relevant to the EMR.

Wave 1 recommendations (early RA)

Question 1 In patients with early RA, should we use treat-to-target strategy versus a non-targeted approach?

Health effects The panelists judged that the balance between benefits and harms probably favors the treat-to-target

Table 3 Key questions for wave 1

Question 1: In patients with early RA, should we use treat-to-target strategy versus a non-targeted approach?
Question 2: In patients with early RA with moderate or high disease activity, who are DMARD-naive, should we use combination double-DMARD therapy versus mono-DMARD therapy?
Question 3: In patients with early RA with moderate or high disease activity, who are DMARD-naive, should we use combination triple traditional DMARD therapy versus mono-DMARD therapy?
Question 4: In patients with early RA with moderate or high disease activity, should we add versus not add long-term low-dose glucocorticoid therapy to traditional DMARDs?
Question 5: In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, should we use TNFi monotherapy versus triple DMARD therapy?
Question 6: In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, should we use TNFi + MTX therapy versus triple DMARD therapy?
Question 7: In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, should we use of TNFi monotherapy versus non-TNF biologic therapy?
Question 8: In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, should we use TNFi + MTX versus non-TNF biologic (specifically abatacept) + MTX?

Table 4 Key questions for wave 2

Question 1: In patients with established RA, should we use a treat-to-target strategy vs. a non-targeted approach?
Question 2: In patients with established RA with moderate or high disease activity, who have failed traditional DMARD therapy, should we use TNFi therapy + MTX vs. combination triple DMARD therapy?
Question 3: In patients with established RA with moderate or high disease activity, who have failed multiple TNFi therapies, should we use a non-TNF biologic therapy + MTX vs. another TNFi + MTX?
Question 4: In patients with established RA with moderate or high disease activity, who have failed a single TNFi therapy, should we use of non-TNF biologic therapy vs. another TNFi?
Question 5: In patients with established RA with moderate or high disease activity, who have failed a single TNFi therapy and currently on DMARD, should we use non-TNF biologic therapy + MTX vs. another TNFi + MTX?
Question 6: In patients with established RA with moderate or high disease activity, who have failed multiple TNFi therapies, should we use oral tofacitinib therapy + MTX vs. another TNFi + MTX?
Question 7: In patients with established RA with moderate or high disease activity, should we add versus not add long-term low-dose glucocorticoid therapy to traditional DMARD therapy?
Question 8: In patients with established RA with moderate or high disease activity with an acute disease flare (RA flare), should we add versus not add short-term high-dose glucocorticoid therapy to traditional DMARDs?

approach. This judgment reflected a higher value placed on possible efficacy relative to a slight increase in side effects.

Contextual factors The panelists judged the intervention to be associated with moderate cost, probably acceptable for most stakeholders, and probably feasible. However, they were unclear about its effects on equity.

Recommendation 1 In patients with early RA, the panel suggests using a treat-to-target strategy versus a non-targeted approach (conditional recommendation, low certainty evidence).

Conditions:

- Consider the potential burden associated with extra costs and time for patients and physicians
- Educate the patient on what treat to target intervention entails

Question 2 In patients with early RA with moderate or high disease activity, who are DMARD-naive, should we use combination double DMARD therapy versus mono-DMARD therapy?

Health effects The panel judged that the balance of benefits and harms was not in favor of either double-DMARD therapy or mono-DMARD therapy.

Contextual factors The panelists judged the intervention to be associated with moderate cost and increased health inequities. They found it to be probably feasible to implement but not acceptable by key stakeholders.

Recommendation 2 In patients with early RA with moderate or high disease activity, who are DMARD-naïve, the panel suggests not using combination double-DMARD therapy versus mono-DMARD (conditional recommendation, low certainty evidence).

Condition:

- Consider patient's perspective related to the number of pills prescribed.

Question 3 In patients with early RA with moderate or high disease activity, who are DMARD-naive, should we use combination triple traditional DMARD therapy versus mono-DMARD therapy?

Health effects The panelists decided that the balance between desirable and undesirable effects probably favors treating patients with early RA with DMARD monotherapy rather than triple DMARD therapy.

Contextual factors The panelists judged the intervention to be associated with moderate cost and increased health inequities. They also judged it to be probably feasible to implement in the EMR but not acceptable by key stakeholders.

Recommendation 3 In patients with early RA with moderate or high disease activity, who are DMARD-naïve, the

Table 5 Checklist to justify issuing a recommendation as a good practice statement

Question	Answer*
(i) Is the statement clear and actionable?	Yes
(ii) Is the message really necessary in regard to actual health care practice?	Yes
(iii) After consideration of all relevant outcomes and potential downstream consequences, will implementing the good practice statement results in large net positive consequences.	Yes
(iv) Is collecting and summarizing the evidence a poor use of a guideline panel's limited time and energy (opportunity cost is large)?	Yes
(v) Is there a well-documented clear and explicit rationale connecting the indirect evidence?	Yes

* The answers to all questions should be yes, in order to proceed with a good practice statement

panel suggests not using combination triple traditional DMARD therapy versus mono-DMARD therapy (Conditional recommendation, Low certainty of evidence).

Condition:

- Consider patient's perspective related to the number of pills prescribed.

Question 4 In patients with early RA with moderate or high disease activity, should we add versus not add long-term low-dose glucocorticoid therapy to traditional DMARDs?

Health effects The panel agreed that the balance between desirable and undesirable effect is variable but probably in favor of adding low-dose glucocorticoids to traditional treatment.

Contextual factors The panel members were not certain about the magnitude of the resource requirements for glucocorticoids. They judged the intervention to probably increase health equities, to be feasible to implement, and to be probably acceptable by key stakeholders in the condition of offering low-dose glucocorticoids for a short period of time.

Recommendation 4 In patients with early RA with moderate or high disease activity, the panel suggests adding over not adding long-term low-dose glucocorticoid therapy to traditional DMARDs (conditional recommendation, very low certainty of evidence).

Conditions:

- Prescribe the lowest possible dose of glucocorticoids for the shortest possible period of time.
- Monitor patients regularly.
- Continuously assess for the development of co-morbidities (e.g., osteoporosis, hypertension, diabetes mellitus, and dyslipidemia).

Question 5 In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, should we use TNFi monotherapy versus triple DMARD therapy?

Health effects The panel judged that the balance between desirable and undesirable effect does not favor either TNFI monotherapy or triple DMARD therapy. These judgments were supported by the indirect evidence brought forward during the panel meeting.

Contextual factors The panel members judged the intervention to be associated with large cost and a reduction in health equities. They deemed it as probably acceptable and probably feasible to key stakeholders.

Recommendation 5 In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, the panel suggests triple DMARD therapy over TNFi monotherapy (conditional recommendation, low certainty of evidence).

Conditions:

- Consider TNFi therapy in patients who do not mind or prefer injections over multiple pill intake and when resources are available.
- Consider the additional possible harms of TNFi in patients at increased risk of developing or are diagnosed with TB.

Question 6 In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, should we use TNFi + MTX therapy versus triple DMARD therapy?

Health effects The panel members judged that the balance between benefits and harms probably favors TNFi + MTX therapy compared to triple DMARD therapy.

Contextual factors The panel members judged the intervention to be associated with large resource requirements and a reduction in health equities, and to be probably acceptable and probably feasible by key stakeholders.

Recommendation 6 In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, the panel suggests using either TNFi + MTX or triple DMARD therapy (conditional recommendation, very low certainty evidence).

Conditions:

- Engage patients and consider their preferences when making the choice; TNFi therapy could be prescribed for patients who prefer injections rather than multiple pill intake.
- Take into consideration the availability of resources.
- Consider the additional possible harms of TNFi in patients at increased risk of developing or are diagnosed with TB.

Question 7 In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, should we use TNFi monotherapy versus non-TNF biologic therapy?

Health effects The panel members agreed that the balance between the benefits and harms favors neither the intervention (TNFi monotherapy) nor the comparator (non-TNFi monotherapy).

Contextual factors The panel members considered that the resource requirements for the intervention vary depending on the weight of the patient, on the mode of administration, and on the cost of the medication. Accordingly, the panel members judged that the impact on health equity would vary. They judged the intervention to be feasible and probably acceptable by key stakeholders.

Recommendation 7 In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, the panel suggests using either TNFi monotherapy or tocilizumab (conditional recommendation, low certainty evidence).

Conditions:

- Consider that some TNFi therapies cannot be used as mono therapies.
- Consider the local price/ cost when choosing the therapy

Question 8 In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, should we use TNFi + MTX versus non-TNF biologic (abatacept specifically) + MTX?

Health effects The panel members judged the balance between the benefits and harms favored neither the intervention (TNFi + MTX therapy) nor the comparator (non-TNFi + MTX).

Contextual factors The panelists judged that the resource requirements for the intervention vary depending on the weight of the patient, on the mode of administration, and on the cost of the medication. Accordingly, the panel members considered that the impact on health equity will vary. The panel members judged the intervention to be feasible and probably acceptable by key stakeholders.

Recommendation 8 In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, the panel suggests using either TNFi + MTX or abatacept + MTX (conditional recommendation, very low certainty evidence).

Established RA recommendations

Results of the general search for wave 2

Our search for systematic reviews of effectiveness yielded 1304 papers, nine [22, 27, 29–35] reports were relevant (Appendix g). Similar to wave 1, the five identified studies addressing patients values [36–40] were not relevant the EMR. Studies on resources use identified none relevant to the EMR. However, we retained six studies assessing cost effectiveness of treatment versus comparators [27, 33, 41–44]. The EtDs can be found in Appendix h.

Wave 2 recommendations (established RA)

Question 1 In patients with established RA, should we use a treat-to-target strategy vs. a non-targeted approach?

Health effects The panel judged that the balance between the desirable and undesirable effects probably favors the treat-to-target approach.

Contextual factors The panelists judged the intervention to be probably acceptable to key stakeholders and feasible to implement. However, they judged that the impact of health inequity varies presumably due to cost. They were unclear regarding the resources requirements.

Recommendation 1 In patients with established RA, the panel suggests using a treat to target strategy versus a non-targeted approach (conditional recommendation, moderate certainty evidence).

Question 2 In patients with established RA with moderate or high disease activity, who have failed traditional DMARD therapy, should we use TNFi therapy + MTX vs. combination triple DMARD therapy?

Health effects The majority of the panelist judged that the desirable consequences probably outweigh undesirable consequences in most settings.

Contextual factors The panelists judged the intervention to be associated with large resource requirements, probably acceptable by key stakeholders, and probably feasible to implement. However, they judged that the impact of health inequity varies.

Recommendation 2 In patients with established RA with moderate or high disease activity, who have failed traditional DMARD therapy, the panel suggests using TNFi therapy + MTX versus combination triple DMARD therapy (conditional recommendation, very low certainty of evidence).

Conditions:

- Consider precautions and contraindications of TNFi therapy when switching patients from traditional DMARD therapy.

- Consider patients with co-morbidities on poly-pharmacy and the patient preferences (e.g., frequency and mode of administration).
- Suggest using a shared decision-making process between the physician and the patient to better select the appropriate treatment.

Question 3 In patients with established RA with moderate or high disease activity, who have failed multiple TNFi therapies, should we use a non-TNFi biologic therapy + MTX vs. another TNFi + MTX?

Health effects The panel judged that the balance between the desirable and undesirable effects probably favors the intervention (non-TNFi biologic + MTX).

Contextual factors The panelists judged the intervention to be associated with negligible costs and savings, probably acceptable by key stakeholders, and probably feasible to implement. However, they judged that the impact of health inequity varies.

Recommendation 3 In patients with established RA with moderate or high disease activity, who have failed multiple TNFi therapies, the panel suggests using non-TNF + MTX biologic therapy over another TNFi + MTX (conditional recommendation, low certainty of evidence).

Condition:

- Take into consideration whether primary failure of multiple TNFi therapies was due to efficacy failure or to side effects.

Question 4 In patients with established RA with moderate or high disease activity, who have failed a single TNFi therapy, should we use of non-TNF biologic therapy vs. another TNFi?

Health effects The panel judged, based on low certainty of evidence, that the balance between the desirable and undesirable effects did favor neither the intervention nor the comparator.

Contextual factors The panelists judged the intervention to be associated with negligible costs and savings, acceptable by key stakeholders, probably feasible to implement, and probably reduced impact on healthy equity.

Recommendation 4 In patients with established RA with moderate or high disease activity, who have failed a single TNFi therapy and are currently on DMARD therapy, the panel suggests using non-TNF biologic therapy over another TNFi (conditional recommendation, low certainty of evidence).

Conditions:

- Consider using second TNFi if the patient has secondary efficacy failure of first TNFi (consider class switch of TNFi: receptor antagonist vs. monoclonal antibody)
- Consider using non-TNF biologic if the primary failure of single TNFi therapy was due to efficacy failure or to side effects.

Question 5 In patients with established RA with moderate or high disease activity, who have failed a single TNFi therapy and currently on DMARD, should we use non-TNF biologic therapy + MTX vs. another TNFi + MTX?

Health effects The panel judged, based on very low certainty of evidence, that the balance between the desirable and undesirable effects did favor neither the intervention nor the comparator.

Contextual factors The panelists judged the intervention to be associated with: negligible costs and savings, probably acceptable by key stakeholders, probably feasible to implement. However, they judged that the impact of health inequity varies.

Recommendation 5 In patients with established RA with moderate or high disease activity who have failed multiple TNFi therapies, the panel suggests using a non-TNF biologic therapy + MTX versus another TNFi + MTX (conditional recommendation, very low certainty of evidence).

Question 6 In patients with established RA with moderate or high disease activity, who have failed multiple TNFi therapies, should we use oral tofacitinib therapy + MTX vs. another TNFi + MTX?

Health effects The panel judged, based on low certainty of evidence, that the balance between the desirable and undesirable effects probably favors the intervention (oral tofacitinib + MTX).

Contextual factors The panelists judged the resource requirements for the intervention to have moderate savings, but there were no studies to assess cost effectiveness. The panel judged the impact on equity to vary. They also judged the intervention to be probably acceptable and feasible.

Recommendation 6 In patients with established RA with moderate or high disease activity who have failed multiple TNFi therapies, the panel suggests using oral tofacitinib therapy + MTX versus another TNFi + MTX (Conditional recommendation, very Low certainty of evidence).

Question 7 In patients with established RA with moderate or high disease activity, should we add versus not add long-term low-dose glucocorticoid therapy to traditional DMARD therapy?

Health effects The panel judged, based on low certainty of evidence, that the balance between the desirable and undesirable effects probably favors the comparator versus the intervention.

Contextual factors The panel judged the resource requirements to be negligible in terms of costs or savings for either but the cost effectiveness could not be assessed, as there were no included studies. The panel judged the impact on equity to probably increase and for the intervention to be probably feasible but to have varying acceptability.

Recommendation 7 In patients with established RA, with moderate or high disease activity, the panel suggests against using long-term-low-dose glucocorticoids + traditional DMARD therapy compared to traditional DMARD without glucocorticoids (conditional recommendation, low certainty of evidence).

Question 8 In patients with established RA with moderate or high disease activity with an acute disease flare (RA flare), should we add versus not add short-term high-dose glucocorticoid therapy to traditional DMARDs?

Health effects The panel judged, based on very low certainty of evidence, that the balance between the desirable and undesirable effects probably favors the intervention versus the comparator.

Contextual factors The panel judged the resource requirements to be negligible in terms of costs or savings for either but the cost effectiveness of the intervention was judged to probably favor the intervention over the comparator. The panel judged the impact on equity to probably increase and for the intervention to be probably feasible and acceptable.

Recommendation 8 In patients with established RA with moderate or high disease activity, who are experiencing an acute disease flare, the panel suggests using short-term-high-dose glucocorticoids + traditional DMARD therapy compared to traditional DMARD therapy alone (conditional recommendation, very low certainty of evidence).

Discussion

Clinical practice guidelines developed based on the GRADE approach are meant to ensure the provision of optimal patient care taking into account the best available evidence and other factors, such as the availability, feasibility, cost of treatment, the patient values and preferences, and equity issues. The adolopment of guidelines can help achieve this goal, and the project described herein is a proof-of-concept for the value of adoption, adaptation, and de novo development of existing guidelines. Indeed, we were able to successfully adolop in two waves 16 recommendations for the management of RA in the EMR.

The process proved to be feasible, with each wave of adaptation lasting 6 months, and requiring a total budget of ~40,000 USD. The feasibility was facilitated by using existing systematic reviews and collaborating with ACR, the source guideline organization [10]. A key factor in ensuring the success of the project was the high level of expertise on both the content and methodological levels.

Also, the adolopment of the original guidelines led to major changes in the recommendations, as the strength of recommendation changed from strong to conditional for five of the eight early RA adapted recommendation, and two of the eight established RA adapted recommendations (Table 6). The process showed the sensitivity of the strength of recommendation to contextual factors. The change in strength was mainly related to cost of medications, impact on health equities, and acceptability, which are of paramount importance in the EMR. Biologics may not be available or affordable in several of the countries represented by the content experts on the panel.

One limitation of our process relates to how we considered values and preferences in adapting the recommendations. We were able to recruit a patient representative only for the second wave. Also, while we conducted a thorough search for all of the selected questions, the search did not generate valuable information that reflect patient values and preferences within the EMR. As a result, the panel judged that there is probably no uncertainty or variability in how much people value the main outcomes, across all guideline questions. The certainty in this judgment is not as high due to the insufficient data. In fact, patient preferences are unknown in the region and

Table 6 Comparison of the original and adoloped recommendations from wave 1 and wave 2

ACR original recommendation	Adoloped recommendation	Change(s) and reason(s)
For early RA patients, the recommendation is strong for using a treat-to-target strategy rather than a non-targeted approach (Strong recommendation with the intervention, low certainty evidence)	In patients with early RA, the panel suggests using a treat to target strategy versus a non- targeted approach (conditional recommendation, low certainty evidence)	Strength changed from strong to conditional; certainty of evidence remained unchanged *Factors in favor of conditional recommendation*: balance of benefits and harms, cost, equity, and acceptability
For patients with early RA with low disease activity who are DMARD-naïve, the recommendation is conditional for using DMARD monotherapy over double-DMARD therapy (Conditional recommendation against the intervention, Low certainty evidence)	In patients with early RA with moderate or high disease activity, who are DMARD-naïve, the panel suggests not using combination double DMARD therapy versus mono-DMARD (conditional recommendation, low certainty evidence)	No change in the strength of the recommendation or in the certainty of evidence
For patients with early RA with low disease activity who are DMARD-naïve, the recommendation is conditional for using DMARD monotherapy over triple DMARD therapy (Conditional recommendation against the intervention, Low certainty evidence)	In patients with early RA with moderate or high disease activity, who are DMARD-naïve, the panel suggests not using combination triple traditional DMARD therapy versus mono-DMARD therapy (conditional recommendation, low certainty of evidence)	No change in the strength of the recommendation or in the certainty of evidence
For patients with early RA with low disease activity who are DMARD-naïve, the recommendation is conditional for using low dose glucocorticoids therapy in combination with DMARD's rather than using DMARD therapy alone (Conditional recommendation with the intervention, Low certainty evidence)	In patients with early RA with moderate or high disease activity, the panel suggests adding over not adding long-term low-dose glucocorticoid therapy to traditional DMARDs (conditional recommendation, very low certainty of evidence)	No change in strength of recommendations; certainty of evidence changed from low to very low
For patients with early RA and moderate or high disease activity despite DMARD monotherapy, the recommendation is strong for using combination DMARD therapy or TNFi or non-TNF biologic therapy (with or without MTX) (Strong recommendation, low certainty evidence)	In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, the panel suggests triple DMARD therapy over TNFi monotherapy (conditional recommendation, low certainty of evidence)	Strength changed from strong to conditional; certainty of evidence remained unchanged *Factors in favor of conditional recommendation*: balance of cost and health equities
For patients with early RA and moderate or high disease activity despite DMARD monotherapy, the recommendation is strong for using combination DMARD therapy or TNFi or non-TNF biologic therapy (with or without MTX) (Strong recommendation, low certainty evidence)	In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, the panel suggests using either TNFi + MTX or triple DMARD therpay (conditional recommendation, very low certainty evidence)	Strength changed from strong to conditional; certainty of evidence changed from low to very low *Factors in favor of conditional recommendation*: balance of cost and health equities
For patients with early RA and moderate or high disease activity despite DMARD monotherapy, the recommendation is strong for using combination DMARD therapy or TNFi or non-TNF biologic therapy (with or without MTX) (Strong recommendation, low certainty evidence)	In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, the panel suggests using either TNFi monotherapy or tocilizumab (conditional recommendation, low certainty evidence)	Strength changed from strong to conditional; certainty of evidence remained unchanged *Factors in favor of conditional recommendation*: balance of cost and health equities
For patients with early RA and moderate or high disease activity despite DMARD monotherapy, the recommendation is strong for using combination DMARD therapy or TNFi or non-TNF biologic therapy (with or without MTX) (Strong recommendation, low certainty evidence)	In patients with early RA with moderate or high disease activity, who have failed traditional DMARD therapy, the panel suggests using either TNFi + MTX or abatacept + MTX (conditional recommendation, very low certainty evidence)	Strength changed from strong to conditional; certainty of evidence changed from low to very low *Factors in favor of conditional recommendation*: the variability in cost of the medication between countries
For established RA patients, the recommendation is strong for using a treat-to-target strategy rather than a non-targeted approach (Strong recommendation with the intervention, moderate certainty evidence)	In patients with established RA, the panel suggests using a treat to target strategy versus a non-targeted approach (conditional recommendation, moderate certainty evidence)	Strength changed from strong to conditional; certainty of evidence remained unchanged *Factors in favor of conditional recommendation*: balance of benefits and harms, cost, equity, and acceptability

Table 6 (continued)

ACR original recommendation	Adoloped recommendation	Change(s) and reason(s)
For patients with established RA and moderate or high disease activity despite DMARD monotherapy, the recommendation is strong for using combination DMARDs or adding a TNFi or a non-TNF biologic or tofacitinib (all choices with or without methotrexate), rather than continuing DMARD monotherapy alone (Strong recommendation with the intervention or the comparator, high certainty evidence)	In patients with established RA with moderate or high disease activity, who have failed traditional DMARD therapy, the panel suggests using TNFi therapy + MTX versus combination triple DMARD therapy (conditional recommendation, very low certainty evidence)	Strength changed from strong to conditional; certainty of evidence changed from high to very low *Factors in favor of conditional recommendation*: balance of benefits and harms, cost, equity, and acceptability
For patients with established RA and disease activity is still moderate or high despite using multiple (2+) TNFi therapies, the recommendation is conditional for using a non-TNF biologic therapy (with methotrexate) rather than another TNFi (with methotrexate) (Conditional recommendation with the intervention, very low certainty evidence)	In patients with established RA with moderate or high disease activity who have failed multiple TNFi therapies, the panel suggests using a non-TNF biologic therapy + MTX versus another TNFi + MTX (conditional recommendation, very low certainty of evidence)	No change in the strength of the recommendation or in the certainty of evidence *Factors in favor of conditional recommendation*: balance of benefits and harms, cost effectiveness, and equity
For patients with established RA and moderate or high disease activity despite use of a single TNFi, not currently on DMARD therapy, the recommendation is conditional for using a non-TNF biologic rather than another TNFi (Conditional recommendation with the intervention, very low certainty evidence)	In patients with established RA with moderate or high disease activity, who have failed a single TNFi therapy, the panel suggests using non-TNF biologic therapy over another TNFi (conditional recommendation, low certainty of evidence)	No change in strength of recommendations; certainty of evidence changed from very low to low *Factors in favor of conditional recommendation*: balance of benefits and harms (probably favors the intervention)
For patients with established RA and moderate or high disease activity despite use of a single TNFi and methotrexate, currently on DMARD therapy, the recommendation is conditional for using a non-TNF biologic rather than another TNFi (Conditional recommendation with the intervention, very low certainty evidence)	In patients with established RA with moderate or high disease activity, who have failed a single TNFi therapy and are currently on DMARD therapy, the panel suggests using non-TNF biologic therapy over another TNFi (conditional recommendation, very low certainty of evidence)	No change in the strength of the recommendation or in the certainty of evidence *Factors in favor of conditional recommendation*: balance of benefits and harms, cost effectiveness, and equity
For patients with established RA with moderate or high disease activity after failing TNFi therapy and for whom non-TNF biologic therapy is not an option, the recommendation is conditional for using tofacitinib (with methotrexate) rather than another TNFi (with methotrexate) (Conditional recommendation, very low certainty of evidence)	In patients with established RA with moderate or high disease activity who have failed multiple TNFi therapies, the panel suggests using oral tofacitinib therapy + MTX versus another TNFi + MTX (conditional recommendation, very low certainty of evidence)	No change in the strength of the recommendation or in the certainty of evidence *Factors in favor of conditional recommendation*: balance of benefits and harms and equity
In patients with established RA and moderate or high disease activity, the recommendation is conditional for adding a short-term, low-dose glucocorticoid therapy in combination with DMARD, TNFi, or non-TNF biologic therapy rather than using DMARD, TNFi, or non-TNF biologic therapies without glucocorticoids (Conditional recommendation, High certainty of evidence)	In patients with established RA, with moderate or high disease activity, the panel suggests against using long-term-low-dose glucocorticoids + traditional DMARD therapy compared to traditional DMARD without glucocorticoids (conditional recommendation, low certainty of evidence)	No change in strength of recommendations Certainty of evidence changed from high to low
In patients with established RA experiencing an acute disease flare, the recommendation is conditional for using short-term glucocorticoid therapy in combination with DMARD, TNFi, or non-TNF biologic therapy over any of these therapies without glucocorticoids (Conditional recommendation, Very low certainty of evidence)	In patients with established RA with moderate or high disease activity, who are experiencing an acute disease flare, the panel suggests using short-term-high-dose glucocorticoids + traditional DMARD therapy traditional DMARD therapy alone (conditional recommendation, very low certainty of evidence)	No change in the strength of the recommendation or in the certainty of evidence

may possibly differ depending on factors such as context, literacy, and health beliefs [45].

In conclusion, this document provides adoloped recommendations for the treatment of early and established RA with moderate to severe activity in the EMR. All the formulated recommendations were conditional recommendations highlighting the need for assessing and evaluating local factors and patient values and preferences.

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