American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis Care & Research
Vol. 73, No. 7, July 2021, pp 924–939
DOI 10.1002/acr.24596

2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

Liana Fraenkel,[1] Joan M. Bathon,[2] Bryant R. England,[3] E. William St.Clair,[4] Thurayya Arayssi,[5] Kristine Carandang,[6] Kevin D. Deane,[7] Mark Genovese,[8] Kent Kwas Huston,[9] Gail Kerr,[10] Joel Kremer,[11] Mary C. Nakamura,[12] Linda A. Russell,[13] Jasvinder A. Singh,[14] Benjamin J. Smith,[15] Jeffrey A. Sparks,[16] Shilpa Venkatachalam,[17] Michael E. Weinblatt,[16] Mounir Al-Gibbawi,[18] Joshua F. Baker,[19] Kamil E. Barbour,[20] Jennifer L. Barton,[21] Laura Cappelli,[22] Fatimah Chamseddine,[18] Michael George,[23] Sindhu R. Johnson,[24] Lara Kahale,[18] Basil S. Karam,[18] Assem M. Khamis,[18] Iris Navarro-Millán,[25] Reza Mirza,[26] Pascale Schwab,[21] Namrata Singh,[27] Marat Turgunbaev,[28] Amy S. Turner,[28] Sally Yaacoub,[18] and Elie A. Akl[18]

Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology (ACR) are intended to provide general guidance for commonly encountered clinical scenarios. The recommendations do not dictate the care for an individual patient. The ACR considers adherence to the recommendations described in this guideline to be voluntary, with the ultimate determination regarding their application to be made by the clinicians in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed and endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice. ACR recommendations are not intended to dictate payment or insurance decisions, or drug formularies or other third-party analyses. Third parties that cite ACR guidelines should state that these recommendations are not meant for this purpose. These recommendations cannot adequately convey all uncertainties and nuances of patient care.
The American College of Rheumatology is an independent, professional, medical and scientific society that does not guarantee, warrant, or endorse any commercial product or service.

Objective. To develop updated guidelines for the pharmacologic management of rheumatoid arthritis.

Methods. We developed clinically relevant population, intervention, comparator, and outcomes (PICO) questions. After conducting a systematic literature review, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the certainty of evidence. A voting panel comprising clinicians and patients achieved consensus on the direction (for or against) and strength (strong or conditional) of recommendations.

Results. The guideline addresses treatment with disease-modifying antirheumatic drugs (DMARDs), including conventional synthetic DMARDs, biologic DMARDs, and targeted synthetic DMARDs, use of glucocorticoids, and use of DMARDs in certain high-risk populations (i.e., those with liver disease, heart failure, lymphoproliferative disorders, previous serious infections, and nontuberculous mycobacterial lung disease). The guideline includes 44 recommendations (7 strong and 37 conditional).

Conclusion. This clinical practice guideline is intended to serve as a tool to support clinician and patient decision-making. Recommendations are not prescriptive, and individual treatment decisions should be made through a shared decision-making process based on patients' values, goals, preferences, and comorbidities.

The findings and conclusions herein are those of the authors and do not represent the official position of the Centers for Disease Control and Prevention. This study did not involve human subjects, and therefore, approval from Human Studies Committees was not required.

This article is published simultaneously in *Arthritis & Rheumatology*.
Supported by the American College of Rheumatology.

[1]Liana Fraenkel, MD, MPH: Berkshire Medical Center, Pittsfield, Massachusetts, and Yale University School of Medicine, New Haven, Connecticut; [2]Joan M. Bathon, MD: Columbia University Irving Medical Center, New York Presbyterian Hospital, New York, New York; [3]Bryant R. England, MD, PhD: University of Nebraska Medical Center and VA Nebraska–Western Iowa Health Care System, Omaha, Nebraska; [4]E. William St.Clair, MD: Duke

INTRODUCTION

To support high-quality clinical care, the American College of Rheumatology (ACR) regularly updates clinical practice guidelines for the management of rheumatoid arthritis (RA), with the most recent update reported in 2015 (1). The current recommendations address treatment with the following: 1) conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs); 2) glucocorticoids; and 3) use of these medications in certain high-risk populations. The use of vaccines and nonpharmacologic treatment approaches (although initially part of this project) will be covered in future ACR treatment guideline publications. For recommendations regarding pretreatment screening and routine laboratory monitoring, we refer readers to the 2008, 2012, and 2015 guidelines (1–3), with newly approved therapies following the screening process recommended for other medications in the same class. Recommendations for the perioperative management of patients undergoing elective orthopedic surgery are addressed in the 2017 guideline for perioperative management (4). For recommendations regarding reproductive health, we refer readers to the 2020 ACR Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases (5).

In keeping with the Grading of Recommendations Assessment, Development and Evaluation [GRADE] methodology), the ACR panel developed recommendations for commonly encountered clinical scenarios (6–8). Both ***strong*** and ***conditional*** recommendations required achieving a 70% level of agreement by the voting panel. Each recommendation is qualified as being strong or conditional. In this context, strong recommendations are those for which the panel is highly confident that the recommended option favorably balances the expected benefits and risks for the majority of patients in clinical practice. In contrast, conditional recommendations are those for which the panel is less confident that the potential benefits outweigh the risks. A recommendation can be conditional either because of low or very low certainty in the evidence supporting one option over another, or because of an expectation of substantial variations in patient preferences for the options under consideration.

METHODS

This guideline follows the ACR guideline development process and ACR policy guiding the management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines) (6,8), which includes GRADE methodology (6,8), and abides by the AGREE Reporting Checklist to ensure the completeness and transparency of reporting in practice guidelines (9). Supplementary Appendix 1, available on the *Arthritis Care & Research* website at http://onlin

University Medical Center, Durham, North Carolina; [5]Thurayya Arayssi, MD: Weill Cornell Medicine–Qatar, Doha, Qatar; [6]Kristine Carandang, PhD, OTR/L: University of California, San Diego; [7]Kevin D. Deane, MD, PhD: University of Colorado, Aurora; [8]Mark Genovese, MD: Stanford University Medical Center, Palo Alto, California; [9]Kent Kwas Huston, MD: The Center for Rheumatic Disease/Allergy and Immunology, Kansas City, Missouri; [10]Gail Kerr, MD, FRCP (Edin): Veterans Affairs Medical Center, Georgetown and Howard University, Washington, DC; [11]Joel Kremer, MD: Albany Medical College and The Center for Rheumatology, Albany, New York; [12]Mary C. Nakamura, MD: University of California, San Francisco; [13]Linda A. Russell, MD: Hospital for Special Surgery, New York, New York; [14]Jasvinder A. Singh, MD, MPH: University of Alabama at Birmingham and Birmingham Veterans Affairs Medical Center, Birmingham, Alabama; [15]Benjamin J. Smith, DMSc, PA-C: Florida State University College of Medicine School of Physician Assistant Practice, Tallahassee; [16]Jeffrey A. Sparks, MD, MMSc, Michael E. Weinblatt, MD: Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [17]Shilpa Venkatachalam, PhD: Global Healthy Living Foundation, Upper Nyack, New York; [18]Mounir Al-Gibbawi, MD, Fatimah Chamseddine, MD, Lara Kahale, RN, MSc, PhD, Basil S. Karam, MD, Assem M. Khamis, MD, MPH, Sally Yaacoub, RPh, MPH, Elie A. Akl, MD, MPH, PhD: American University of Beirut, Beirut, Lebanon; [19]Joshua F. Baker, MD, MSCE: Corporal Michael J. Crescenz VA Medical Center and the University of Pennsylvania, Philadelphia, Pennsylvania; [20]Kamil E. Barbour, PhD, MPH, MS: Centers for Disease Control and Prevention, Atlanta, Georgia; [21]Jennifer L. Barton, MD, MCR, Pascale Schwab, MD: Oregon Health & Science University and VA Portland Health Care System, Portland, Oregon; [22]Laura Cappelli, MD, MHS, MS: Johns Hopkins Medicine, Baltimore, Maryland; [23]Michael George, MD, MSCE: University of Pennsylvania, Philadelphia; [24]Sindhu R. Johnson, MD, PhD, FRCPC: Toronto Western Hospital, Mount Sinai Hospital, Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada; [25]Iris Navarro-Millán, MD, MSPH: Weill Cornell Medicine, New York, New York; [26]Reza Mirza, MD: University of Toronto, Toronto, Ontario, Canada; [27]Namrata Singh, MD, MSCI, FACP: University of Washington, Seattle; [28]Marat Turgunbaev, MD, MPH, Amy S. Turner: American College of Rheumatology, Atlanta, Georgia.

Dr. Bathon has received consulting fees, speaking fees, and/or honoraria from Gilead Biosciences (less than $10,000). Dr. St.Clair has received consulting fees, speaking fees, and/or honoraria from Bristol Myers Squibb (less than $10,000) and royalties from UpToDate. Dr. Deane has received consulting fees, speaking fees, and/or honoraria from Bristol Myers Squibb, Inova Diagnostics, Janssen, and Microdrop (less than $10,000 each). Dr. Genovese has received consulting fees, speaking fees, and/or honoraria from AbbVie, Amgen, BeiGene, Eli Lilly and Company, GlaxoSmithKline, Pfizer, Sanofi, R-Pharm, and SetPoint Medical (less than $10,000 each) and owns stock or stock options in Gilead Sciences. Dr. Huston has received consulting fees and/or honoraria from Trio Health Advisory (less than $10,000). Dr. Kerr has received consulting fees, speaking fees, and/or honoraria from Jansen, Sanofi, and Genzyme (less than $10,000 each). Dr. Kremer has received consulting fees, speaking fees, and/or honoraria from AbbVie, Bristol Myers Squibb, Gilead, Eli Lilly and Company, and Pfizer (less than $10,000 each) and owns stock or stock options in Corrona. Dr. Singh has received consulting fees, speaking fees, and/or honoraria from MediSYS, Fidia Pharma, UBM, Trio Health, Medscape, WebMD, Clinical Care Options, Clearview Healthcare Partners, Putnam Associates, Focus Forward, Navigant Consulting, Spherix, Practice Point Communications (less than $10,000 each), and Simply Speaking (more than $10,000) and owns stock or stock options in Vaxart Pharmaceuticals. Dr. Weinblatt has received consulting fees, speaking fees, and/or honoraria from AbbVie, Amgen, Canfite, Crescendo, GlaxoSmithKline, Horizon, Johnson & Johnson, Genentech/Roche, Scipher, SetPoint, Tremeau (less than $10,000 each), Eli Lilly and Company, Bristol Myers Squibb, Gilead, and Corrona (more than $10,000 each), royalties from Elsevier, and owns stock or stock options in Canfite, Scipher, Inmedix, and Vorso. Dr. Baker has received consulting fees, speaking fees, and/or honoraria from Bristol Myers Squibb, Gilead, Burns-White, and Simply Speaking Rheumatology (less than $10,000 each). Dr. Cappelli has received consulting fees, speaking fees, and/or honoraria from AbbVie (less than $10,000) and research support from Bristol Myers Squibb. Dr. George has received honoraria from Paradigm Medical Communications (less than $10,000) and research support from Bristol Myers Squibb. Dr. Johnson has received consulting fees and/or honoraria from Boehringer Ingelheim and Ikaria (less than $10,000 each) and research support from GlaxoSmithKline, Corbus, Roche, Merck, Boehringer Ingelheim, and Bayer. No other disclosures relevant to this article were reported.

Address correspondence to Liana Fraenkel, MD, MPH, 725 North Street, Pittsfield, MA 01201. Email: liana.fraenkel@yale.edu.

Submitted for publication September 8, 2020; accepted in revised form March 15, 2021.

elibrary.wiley.com/doi/10.1002/acr.24596/abstract), includes a detailed description of the methods. Briefly, the core leadership team drafted clinical population, intervention, comparator, and outcomes (PICO) questions. The literature review team performed systematic literature reviews for the PICO questions, selected and evaluated individual studies and graded the quality of the body of evidence available for each outcome, and produced the evidence report that summarizes these assessments (see Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract). The core team defined the critical study outcome as disease activity for most PICO questions. Because the ACR has, in a separate project, endorsed several disease activity measures for use in clinical practice, this guideline does not define levels of disease activity or the instruments a clinician should use to measure it (10). For PICO questions related to tapering, the critical outcomes were disease flare and subsequent return to the treatment target. Physical function, radiographic progression, quality of life, other patient-reported outcome measures, and adverse events were defined as important outcomes. Additional clinical outcomes were defined for PICO questions pertaining to select high-risk conditions (see Supplementary Appendix 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract). When available, cost-effectiveness studies were included with the evidence reports. Cost estimates (average wholesale prices) were retrieved from Lexicomp (see Supplementary Appendix 4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract). The panel considered these estimates from a societal perspective, i.e., based on the list price, and not the copay.

An in-person panel of 10 patients with RA, moderated by the project's principal investigator, reviewed the evidence report (along with a summary and interpretation by the moderator) and provided patient perspectives for consideration by the voting panel. The voting panel (13 clinicians and 2 patients) reviewed the evidence reports and patient perspectives and voted on recommendation statements. Rosters of the core leadership, literature review team, and panel members are listed in Supplementary Appendix 5, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract.

Several guiding principles, definitions, and assumptions were established a priori (Table 1). Because poor prognostic factors (11) have had less impact than other factors on prior RA treatment recommendations, they were not explicitly considered in formulating the PICO questions. However, poor prognostic factors were considered as possible influential factors in physicians' and patients' decision-making when developing recommendations. In contrast to the 2015 guideline (1), recommendations were not provided for subgroups defined by early versus late RA disease duration. This change was made because current disease activity, prior therapies used, and the presence of comorbidities were felt to be more relevant than disease duration for most treatment decisions. However, early diagnosis and treatment in RA is associated with improved outcomes and is thus an important overarching principle in its management (12). Recommendations are intended for the general RA patient population and assume that patients do not have contraindications to the options under consideration.

Table 1. Guiding principles*

RA requires early evaluation, diagnosis, and management.
Treatment decisions should follow a shared decision-making process.
Treatment decisions should be reevaluated within a minimum of 3 months based on efficacy and tolerability of the DMARD(s) chosen.
Disease activity levels refer to those calculated using RA disease activity measures endorsed by the ACR (10).
Recommendations are intended for the general RA patient population and assume that patients do not have contraindications to the options under consideration.
Recommendations are limited to DMARDs approved by the US FDA for treatment of RA. csDMARDs: hydroxychloroquine, sulfasalazine, methotrexate, leflunomide bDMARDs: TNF inhibitors (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), T cell costimulatory inhibitor (abatacept), IL-6 receptor inhibitors (tocilizumab, sarilumab), anti-CD20 antibody (rituximab)† tsDMARDs: JAK inhibitors (tofacitinib, baricitinib, upadacitinib)
Triple therapy refers to hydroxychloroquine, sulfasalazine, and either methotrexate or leflunomide.
Serious infection refers to an infection requiring intravenous antibiotics or hospitalization.
Biosimilars are considered equivalent to FDA-approved originator bDMARDs.
Recommendations referring to bDMARDs exclude rituximab unless patients have had an inadequate response to TNF inhibitors (in order to be consistent with FDA approval) or have a history of lymphoproliferative disorder for which rituximab is an approved therapy.
Treat-to-target refers to a systematic approach involving frequent monitoring of disease activity using validated instruments and modification of treatment to minimize disease activity with the goal of reaching a predefined target (low disease activity or remission).
Target refers to low disease activity or remission.
Recommendations specify that patients be at target (low disease activity or remission) for at least 6 months prior to tapering.
Dose reduction refers to lowering the dose or increasing the dosing interval of a DMARD. Gradual discontinuation of a DMARD is defined as gradually lowering the dose of a DMARD and subsequently stopping it.

* RA = rheumatoid arthritis; DMARDs = disease-modifying antirheumatic drugs; ACR = American College of Rheumatology; FDA = Food and Drug Administration; csDMARDs = conventional DMARDs; bDMARDs = biologic DMARDs; TNF = tumor necrosis factor; IL-6 = interleukin-6; tsDMARDs = targeted synthetic DMARDs.
† Anakinra was not included due to infrequent use for patients with RA.

RESULTS/RECOMMENDATIONS

The recommendations are based on a set of 81 PICO questions. The literature review initially identified 22,971 manuscripts (for the full set of PICO questions covering both pharmacologic and nonpharmacologic treatment). After excluding 18,333 titles

and abstracts, 4,038 full-text articles were screened, of which 1,392 were excluded and 2,646 were considered for the evidence report. After full-text screening, 133 manuscripts were mapped to ≥1 PICO questions addressing pharmacologic treatment (see Supplementary Appendix 6, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract). The literature review did not identify any evidence for 41% (n = 33) of the PICO questions.

Recommendations for DMARD-naive patients with moderate-to-high disease activity (Table 2)

DMARD monotherapy

Methotrexate is strongly recommended over hydroxychloroquine or sulfasalazine for DMARD-naive patients with moderate-to-high disease activity

This recommendation is strongly in favor of methotrexate despite very low-certainty evidence for hydroxychloroquine and low-certainty evidence for sulfasalazine based on the amount of data supporting the disease-modifying properties of methotrexate monotherapy compared to hydroxychloroquine or sulfasalazine and concerns over the long-term tolerability of sulfasalazine (13,14).

Methotrexate is conditionally recommended over leflunomide for DMARD-naive patients with moderate-to-high disease activity

Despite low-certainty evidence of comparable efficacy, methotrexate is preferred over leflunomide because of the evidence supporting its value as an anchor DMARD in combination regimens. Additional advantages of methotrexate include its greater dosing flexibility and lower cost.

Methotrexate monotherapy is strongly recommended over bDMARD or tsDMARD monotherapy for DMARD-naive patients with moderate-to-high disease activity

There is low-certainty evidence suggesting superiority of tocilizumab monotherapy (15) over methotrexate monotherapy and moderate-certainty evidence suggesting greater efficacy

Table 2. Disease-modifying antirheumatic drugs (DMARDs) initiation*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)†	Evidence table(s), in Supp. App. 2
Initiation of treatment in DMARD-naive patients with moderate-to-high disease activity			
Methotrexate monotherapy is **strongly** recommended over:			
Hydroxychloroquine or sulfasalazine	Very low/low‡	PICO 2a.C1/C2	p. 14–5
bDMARD or tsDMARD monotherapy	Very low/moderate	PICO 5a.C1–4/C5§	p. 61–78
Combination of methotrexate plus a non–TNF inhibitor bDMARD or tsDMARD¶	Low/very low	PICO 6a.C2–4/C5§	p. 109, 117–28
Methotrexate monotherapy is **conditionally** recommended over:			
Leflunomide	Low	PICO 2a.C3	p. 18
Dual or triple csDMARD therapy¶	Moderate	PICO 4a.C1–C2	p. 46–9
Combination of methotrexate plus a TNF inhibitor¶	Low	PICO 6a.C1	p. 110
Initiation of a csDMARD without short-term (<3 months) glucocorticoids is **conditionally** recommended over initiation of a csDMARD with short-term glucocorticoids.	Very low	PICO 7a	p. 167
Initiation of a csDMARD without longer-term (≥3 months) glucocorticoids is **strongly** recommended over initiation of a csDMARD with longer-term glucocorticoids.	Moderate	PICO 8a	p. 170
Initiation of treatment in DMARD-naive patients with low disease activity			
Hydroxychloroquine is **conditionally** recommended over other csDMARDs.	Very low	PICO 1a.C1–4	p. 1–6
Sulfasalazine is **conditionally** recommended over methotrexate.	Very low	PICO 1a.C2	p. 2
Methotrexate is **conditionally** recommended over leflunomide.	Very low	PICO 1a.C3	p. 5
Initiation of treatment in csDMARD-treated, but methotrexate-naive, patients with moderate-to-high disease activity#			
Methotrexate monotherapy is **conditionally** recommended over the combination of methotrexate plus a bDMARD or tsDMARD.**	Moderate/very low	PICO 6b.C1–4/C5§	p. 136–56

* PICO = population, intervention, comparator, and outcomes; Supp. App. 2 = Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract; bDMARD = biologic DMARD; tsDMARD = targeted synthetic DMARD; TNF = tumor necrosis factor; csDMARD = conventional synthetic DMARD.
† The closest matching PICO questions to each recommendation are provided.
‡ The first certainty of evidence applies to the first listed option; the second certainty of evidence applies to the second listed option.
§ The original PICO included individual DMARDs as comparators. The recommendation considers bDMARDs as a group.
¶ The direction of the beneficial effect is in favor of the nonpreferred option.
# Other recommendations for this patient population are the same as those for DMARD-naive patients.
** The direction of the beneficial effect is in favor of the nonpreferred option. The certainty of evidence is high for the combination of methotrexate plus a TNF inhibitor and moderate for other bDMARDs.

of JAK inhibitor monotherapy over methotrexate monotherapy. The study by van Vollenhoven et al (16) was not considered by the voting panel as it was published after the evidence report was updated. However, methotrexate monotherapy is preferred because of its established efficacy and safety as a first-line DMARD and low cost. Moreover, tocilizumab and JAK inhibitors are not approved by the US Food and Drug Administration (FDA) for use in csDMARD-naive patients. Safety concerns released in early 2021 associated with JAK inhibitors (17,18) further support the recommendation of methotrexate monotherapy over tsDMARDs as initial DMARD therapy at this time.

Methotrexate monotherapy is conditionally recommended over dual or triple csDMARD therapy for DMARD-naive patients with moderate-to-high disease activity

The recommendation favors methotrexate monotherapy because the higher burden of combination therapy (e.g., multiple medications, higher cost) outweighs the moderate-quality evidence suggesting greater improvements in disease activity associated with combination csDMARDs (19). The recommendation is conditional because some patients may choose csDMARD combination therapy for an increased probability of obtaining a better response despite the added burden of taking multiple medications.

Methotrexate monotherapy is conditionally recommended over methotrexate plus a tumor necrosis factor (TNF) inhibitor for DMARD-naive patients with moderate-to-high disease activity

Despite low-certainty evidence supporting greater improvement in disease activity with methotrexate plus a TNF inhibitor, methotrexate monotherapy is preferred over the combination because many patients will reach their goal on methotrexate monotherapy and because of the additional risks of toxicity and higher costs associated with TNF inhibitors. The recommendation is conditional because some patients, especially those with poor prognostic factors, may prioritize more rapid onset of action and greater chance of improvement associated with combination therapy (20–22) over the additional risks and costs associated with initial use of methotrexate in combination with a TNF inhibitor.

Methotrexate monotherapy is strongly recommended over methotrexate plus a non–TNF inhibitor bDMARD or tsDMARD for DMARD-naive patients with moderate-to-high disease activity

There is very low-certainty evidence supporting the superiority of methotrexate plus a non–TNF inhibitor bDMARD or tsDMARD over methotrexate monotherapy in DMARD-naive patients; thus, methotrexate monotherapy is strongly preferred given the lack of proven benefit and additional risks and costs associated with the addition of a non–TNF inhibitor bDMARD or tsDMARD in this patient population.

Glucocorticoids

Initiation of a csDMARD without short-term (<3 months) glucocorticoids is conditionally recommended over initiation of a csDMARD with short-term glucocorticoids for DMARD-naive patients with moderate-to-high disease activity

While the voting panel agreed that glucocorticoids should not be systematically prescribed, the recommendation is conditional because all members acknowledged that short-term glucocorticoids are frequently necessary to alleviate symptoms prior to the onset of action of DMARDs. Treatment with glucocorticoids should be limited to the lowest effective dose for the shortest duration possible. The toxicity associated with glucocorticoids was judged to outweigh potential benefits.

Initiation of a csDMARD without longer-term (≥3 months) glucocorticoids is strongly recommended over initiation of a csDMARD with longer-term glucocorticoids for DMARD-naive patients with moderate-to-high disease activity

Although some patients may require longer-term glucocorticoids, this strong recommendation *against* longer-term glucocorticoid therapy is made because of its significant toxicity.

Recommendations for DMARD-naive patients with low disease activity (Table 2)

Hydroxychloroquine is conditionally recommended over other csDMARDs, sulfasalazine is conditionally recommended over methotrexate, and methotrexate is conditionally recommended over leflunomide for DMARD-naive patients with low disease activity

Hydroxychloroquine is conditionally recommended over other csDMARDs because it is better tolerated and has a more favorable risk profile in patients with RA. Sulfasalazine is recommended over methotrexate because it is less immunosuppressive, and the patient panel felt that many patients with low disease activity would prefer to avoid the side effects associated with methotrexate. The recommendations are conditional because methotrexate may be the preferred initial therapy in patients at the higher end of the low disease activity range and in those with poor prognostic factors (11). Methotrexate is recommended over leflunomide because of its greater dosing flexibility and lower cost.

Recommendation for patients who have been treated with csDMARDs, excluding methotrexate, and who have moderate-to-high disease activity (Table 2)

Recommendations are the same as for DMARD-naive patients except for this population. The strength of the following recommendation is conditional for all bDMARDs and tsDMARDs.

Methotrexate monotherapy is conditionally recommended over the combination of methotrexate plus a bDMARD or tsDMARD

The recommendation is conditional because the voting panel thought that some patients who have already had persistent disease activity despite use of ≥1 csDMARD will prefer combination treatment for a more rapid response.

Recommendations for administration of methotrexate (Table 3)

Oral methotrexate is conditionally recommended over subcutaneous methotrexate for patients initiating methotrexate

Oral administration is preferred, despite moderate evidence suggesting superior efficacy of subcutaneous injections, due to the ease of oral administration and similar bioavailability at typical starting doses (23).

Initiation/titration of methotrexate to a weekly dose of at least 15 mg within 4 to 6 weeks is conditionally recommended over initiation/titration to a weekly dose of <15 mg

The recommendation is conditional because there are few studies comparing different dosing strategies and wide variation in physician and patient preferences regarding the tradeoff between the increased efficacy and risks of toxicity associated with higher starting doses. This recommendation refers only to the initial prescribing of methotrexate and is not meant to limit further dose escalation, which often provides additional efficacy (24).

A split dose of oral methotrexate over 24 hours or weekly subcutaneous injections, and/or an increased dose of folic/folinic acid, is conditionally recommended over switching to alternative DMARD(s) for patients not tolerating oral weekly methotrexate

Despite the very low certainty of evidence supporting these strategies for alleviating side effects related to methotrexate, split dosing, changing to the subcutaneous route of administration, and increased doses of folic/folinic acid are the preferred initial strategies over switching to another DMARD because of the efficacy, long-term safety, and low costs associated with methotrexate. The recommendation is conditional because patient preferences play an important role in the decision whether to continue methotrexate or switch to other DMARDs.

Switching to subcutaneous methotrexate is conditionally recommended over the addition of/switching to alternative DMARD(s) for patients taking oral methotrexate who are not at target

This recommendation is consistent with the voting panel's overarching principle of maximizing use of methotrexate prior to switching/adding DMARDs. However, there are no data comparing outcomes in patients who switch to subcutaneous methotrexate versus another treatment strategy that includes other DMARDs. The recommendation is conditional because patient preferences and the magnitude of previous response to methotrexate play an important role in this decision.

Table 3. Methotrexate administration*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)	Evidence table(s), in Supp. App. 2
Oral methotrexate is **conditionally** recommended over subcutaneous methotrexate for patients initiating methotrexate.	Moderate	PICO 9	p. 181
Initiation/titration of methotrexate to a weekly dose of at least 15 mg within 4 to 6 weeks is **conditionally** recommended over initiation/titration to a weekly dose of <15 mg.†	Moderate/ very low‡	PICO 10.C1–C3	p. 184–5
A split dose of oral methotrexate over 24 hours or subcutaneous injections, and/or an increased dose of folic/folinic acid, is **conditionally** recommended over switching to alternative DMARD(s) for patients not tolerating oral weekly methotrexate.	Very low	PICO 16 and PICO 15	p. 206–10
Switching to subcutaneous methotrexate is **conditionally** recommended over the addition of/switching to alternative DMARD(s) for patients taking oral methotrexate who are not at target.	Very low	PICO 18	p. 235

* PICO = population, intervention, comparator, and outcomes; Supp. App. 2 = Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract; DMARD = disease-modifying antirheumatic drug.
† This recommendation refers only to the initial prescribing of methotrexate and is not meant to limit further dose escalation, which often provides additional efficacy.
‡ The first certainty of evidence applies to the first listed option; the second certainty of evidence applies to the second option.

Recommendations for treatment modification in patients treated with DMARDs who are not at target (Table 4)

Treat-to-target

A treat-to-target approach is strongly recommended over usual care for patients who have not been previously treated with bDMARDs or tsDMARDs

This recommendation applies to dose optimization of methotrexate and to the subsequent addition of DMARDs when required. The recommendation is strong despite low-certainty evidence because of the recognized importance of systematic monitoring and adjustment of treatment to minimize inflammation to prevent joint damage, as well as other long-term sequelae including cardiovascular disease and osteoporosis.

A treat-to-target approach is conditionally recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs

The recommendation is conditional because of the uncertain incremental benefits of treat-to-target over usual care in this patient population. In this context, usual care refers to commonly employed practice patterns, i.e., adjustment of treatment based on shared decision-making, albeit typically without systematic monitoring of disease activity using validated measures to reach a predefined target. Moreover, 1) the number of remaining available treatment options, 2) the impact of noninflammatory causes of pain, comorbidities, and/or damage on the accuracy of validated disease activity assessments, and 3) the patient's threshold for changing medications may have a more significant influence on the decision to follow a treat-to-target approach in this population compared to patients who are bDMARD- and tsDMARD-naive.

A minimal initial treatment goal of low disease activity is conditionally recommended over a goal of remission

An initial target of low disease activity is preferred because remission by established criteria may not be achievable for many patients (25). In addition, the patient panel emphasized that failure to reach a specified target may be disheartening and stressful for some patients. They emphasized that it would be preferable to *initially* aim for low disease activity and *subsequently* consider a goal of remission. However, treatment goals should be systematically reassessed over time and individualized to each patient to ensure that remission is targeted when possible. The recommendation is conditional because remission is a reasonable initial goal for patients with early disease and minimal exposure to bDMARDs and tsDMARDs, and patient preferences play a significant role in this decision.

Modification of DMARD(s)

Addition of a bDMARD or tsDMARD is conditionally recommended over triple therapy (i.e., addition of sulfasalazine and hydroxychloroquine) for patients taking maximally tolerated doses of methotrexate who are not at target

The panel vigorously debated whether to recommend addition of a bDMARD or tsDMARD versus sulfasalazine and

Table 4. Treatment modification*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)	Evidence table(s), in Supp. App. 2
A TTT approach is **strongly** recommended over usual care for patients who have not been previously treated with bDMARDs or tsDMARDs.	Low	PICO 12.a	p. 191
A TTT approach is **conditionally** recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs.	Very low	PICO 12.b	p. 199
A minimal initial treatment goal of low disease activity is **conditionally** recommended over a goal of remission.	Low	PICO 13	p. 201
Addition of a bDMARD or tsDMARD is **conditionally** recommended over triple therapy for patients taking maximally tolerated doses of methotrexate who are not at target.	Very low	PICO 19.C2–C6†	p. 240–1
Switching to a bDMARD or tsDMARD of a different class is **conditionally** recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target.	Very low	PICO 24–27†	p. 293–338
Addition of/switching to DMARDs is **conditionally** recommended over continuation of glucocorticoids for patients taking glucocorticoids to remain at target.	Very low	PICO 23	p. 292
Addition of/switching to DMARDs (with or without IA glucocorticoids) is **conditionally** recommended over the use of IA glucocorticoids alone for patients taking DMARDs who are not at target.	Very low	PICO 28.C1–C2	p. 339–40

* PICO = population, intervention, comparator, and outcomes; Supp. App. 2 = Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract; TTT = treat-to-target; bDMARDs = biologic disease-modifying antirheumatic drugs; tsDMARDs = targeted synthetic DMARDs; IA = intraarticular.
† The original PICO included individual DMARDs as comparators. The recommendation considers bDMARDs as a group.

hydroxychloroquine (triple therapy) for patients with an inadequate response to methotrexate monotherapy in view of very low-certainty evidence favoring bDMARDs or tsDMARDs, randomized controlled trials demonstrating equivalent long-term outcomes across both treatment strategies, and significantly less societal cost associated with triple therapy (26–29). Addition of a bDMARD or tsDMARD was ultimately preferred because the patient panel strongly prioritized maximizing improvement as quickly as possible. In addition, both the patient and voting panels valued the greater persistence of methotrexate plus a bDMARD or tsDMARD compared to triple therapy (defined in Table 1) (13,30). The recommendations from these studies (13,31) are conditional because triple therapy may be preferred in lower resource settings as well as in patients with specific comorbidities for whom triple therapy may be associated with significantly less risk of adverse events. This choice is highly preference sensitive, and decisions on how best to escalate care should incorporate patients' preferences. There is no current recommendation for a bDMARD versus a tsDMARD when adjusting treatment; however, the voting panel acknowledged that safety data released in early 2021 (17,18) may require a modification of this recommendation when peer-reviewed results are published.

Switching to a bDMARD or tsDMARD of a different class is conditionally recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target

The recommendation is based on very low-certainty evidence supporting greater improvement in disease activity and drug survival among patients switching classes. The recommendation is conditional because patient and physician preferences are likely to vary based on prior experiences with specific DMARDs.

Use of glucocorticoids

Addition of/switching to DMARDs is conditionally recommended over continuation of glucocorticoids for patients taking glucocorticoids to remain at target

This recommendation assumes that improved disease control with DMARDs should allow less use of glucocorticoids. The recommendation is conditional because the continued use of glucocorticoids may be required for patients who do not respond to DMARDs even after maximizing methotrexate dosage and switching DMARD classes.

Addition of/switching to DMARDs (with or without intraarticular [IA] glucocorticoids) is conditionally recommended over the use of IA glucocorticoids alone for patients taking DMARDs who are not at target

This recommendation was based on the premise that DMARDs should be adjusted to reduce disease activity, irrespective of treatment with IA glucocorticoids. The recommendation is conditional because patients may choose to defer adding/switching DMARDs if they obtain relief from IA injection(s).

Recommendations for tapering/discontinuing DMARDs (Table 5)

Because of the moderate-to-high risk for flare and the potential for irreversible long-term damage associated with stopping all DMARDs, the following recommendations presume that patients maintain a therapeutic dose of at least 1 DMARD. In addition, the recommendations specify that patients be at target (low disease activity or remission) for at least 6 months

Table 5. Tapering disease-modifying antirheumatic drugs (DMARDs)*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)	Evidence table(s), in Supp. App. 2
Continuation of all DMARDs at their current dose is **conditionally** recommended over a dose reduction of a DMARD.	Low	PICO 54.a	p. 381
Dose reduction is **conditionally** recommended over gradual discontinuation of a DMARD.	Low	PICO 52.C2 and PICO 53. C2	p. 351–5, p. 372–6
Gradual discontinuation is **conditionally** recommended over abrupt discontinuation of a DMARD.	Low	PICO 52.C1 and PICO 53.C1	p. 351, 372
Gradual discontinuation of sulfasalazine is **conditionally** recommended over gradual discontinuation of hydroxychloroquine for patients taking triple therapy who wish to discontinue a DMARD.	Very low	PICO 58	p. 400
Gradual discontinuation of methotrexate is **conditionally** recommended over gradual discontinuation of the bDMARD or tsDMARD for patients taking methotrexate plus a bDMARD or tsDMARD who wish to discontinue a DMARD.	Very low	PICO 59.C1	p. 401

* PICO = population, intervention, comparator, and outcomes; Supp. App. 2 = Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract; bDMARD = biologic DMARD; tsDMARD = targeted synthetic DMARD.

prior to tapering. Patients in remission for <6 months should not routinely be considered for dose reduction or withdrawal. Although the optimal time at target prior to tapering has not been established, the voting panel considered 6 months to be a reasonable minimal length of time to ensure stable disease control. "Dose reduction" refers to lowering the dose or increasing the dosing interval of a DMARD. "Gradual discontinuation" denotes gradually lowering the dose of a DMARD and subsequently stopping it.

Continuation of all DMARDs at their current dose is conditionally recommended over a dose reduction of a DMARD, dose reduction is conditionally recommended over gradual discontinuation of a DMARD, and gradual discontinuation is conditionally recommended over abrupt discontinuation of a DMARD for patients who are at target for at least 6 months

These recommendations are based on studies demonstrating a higher risk of flare in patients who are 1) lowering the dose of a DMARD versus continuing DMARDs at the same dose, and 2) abruptly versus gradually discontinuing a DMARD (32–36). The recommendations are conditional because patient and physician preferences are expected to vary.

Gradual discontinuation of sulfasalazine is conditionally recommended over gradual discontinuation of hydroxychloroquine for patients taking triple therapy who wish to discontinue a DMARD

Gradually discontinuing sulfasalazine is recommended because of its poorer treatment persistence due to adverse events (14). The recommendation is conditional because patient and physician preferences are expected to vary.

Gradual discontinuation of methotrexate is conditionally recommended over gradual discontinuation of the bDMARD or tsDMARD for patients taking methotrexate plus a bDMARD or tsDMARD who wish to discontinue a DMARD

In the absence of direct evidence, gradually discontinuing methotrexate is preferred because a bDMARD or tsDMARD is typically added following an inadequate response to methotrexate. Thus, the continued use of the bDMARD or tsDMARD is more likely to maintain disease control than the continued use of methotrexate. The recommendation is conditional because gradual discontinuation of the bDMARD or tsDMARD may be favored depending on comorbidities, risk for infection, cost concerns, as well as patient and clinician preferences. The voting panel cautioned that many patients treated with certain monoclonal antibodies may require ongoing treatment with methotrexate to prevent the formation of antidrug antibodies (37).

Recommendations for specific patient populations (Table 6)

Subcutaneous nodules

Methotrexate is conditionally recommended over alternative DMARDs for patients with subcutaneous nodules who have moderate-to-high disease activity

Switching to a non-methotrexate DMARD is conditionally recommended over continuation of methotrexate for patients taking methotrexate with progressive subcutaneous nodules

While accelerated nodulosis has been observed in patients starting methotrexate (38), there are no studies examining comparative strategies for patients with stable or progressive subcutaneous nodules. The preceding 2 recommendations are conditional because patient and clinician preferences are expected to vary. The recommendation to switch is based on the premise that methotrexate is a contributing factor to progressive nodulosis.

Pulmonary disease

Methotrexate is conditionally recommended over alternative DMARDs for the treatment of inflammatory arthritis for patients with clinically diagnosed mild and stable airway or parenchymal lung disease, or incidental disease detected on imaging, who have moderate-to-high disease activity

Studies indicate that preexisting lung disease is a risk factor for methotrexate-related pneumonitis (39,40). However, the overall risk of worsening lung disease attributable to methotrexate is uncertain, and alternative DMARDs have also been associated with lung disease (41–45). The recommendation is in favor of methotrexate because of its important role as an anchor treatment in RA and the lack of alternatives with similar efficacy and/or superior long-term safety profiles. The recommendation is conditional because some clinicians (rheumatologists and pulmonologists) and patients will prefer an alternative option rather than accept any additional risk of lung toxicity. Patients with preexisting lung disease should be informed of their increased risk of methotrexate pneumonitis prior to initiating treatment with methotrexate.

Table 6. Specific patient populations*

Recommendations	Certainty of evidence	Based on the evidence report(s) of the following PICO(s)	Evidence table(s), in Supp. App. 2
Subcutaneous nodules			
Methotrexate is **conditionally** recommended over alternative DMARDs for patients with subcutaneous nodules who have moderate-to-high disease activity.	Very low	PICO 64	p. 427
Switching to a non-methotrexate DMARD is **conditionally** recommended over continuation of methotrexate for patients taking methotrexate with progressive subcutaneous nodules.	Very low	PICO 65	p. 428
Pulmonary disease			
Methotrexate is **conditionally** recommended over alternative DMARDs for the treatment of inflammatory arthritis for patients with clinically diagnosed mild and stable airway or parenchymal lung disease who have moderate-to-high disease activity.	Very low	PICO 67	p. 430
Heart failure			
Addition of a non–TNF inhibitor bDMARD or tsDMARD is **conditionally** recommended over addition of a TNF inhibitor for patients with NYHA class III or IV heart failure and an inadequate response to csDMARDs.	Very low	PICO 70	p. 435
Switching to a non–TNF inhibitor bDMARD or tsDMARD is **conditionally** recommended over continuation of a TNF inhibitor for patients taking a TNF inhibitor who develop heart failure.	Very low	PICO 71	p. 436
Lymphoproliferative disorder			
Rituximab is **conditionally** recommended over other DMARDs for patients who have a previous lymphoproliferative disorder for which rituximab is an approved treatment and who have moderate-to-high disease activity.	Very low	PICO 75 and PICO 76	p. 446–7
Hepatitis B infection			
Prophylactic antiviral therapy is **strongly** recommended over frequent monitoring alone for patients initiating rituximab who are hepatitis B core antibody positive (regardless of hepatitis B surface antigen status).	Very low	PICO 82	p. 459
Prophylactic antiviral therapy is **strongly** recommended over frequent monitoring alone for patients initiating any bDMARD or tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen positive.	Very low	PICO 83	p. 464
Frequent monitoring alone is **conditionally** recommended over prophylactic antiviral therapy for patients initiating a bDMARD other than rituximab or a tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen negative.	Very low	PICO 84	p. 471
Nonalcoholic fatty liver disease			
Methotrexate is **conditionally** recommended over alternative DMARDs for DMARD-naive patients with nonalcoholic fatty liver disease, normal liver enzymes and liver function tests, and no evidence of advanced liver fibrosis who have moderate-to high disease activity.	Very low	PICO 87	p. 489
Persistent hypogammaglobulinemia without infection			
In the setting of persistent hypogammaglobulinemia without infection, continuation of rituximab therapy for patients at target is **conditionally** recommended over switching to a different bDMARD or tsDMARD.	Very low	PICO 66	p. 429
Previous serious infection			
Addition of csDMARDs is **conditionally** recommended over addition of a bDMARD or tsDMARD for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity despite csDMARD monotherapy.	Very low	PICO 88	p. 490
Addition of/switching to DMARDs is **conditionally** recommended over initiation/dose escalation of glucocorticoids for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity.	Very low	PICO 90 and PICO 91	p. 496–7
Nontuberculous mycobacterial lung disease			
Use of the lowest possible dose of glucocorticoids (discontinuation if possible) is **conditionally** recommended over continuation of glucocorticoids for patients with nontuberculous mycobacterial lung disease.	Very low	No relevant PICO	
Addition of csDMARDs is **conditionally** recommended over addition of a bDMARD or tsDMARD for patients with nontuberculous mycobacterial lung disease who have moderate-to-high disease activity despite csDMARD monotherapy.	Very low	PICO 92	p. 498
Abatacept is **conditionally** recommended over other bDMARDs and tsDMARDs for patients with nontuberculous mycobacterial lung disease who have moderate-to-high disease activity despite csDMARDs.	Very low	PICO 93	p. 499

* PICO = population, intervention, comparator, and outcomes; Supp. App. 2 = Supplementary Appendix 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24596/abstract; DMARDs = disease-modifying antirheumatic drugs; TNF = tumor necrosis factor; bDMARD = biologic DMARD; tsDMARD = targeted synthetic DMARD; NYHA = New York Heart Association; csDMARDs = conventional synthetic DMARDs.

Table 7. Key clinical questions requiring further research*

Methotrexate administration
At what dose and route of administration should methotrexate be started?
Does switching to non-methotrexate DMARDs improve tolerability over increasing the dose of folic acid, or using folinic acid or using split dose or subcutaneous dosing, for RA patients with side effects when taking methotrexate?
TTT
What is the efficacy of TTT in different patient populations (early versus late, bDMARD- or tsDMARD-exposed, elderly-onset, comorbidities)?
What is the optimal target and method of assessment of disease activity for TTT in different populations?
Comparative effectiveness/safety
What is the comparative effectiveness/safety between bDMARDs and tsDMARDs?
What is the comparative effectiveness/safety between adding bDMARDs or tsDMARDs to methotrexate and switching to bDMARD or tsDMARD monotherapy?
What is the comparative effectiveness/safety between TTT by maximizing use of methotrexate (i.e., escalating dose via subcutaneous route) and adding/switching to bDMARD or tsDMARD monotherapy?
When, which, and how should DMARDs be tapered/discontinued?
Do clinical or biologic markers predict a differential response to DMARDs?
Comorbidities
What is the effectiveness/safety of alternative treatment strategies in RA patients with clinical lung disease or NAFLD?
Which DMARDs can be initiated or continued after receiving checkpoint inhibitor therapy?
Which DMARDs should be used in patients with solid malignancies, including skin cancer?
Is there a time frame before which DMARDs can be started/resumed in patients with concomitant solid malignancies?

* DMARDs = biologic disease-modifying antirheumatic drugs; RA = rheumatoid arthritis; TTT = treat-to-target; bDMARD = biologic DMARD; tsDMARD = targeted synthetic DMARD; NAFLD = nonalcoholic fatty liver disease.

Heart failure

Addition of a non–TNF inhibitor bDMARD or tsDMARD is conditionally recommended over addition of a TNF inhibitor for patients with New York Heart Association (NYHA) class III or IV heart failure and an inadequate response to csDMARDs

Switching to a non–TNF inhibitor bDMARD or tsDMARD is conditionally recommended over continuation of a TNF inhibitor for patients taking a TNF inhibitor who develop heart failure

These recommendations are based on the risk of worsening heart failure observed in randomized clinical trials of TNF inhibitors in patients with NYHA class III or IV heart failure without RA (46,47). Both recommendations are conditional because of the very low-certainty evidence supporting these PICO questions.

Lymphoproliferative disorder

Rituximab is conditionally recommended over other DMARDs for patients who have a previous lymphoproliferative disorder for which rituximab is an approved treatment and who have moderate-to-high disease activity

Rituximab is preferred over other DMARDs, regardless of previous DMARD experience, because it would not be expected to increase the risk of recurrence or worsening of these lymphoproliferative disorders. The recommendation is conditional because of the very low-certainty evidence supporting this PICO question.

Hepatitis B infection

Prophylactic antiviral therapy is strongly recommended over frequent monitoring of viral load and liver enzymes alone for patients initiating rituximab who are hepatitis B core antibody positive (regardless of hepatitis B surface antigen status)

Prophylactic antiviral therapy is strongly recommended over frequent monitoring alone for patients initiating any bDMARD or tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen positive

Frequent monitoring alone of viral load and liver enzymes is conditionally recommended over prophylactic antiviral therapy for patients initiating a bDMARD other than rituximab or a tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen negative

These recommendations were made based on the risk of hepatitis B reactivation due to core antibody and surface antigen status and the specific DMARD being initiated and are consistent with the updated American Association for the Study of Liver Diseases guidance (48). Patients at risk for hepatitis B reactivation should be comanaged with a hepatologist. The third recommendation is conditional because it is less certain whether the benefit of prophylactic antiviral therapy outweighs the risks and cost of this treatment in the specified patient population.

Nonalcoholic fatty liver disease (NAFLD)

Methotrexate is conditionally recommended over alternative DMARDs for DMARD-naive patients with NAFLD, normal liver enzymes and liver function tests, and no evidence of advanced liver fibrosis who have moderate-to-high disease activity

Given the concerns about the risk of hepatotoxicity associated with methotrexate therapy in patients with NAFLD, use of methotrexate should be restricted to patients with normal liver enzymes and liver function tests and without evidence of liver disease or liver fibrosis (Stage 3 or 4). Noninvasive testing to diagnose and stage liver fibrosis as well as consultation with a gastroenterologist or hepatologist should be considered in patients prior to initiating methotrexate (49). In addition, more frequent monitoring should be performed in this patient population (every 4 to 8 weeks). The recommendation is conditional because patients' and clinicians' risk tolerance varies.

Persistent hypogammaglobulinemia without infection

In the setting of persistent hypogammaglobulinemia without infection, continuation of rituximab therapy for patients at target is conditionally recommended over switching to a different bDMARD or tsDMARD

Continuing rituximab in patients who are at target is preferred because of the uncertain clinical significance of hypogammaglobulinemia in patients without infection. Although an increased risk of infection has been described in RA patients with hypogammaglobulinemia, it is not known if a switch in DMARDs in patients who are at target is more effective in lowering infection risk while maintaining disease control than continuation of rituximab. The recommendation is conditional because physician and patient risk tolerance is likely to vary depending on the degree of hypogammaglobulinemia and patient-specific risk factors for infection.

Previous serious infection

Addition of csDMARDs is conditionally recommended over addition of a bDMARD or tsDMARD for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity despite csDMARD monotherapy

This conditional recommendation is made based on observational data suggesting a lower risk of infection associated with combination csDMARDs (dual or triple therapy) compared to bDMARDs or tsDMARDs (50). Some clinicians may prefer csDMARDs even if the serious infection occurred >12 months prior to considering a change.

Addition of/switching to DMARDs is conditionally recommended over initiation/dose escalation of glucocorticoids for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity

This conditional recommendation is made based on observational studies suggesting a strong association between dose and duration of glucocorticoids with the risk of serious infection (51–53).

Nontuberculous mycobacterial (NTM) lung disease

Given the variability of NTM lung disease severity and response to treatment, patients should be closely comanaged with an infectious disease or pulmonary specialist.

Use of the lowest possible dose of glucocorticoids (discontinuation if possible) is conditionally recommended over continuation of glucocorticoids without dose modification for patients with NTM lung disease

This recommendation is based on studies suggesting an increased risk of NTM lung disease in patients receiving either inhaled or oral glucocorticoids (54,55).

Addition of csDMARDs is conditionally recommended over addition of a bDMARD or tsDMARD for patients with NTM lung disease who have moderate-to-high disease activity despite csDMARD monotherapy

This recommendation is based on the lower expected risk of NTM lung disease associated with csDMARDs compared to bDMARDs and tsDMARDs (56).

Abatacept is conditionally recommended over other bDMARDs and tsDMARDs for patients with NTM lung disease who have moderate-to-high disease activity despite csDMARDs

Abatacept is conditionally recommended over other bDMARDs and tsDMARDs based on population data extrapolated from studies on tuberculosis (57). There is considerable uncertainty regarding the risk of mycobacterial infections associated with non–TNF inhibitor bDMARDs and tsDMARDs; however, TNF inhibitors are associated with increased rates of mycobacterial infections and should be avoided (58).

The preceding 3 recommendations are conditional because of the very low-certainty evidence supporting the analysis of the differences in treatment outcomes posed by these PICO questions.

DISCUSSION

The ACR guidelines were developed to provide clinicians with recommendations for decisions frequently faced in clinical practice. Several new topics are included in this update, including recommendations for administration of methotrexate, use of methotrexate in patients with subcutaneous nodules, pulmonary disease, and NAFLD, use of rituximab in patients with hypogammaglobulinemia, and treatment of RA in patients with NTM lung disease. Areas covered in the 2015 guidelines that are not covered in this update include recommendations for patients with hepatitis C and solid malignancies. The panel did not vote on specific recommendations for patients with hepatitis C because curative antiviral therapy is now widely available. The panel did deliberate over PICO questions related to use of DMARDs in patients with solid malignancies. However, given the changing landscape of personalized treatments for many solid malignancies, the voting panel felt that a generalized recommendation was not possible.

On February 4, 2021, the FDA released a Drug Safety Alert noting a possible increased risk of major cardiovascular events and malignancies (excluding non-melanoma skin cancer) in patients with RA (over the age of 50 years with at least 1 risk factor for cardiovascular disease) participating in a randomized controlled trial designed to compare the safety of tofacitinib to adalimumab (18). Recommendations will be reviewed once peer-reviewed results are published. Rapidly evolving comparative effectiveness and safety signals associated with JAK inhibitors highlight the need to engage in a shared decision-making process when adjusting DMARDs (16,59). In addition, although previous recommendations cautioned against the use of TNF inhibitors in patients with skin cancer (1), the results of more recently published studies examining specific DMARD-related risks of non-melanoma skin cancer and melanoma do not support making a definite recommendation for or against specific DMARDs (60,61).

The panel also considered PICO questions related to current use of checkpoint inhibitor therapy, but the variability in current practice patterns and differences in treatment for specific cancer types precluded the development of specific recommendations for patients who are candidates for, or are currently receiving checkpoint inhibitor therapy. We anticipate that additional recommendations for patients with systemic rheumatic diseases and solid malignancies will be developed as further data become available. There were vigorous discussions pertaining to recommendations for specific DMARDs in patients with moderate-to-high disease activity despite csDMARDs and with a history of serious infection. However, the evidence was insufficient to support a recommendation. Future studies (using large registries and network meta-analyses) are needed to support specific recommendations for this patient population.

The recommendation statements in this update are not directly comparable to the ACR 2015 guidelines (1) because they do not retain the early versus established RA subgroups. Nevertheless, there are some notable differences. First, the 2015 guidelines recommend csDMARD monotherapy, preferably with methotrexate, for patients with both low and moderate/high disease activity, whereas this update recommends an initial trial of hydroxychloroquine or sulfasalazine for those with low disease activity. Second, the 2015 guidelines recommended DMARD tapering for patients who are in remission. In this update, tapering recommendations are made for patients who are in low disease activity or remission in the face of a paucity of data about when and how best to taper. The panel recommended that careful tapering might be considered if the patient wishes to cut back on their use of DMARDs. However, patients should be closely evaluated during any taper, and if a flare occurs, the prior regimen should be reinstituted promptly. Last, this update includes several recommendations *against* the use of glucocorticoid therapy. These recommendations were made in recognition of the frequent difficulty tapering glucocorticoids leading to undesirable prolonged use and the increasing evidence of the negative impact of glucocorticoids on long-term patient outcomes, including risk for infection, osteoporosis, and cardiovascular disease, in RA and other rheumatic diseases (62–65).

While consensus was easily reached on the majority of statements, 2 issues required prolonged discussion and debate. The decision on whether patients with an inadequate response to methotrexate should escalate to a bDMARD, tsDMARD, or triple therapy engendered much discussion with contrasting points of view. In the end, a recommendation was made in favor of a bDMARD or tsDMARD because of the more rapid onset of benefit and concerns related to the poor tolerability and durability of triple therapy in real-world practice (13,14). In particular, the patient panel highlighted the importance of a rapid onset of benefit after already having had an inadequate response to methotrexate. The conditional recommendation to initiate methotrexate therapy for patients with preexisting mild, stable lung disease was also rigorously debated. While minimizing the risk of toxicity is paramount, the voting panel favored a conditional recommendation to initiate methotrexate therapy in this clinical setting because of the vital role of this DMARD in the overall treatment of RA and lack of other comparable therapies without pulmonary risks.

Members of the voting panel agreed with the patient panel on the direction and strength of all but 2 recommendations. Patients were in favor of initial treatment with combination csDMARDs over methotrexate monotherapy because they placed greater value on the incremental benefits associated with combination therapy compared to clinicians. This preference was also stated in the 2015 guidelines (66). Patients also strongly preferred

discontinuing over a dose reduction of a DMARD whenever possible, whereas most clinicians on the voting panel preferred dose reduction. This discordance reflects patient preference to minimize use of medications once they reach target versus physician preference to minimize flare. However, both the patient and voting panel stressed the variability in patient preferences for tapering. These differences reinforce the importance of using a shared decision-making approach in RA.

When clinically relevant, recommendations specify the level of disease activity in the patient population (Table 1). However, evidence tables include pooled data from studies that often use different measures of disease activity; thus, specific definitions of low versus moderate-to-high disease activity are not provided for specific recommendations. Despite the large body of literature related to pharmacologic treatments for RA, the review team did not identify high-certainty evidence for many of the questions addressed. This discrepancy is due to the differences between clinically important PICO questions and the specific objectives of clinical trials. For example, few studies have examined how to best dose and administer methotrexate, the most effective and safe use of DMARDs in high-risk populations, and the risk–benefit tradeoffs associated with glucocorticoid use. Moreover, many trials could not be matched to specific PICO questions because of differences between the trials and the PICO questions' specified study populations and treatment comparisons. Thus, many recommendations are based largely on very low-certainty or low-certainty evidence. Incorporating medical evidence and expert input and consensus into clinical guidelines is core to the GRADE process and strengthens recommendations, particularly when there is limited evidence. Important gaps in knowledge are described in Table 7.

In summary, this update includes recommendations related to initiation and adjustment of DMARD therapy in patients with RA. It also emphasizes the importance of minimizing use of glucocorticoids. It is expected that additional data may modify the direction and/or strength of specific recommendations. The ACR will update the recommendations and answer these and other questions as new data are published.

ACKNOWLEDGMENTS

We thank Stanley B. Cohen, MD, for his contributions during the scoping phase of the project. We thank Cassandra Calabrese, DO, Leonard Calabrese, DO, Joseph Lim, MD, Danielle Antin-Ozerkis, MD, Marcus R. Pereira, MD, MPH, Jason E. Stout, MD, MHS, and Kevin Winthrop, MD, MPH, for their expert input as the voting panel considered recommendations related to comorbidities. We thank Nancy Baker, ScD, MPH, OTR/l, and Daniel White, PT, ScD, MSc, for their contributions during the scoping phase of the project, as well as their input during early deliberations by the voting panel. We thank the patients who (along with authors Kristine Carandang, PhD, OTR/L, and Shilpa Venkatachalam, PhD) participated in the patient panel meeting: Susan Campbell, Rachelle Crow-Hercher, MEd, Doug Davis, Sidney Harper, Faith Powell, Zenethia Roberts, Mary Turner, and C. Whitney White, PharmD. We thank the ACR staff, including Regina Parker for assistance in organizing the face-to-face meeting and coordinating the administrative aspects of the project, Robin Lane for assistance in manuscript preparation, and Jocelyn Givens for assistance with recruitment for the patient panel. We thank Janet Waters and Janet Joyce for their assistance in developing the literature search strategy, as well as performing the initial literature search and update searches.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Fraenkel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Fraenkel, Bathon, England, St.Clair, Deane, Genovese, Kerr, Kremer, Sparks, Venkatachalam, Weinblatt, George, Johnson, Turner, Yaacoub, Akl.

Acquisition of data. Fraenkel, Bathon, England, St.Clair, Carandang, Deane, Genovese, Kerr, Kremer, J. Singh, Sparks, Al-Gibbawi, Baker, Barton, Cappelli, George, Johnson, Kahale, Karam, Khamis, Navarro-Millán, Mirza, Schwab, N. Singh, Turgunbaev, Turner, Yaacoub, Akl.

Analysis and interpretation of data. Fraenkel, Bathon, England, St.Clair, Arayssi, Deane, Genovese, Huston, Kerr, Kremer, Nakamura, Russell, J. Singh, Smith, Sparks, Venkatachalam, Weinblatt, Al-Gibbawi, Barbour, Barton, Chamseddine, Johnson, Kahale, Karam, Khamis, Navarro-Millán, Mirza, Schwab, N. Singh, Turgunbaev, Yaacoub, Akl.

ADDITIONAL DISCLOSURES

Author Genovese was employed by Stanford University Medical Center during development of this guideline but at the time of publication will also be employed by Gilead Sciences. Gilead Sciences had no financial or other interest in this project, had no input in the design, content, data collection, or analysis, and had no role in the writing or approval of this article.

REFERENCES

1. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2016;68:1–26.
2. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008;59:762–84.
3. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2012;64:625–39.
4. Goodman SM, Springer B, Guyatt G, Abdel MP, Dasa V, George M, et al. 2017 American College of Rheumatology/American Association of Hip and Knee Surgeons guideline for the perioperative management of antirheumatic medication in patients with rheumatic diseases undergoing elective total hip or total knee arthroplasty. Arthritis Rheumatol 2017;69:1538–51.
5. Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse ME, Lockshin MD, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. Arthritis Care Res (Hoboken) 2020; 72:461–88.
6. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66:726–35.

7. Alexander PE, Gionfriddo MR, Li SA, Bero L, Stoltzfus RJ, Neumann I, et al. A number of factors explain why WHO guideline developers make strong recommendations inconsistent with GRADE guidance. J Clin Epidemiol 2016;70:111–22.
8. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.
9. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ 2010;182:E839–42.
10. England BR, Tiong BK, Bergman MJ, Curtis JR, Kazi S, Mikuls TR, et al. 2019 Update of the American College of Rheumatology recommended rheumatoid arthritis disease activity measures. Arthritis Care Res (Hoboken) 2019;71:1540–55.
11. Albrecht K, Zink A. Poor prognostic factors guiding treatment decisions in rheumatoid arthritis patients: a review of data from randomized clinical trials and cohort studies. Arthritis Res Ther 2017; 19:68.
12. Burgers LE, Raza K, van der Helm-van Mil AH. Window of opportunity in rheumatoid arthritis—definitions and supporting evidence: from old to new perspectives. RMD Open 2019;5:e000870.
13. Curtis JR, Palmer JL, Reed GW, Greenberg J, Pappas DA, Harrold LR, et al. Real-world outcomes associated with triple therapy versus tumor necrosis factor inhibitor/methotrexate therapy. Arthritis Care Res (Hoboken) doi: http://onlinelibrary.wiley.com/doi/10.1002/acr.24253/abstract. E-pub ahead of print.
14. Erhardt DP, Cannon GW, Teng CC, Mikuls TR, Curtis JR, Sauer BC. Low persistence rates in patients with rheumatoid arthritis treated with triple therapy and adverse drug events associated with sulfasalazine. Arthritis Care Res (Hoboken) 2019;71:1326–35.
15. Burmester GR, Rigby WF, van Vollenhoven RF, Kay J, Rubbert-Roth A, Kelman A, et al. Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. Ann Rheum Dis 2016;75:1081–91.
16. Van Vollenhoven R, Takeuchi T, Pangan AL, Friedman A, Mohamed ME, Chen S, et al. Efficacy and safety of upadacitinib monotherapy in methotrexate-naive patients with moderately-to-severely active rheumatoid arthritis (SELECT-EARLY): a multicenter, multi-country, randomized, double-blind, active comparator–controlled trial. Arthritis Rheumatol 2020;72:1607–20.
17. Pfizer. Pfizer shares co-primary endpoint results from post-marketing required safety study of Xeljanz (Tofacitinib) in subjects with rheumatoid arthritis (RA). URL: https://investors.pfizer.com/investor-news/press-release-details/2021/Pfizer-Shares-Co-Primary-Endpoint-Results-from-Post-Marketing-Required-Safety-Study-of-XELJANZ-tofacitinib-in-Subjects-with-Rheumatoid-Arthritis-RA/default.aspx.
18. US Food and Drug Administration. Xeljanz, Xeljanz XR (tofacitinib): drug safety communication—initial safety trial results find increased risk of serious heart-related problems and cancer with arthritis and ulcerative colitis medicine. URL: https://www.fda.gov/safety/medical-product-safety-information/xeljanz-xeljanz-xr-tofacitinib-drug-safety-communication-initial-safety-trial-results-find-increased?utm_medium=email&utm_source=govdelivery.
19. Katchamart W, Trudeau J, Phumethum V, Bombardier C. Efficacy and toxicity of methotrexate (MTX) monotherapy versus MTX combination therapy with non-biological disease-modifying antirheumatic drugs in rheumatoid arthritis: a systematic review and meta-analysis. Ann Rheum Dis 2009;68:1105–12.
20. Emery P, Bingham CO, Burmester GR, Bykerk VP, Furst DE, Mariette X, et al. Certolizumab pegol in combination with dose-optimised methotrexate in DMARD-naïve patients with early, active rheumatoid arthritis with poor prognostic factors: 1-year results from C-EARLY, a randomised, double-blind, placebo-controlled phase III study. Ann Rheum Dis 2017;76:96–104.
21. Detert J, Bastian H, Listing J, Weiss A, Wassenberg S, Liebhaber A, et al. Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naive patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. Ann Rheum Dis 2013;72:844–50.
22. Nam JL, Villeneuve E, Hensor EM, Wakefield RJ, Conaghan PG, Green MJ, et al. A randomised controlled trial of etanercept and methotrexate to induce remission in early inflammatory arthritis: the EMPIRE trial. Ann Rheum Dis 2014;73:1027–36.
23. Schiff MH, Jaffe JS, Freundlich B. Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses ≥15 mg may be overcome with subcutaneous administration. Ann Rheum Dis 2014;73:1549–51.
24. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. Ann Rheum Dis 2009;68:1094–9.
25. Scott IC, Ibrahim F, Panayi G, Cope AP, Garrood T, Vincent A, et al. The frequency of remission and low disease activity in patients with rheumatoid arthritis, and their ability to identify people with low disability and normal quality of life. Semin Arthritis Rheum 2019; 49:20–6.
26. Bansback N, Phibbs CS, Sun H, O'Dell JR, Brophy M, Keystone EC, et al. Triple therapy versus biologic therapy for active rheumatoid arthritis: a cost-effectiveness analysis. Ann Intern Med 2017; 167:8–16.
27. Moreland LW, O'Dell JR, Paulus HE, Curtis JR, Bathon JM, St.Clair EW, et al. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the Treatment of Early Aggressive Rheumatoid Arthritis Trial. Arthritis Rheum 2012;64:2824–35.
28. O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, et al. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med 2013;369:307–18.
29. Van Vollenhoven RF, Geborek P, Forslind K, Albertsson K, Ernestam S, Petersson IF, et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet 2012;379:1712–20.
30. Sauer BC, Teng CC, Tang D, Leng J, Curtis JR, Mikuls TR, et al. Persistence with conventional triple therapy versus a tumor necrosis factor inhibitor and methotrexate in US veterans with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2017;69:313–22.
31. Bergstra SA, Winchow LL, Murphy E, Chopra A, Salomon-Escoto K, Fonseca JE, et al. How to treat patients with rheumatoid arthritis when methotrexate has failed? The use of a multiple propensity score to adjust for confounding by indication in observational studies. Ann Rheum Dis 2019;78:25–30.
32. Pavelka K, Akkoç N, Al-Maini M, Zerbini CA, Karateev DE, Nasonov EL, et al. Maintenance of remission with combination etanercept-DMARD therapy versus DMARDs alone in active rheumatoid arthritis: results of an international treat-to-target study conducted in regions with limited biologic access. Rheumatol Int 2017;37:1469–79.
33. Ghiti Moghadam M, Vonkeman HE, ten Klooster PM, Tekstra J, van Schaardenburg D, Starmans-Kool M, et al. Stopping tumor necrosis factor inhibitor treatment in patients with established rheumatoid arthritis in remission or with stable low disease activity: a pragmatic multicenter, open-label randomized controlled trial. Arthritis Rheumatol 2016;68:1810–7.

34. Van Herwaarden N, van der Maas A, Minten MJ, van den Hoogen FH, Kievit W, van Vollenhoven RF, et al. Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial. BMJ 2015;350:h1389.
35. Van Vollenhoven RF, Østergaard M, Leirisalo-Repo M, Uhlig T, Jansson M, Larsson E, et al. Full dose, reduced dose or discontinuation of etanercept in rheumatoid arthritis. Ann Rheum Dis 2016; 75:52–8.
36. Weinblatt ME, Bingham CO III, Burmester GR, Bykerk VP, Furst DE, Mariette X, et al. A phase III study evaluating continuation, tapering, and withdrawal of certolizumab pegol after one year of therapy in patients with early rheumatoid arthritis. Arthritis Rheumatol 2017;69:1937–48.
37. Strand V, Balsa A, Al-Saleh J, Barile-Fabris L, Horiuchi T, Takeuchi T, et al. Immunogenicity of biologics in chronic inflammatory diseases: a systematic review. BioDrugs 2017;31:299–316.
38. Patatanian E, Thompson DF. A review of methotrexate-induced accelerated nodulosis. Pharmacotherapy 2002;22:1157–62.
39. Alarcon GS, Kremer JM, Macaluso M, Weinblatt ME, Cannon GW, Palmer WR, et al. Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis: a multicenter, case-control study. Ann Intern Med 1997;127:356–64.
40. Bartram SA. Experience with methotrexate-associated pneumonitis in northeastern England: comment on the article by Kremer et al [letter]. Arthritis Rheum 1998;41:1327–8.
41. Kawashiri SY, Kawakami A, Sakamoto N, Ishimatsu Y, Eguchi K. A fatal case of acute exacerbation of interstitial lung disease in a patient with rheumatoid arthritis during treatment with tocilizumab. Rheumatol Int 2012;32:4023–6.
42. Ostor AJ, Crisp AJ, Somerville MF, Scott DG. Fatal exacerbation of rheumatoid arthritis associated fibrosing alveolitis in patients given infliximab. BMJ 2004;329:1266.
43. Schoe A, van der Laan-Baalbergen NE, Huizinga TW, Breedveld FC, van Laar JM. Pulmonary fibrosis in a patient with rheumatoid arthritis treated with adalimumab. Arthritis Rheum 2006;55:157–9.
44. Taki H, Kawagishi Y, Shinoda K, Hounoki H, Ogawa R, Sugiyama E, et al. Interstitial pneumonitis associated with infliximab therapy without methotrexate treatment. Rheumatol Int 2009;30:275–6.
45. Roubille C, Haraoui B. Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: a systematic literature review. Semin Arthritis Rheum 2014; 43:613–26.
46. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation 2003;107:3133–40.
47. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation 2004;109:1594–602.
48. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560–99.
49. American Association for the Study of Liver Diseases. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Clin Liver Dis (Hoboken) 2018;11:81.
50. Ozen G, Pedro S, England BR, Mehta B, Wolfe F, Michaud K. Risk of serious infection in patients with rheumatoid arthritis treated with biologic versus nonbiologic disease-modifying antirheumatic drugs. ACR Open Rheumatol 2019;1:424–32.
51. Lacaille D, Guh DP, Abrahamowicz M, Anis AH, Esdaile JM. Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. Arthritis Rheum 2008; 59:1074–81.
52. Dixon WG, Abrahamowicz M, Beauchamp ME, Ray DW, Bernatsky S, Suissa S, et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case–control analysis. Ann Rheum Dis 2012;71:1128–33.
53. George MD, Baker JF, Winthrop K, Alemao E, Chen L, Connolly S, et al. Risk of biologics and glucocorticoids in patients with rheumatoid arthritis undergoing arthroplasty: a cohort study. Ann Intern Med 2019;170:825–36.
54. Liu VX, Winthrop KL, Lu Y, Sharifi H, Nasiri HU, Ruoss SJ. Association between inhaled corticosteroid use and pulmonary nontuberculous mycobacterial infection. Ann Am Thorac Soc 2018;15:1169–76.
55. Liao TL, Lin CF, Chen YM, Liu HJ, Chen DY. Risk factors and outcomes of nontuberculous mycobacterial disease among rheumatoid arthritis patients: a case-control study in a TB endemic area. Sci Rep 2016;6:29443.
56. Brode SK, Jamieson FB, Ng R, Campitelli MA, Kwong JC, Paterson JM, et al. Increased risk of mycobacterial infections associated with anti-rheumatic medications. Thorax 2015;70:677–82.
57. Cantini F, Niccoli L, Goletti D. Tuberculosis risk in patients treated with non-anti-tumor necrosis factor-α (TNF-α) targeted biologics and recently licensed TNF-α inhibitors: data from clinical trials and national registries. J Rheumatol Suppl 2014;91:56–64.
58. Winthrop KL, Baxter R, Liu L, Varley CD, Curtis JR, Baddley JW, et al. Mycobacterial diseases and antitumour necrosis factor therapy in USA. Ann Rheum Dis 2013;72:37–42.
59. Rubbert-Roth A, Enejosa J, Pangan AL, Haraoui B, Rischmueller M, Khan N, et al. Trial of upadacitinib or abatacept in rheumatoid arthritis. N Engl J Med 2020;383:1511–21.
60. Buchbinder R, Barber M, Heuzenroeder L, Wluka AE, Giles G, Hall S, et al. Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate. Arthritis Rheum 2008;59:794–9.
61. Mercer LK, Askling J, Raaschou P, Dixon WG, Dreyer L, Hetland ML, et al. Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: results from a collaborative project of 11 European biologic registers. Ann Rheum Dis 2017;76:386–91.
62. Del Rincón I, Battafarano DF, Restrepo JF, Erikson JM, Escalante A. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. Arthritis Rheumatol 2014;66:264–72.
63. Bijlsma JW, Buttgereit F. Adverse events of glucocorticoids during treatment of rheumatoid arthritis: lessons from cohort and registry studies. Rheumatology (Oxford) 2016;55 Suppl 2:ii3–5.
64. Curtis JR, Westfall AO, Allison J, Bijlsma JW, Freeman A, George V, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis Rheum 2006;55: 420–6.
65. Huscher D, Thiele K, Gromnica-Ihle E, Hein G, Demary W, Dreher R, et al. Dose-related patterns of glucocorticoid-induced side effects. Ann Rheum Dis 2009;68:1119–24.
66. Fraenkel L, Miller AS, Clayton K, Crow-Hercher R, Hazel S, Johnson B, et al. When patients write the guidelines: patient panel recommendations for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2016;68:26–35.