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SPECIAL ARTICLE

2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis

Jasvinder A. Singh,[1] Kenneth G. Saag,[1] S. Louis Bridges Jr.,[1] Elie A. Akl,[2] Raveendhara R. Bannuru,[3] Matthew C. Sullivan,[3] Elizaveta Vaysbrot,[3] Christine McNaughton,[3] Mikala Osani,[3] Robert H. Shmerling,[4] Jeffrey R. Curtis,[1] Daniel E. Furst,[5] Deborah Parks,[6] Arthur Kavanaugh,[7] James O'Dell,[8] Charles King,[9] Amye Leong,[10] Eric L. Matteson,[11] John T. Schousboe,[12] Barbara Drevlow,[13] Seth Ginsberg,[14] James Grober,[13] E. William St.Clair,[15] Elizabeth Tindall,[16] Amy S. Miller,[17] and Timothy McAlindon[3]

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[1]Jasvinder A. Singh, MBBS, MPH, Kenneth G. Saag, MD, MSc, S. Louis Bridges Jr., MD, PhD, Jeffrey R. Curtis, MD, MS, MPH: University of Alabama at Birmingham; [2]Elie A. Akl, MD, MPH, PhD: American University of Beirut, Beirut, Lebanon, and McMaster University, Hamilton, Ontario, Canada; [3]Raveendhara R. Bannuru, MD, PhD, Matthew C. Sullivan, BA, Elizaveta Vaysbrot, MD, MS, Christine McNaughton, BS, Mikala Osani, BA, Timothy McAlindon, MD, MPH: Tufts Medical Center, Boston, Massachusetts; [4]Robert H. Shmerling, MD: Beth Israel Deaconess Medical Center, Boston, Massachusetts; [5]Daniel E. Furst, MD: University of California, Los Angeles; [6]Deborah Parks, MD: Washington University School of Medicine, St. Louis, Missouri; [7]Arthur Kavanaugh, MD: University of California, San Diego; [8]James O'Dell, MD: University of Nebraska Medical Center, Omaha; [9]Charles King, MD: North Mississippi Medical Center, Tupelo; [10]Amye Leong, MBA: Healthy Motivation, Santa Barbara, California; [11]Eric L. Matteson, MD, MPH: Mayo Clinic, Rochester, Minnesota; [12]John T. Schousboe, MD, PhD: University of Minnesota and Park Nicollet Clinic, St. Louis Park; [13]Barbara Drevlow, MD, James Grober, MD: NorthShore University Health System, Evanston, Illinois; [14]Seth Ginsberg, BSc: Global Healthy Living Foundation,

Objective. **To develop a new evidence-based, pharmacologic treatment guideline for rheumatoid arthritis (RA).**

Methods. **We conducted systematic reviews to synthesize the evidence for the benefits and harms of various treatment options. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence. We employed a group consensus process to grade the strength of recommendations (either strong or conditional). A strong recommendation indicates that clinicians are certain that the benefits of an intervention far outweigh the harms (or vice versa). A conditional recommendation denotes uncertainty over the balance of benefits and harms and/or more significant variability in patient values and preferences.**

Results. **The guideline covers the use of traditional disease-modifying antirheumatic drugs (DMARDs), biologic agents, tofacitinib, and glucocorticoids in early (<6 months) and established (≥6 months) RA. In addition, it provides recommendations on using a treat-to-target approach, tapering and discontinuing medications, and the use of biologic agents and DMARDs in patients with hepatitis, congestive heart failure, malignancy, and serious infections. The guideline addresses the use of vaccines in patients starting/receiving DMARDs or biologic agents, screening for tuberculosis in patients starting/receiving biologic agents or tofacitinib, and laboratory monitoring for traditional DMARDs. The guideline includes 74 recommendations: 23% are strong and 77% are conditional.**

Conclusion. **This RA guideline should serve as a tool for clinicians and patients (our two target audiences) for pharmacologic treatment decisions in commonly encountered clinical situations. These recommendations are not prescriptive, and the treatment decisions should be made by physicians and patients through a shared decision-making process taking into account patients' values, preferences, and comorbidities. These recommendations should not be used to limit or deny access to therapies.**

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis in adults (1). RA has a significant negative impact on the ability to perform daily activities, including work and household tasks, and health-related quality of life, and it increases mortality (2–4). The American College of Rheumatology (ACR) last published a guideline for RA management in 2012 (5), which was an update of the 2008 RA guideline (6).

Because there has been rapid accrual of evidence and new therapies, advancement of guideline development methodologies, and the need to broaden the scope of its 2012 RA recommendations, the ACR has developed a new 2015 RA pharmacologic treatment guideline. This guideline addresses 6 major topics: 1) use of traditional disease-modifying antirheumatic drugs (traditional/conventional DMARDs, herein referred to as DMARDs), biologic DMARDs (herein referred to as biologics), and tofacitinib, including tapering and discontinuing medications, and a treat-to-target approach; 2) use of glucocorticoids; 3) use of biologics and DMARDs in high-risk populations (i.e., those with hepatitis, congestive heart failure, malignancy, and serious infections); 4) use of vaccines in patients starting/receiving DMARDs or biologics; 5) screening for tuberculosis (TB) in the context of biologics or tofacitinib; and 6) laboratory monitoring for traditional DMARDs.

New York, New York; [15]E. William St.Clair, MD: Duke University Medical Center, Durham, North Carolina; [16]Elizabeth Tindall, MD: Rheumatology Consultants of Oregon, West Linn; [17]Amy S. Miller: American College of Rheumatology, Atlanta, Georgia.

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Address correspondence to Jasvinder A. Singh, MBBS, MPH, University of Alabama, Faculty Office Tower 805B, 510 20th Street S, Birmingham, AL 35294. E-mail: Jasvinder.md@gmail.com.

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METHODS

Overall methodology. We developed this guideline following the recently revised ACR guideline development process (http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines). This process includes the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology (available at www.gradeworkinggroup.org) (7–9).

Teams involved. A Core Leadership Team (see Appendix A for a list of Panel and Team members) supervised the project and was responsible for defining the project scope, drafting the clinical questions to be addressed by the guideline, coordinating with the Literature Review Team's efforts, and drafting the manuscript based on voting by a panel (described below). The Core Leadership Team was led by a chair (JAS) who possessed both content and methodologic expertise. The Core Leadership Team also included a methodologist (EAA), who advised on the process and provided input on the GRADE summary of findings tables (see Evidence Report as part of Supplementary Appendix 1 available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39480/abstract), and experts in guideline development. A Literature Review Team (see Appendix A for a list of Panel and Team members) conducted the literature review, graded the quality of evidence, developed the summary of findings tables, and produced an evidence report. A Content Panel, composed of 4 content experts (see Appendix A for a list of Panel and Team members), reviewed and provided feedback on the clinical questions and the evidence report, and provided consultation throughout the project. Finally, a Voting Panel (see Appendix A for a list of Panel and Team members) helped determine which clinical questions would be asked and which outcomes were critical, and they voted on the final recommendations after reviewing the evidence provided by the Literature Review Team. The Voting Panel included rheumatologists with expertise and clinical experience in treating RA (AK, JOD, CK, ELM, JTS, BD, JG, EWSC, ET), as well as 2 patient representatives (AL, SG). Training was conducted with all members of the guideline development group to prepare them for their roles, including specific sessions on the ACR guideline process and GRADE methodology.

Disclosures and management of conflicts of interest. In accordance with ACR policy, everyone who was intellectually involved in the project (i.e., considered for guideline authorship) disclosed all relationships in writing at the beginning, middle, and end of the project. Disclosures were compared against a previously drafted list of "affected companies" (i.e., companies or organizations that were considered reasonably likely to be positively or negatively affected by care delivered in accordance with the guideline) to determine which relationships were considered conflicts of interest for purposes of this project. Individuals whose primary employment (>51% of work time/effort) was with a company that manufactured or sold therapeutics or diagnostics were not eligible to participate.

The project Principal Investigator (JAS) and Literature Review Team Leader (TM) had no relevant conflicts of interest for the full 12 months before this project began, and a majority (>51%) of all guideline development team members, including the Principal Investigator and Literature Review Team Leader, had no relevant conflicts of interest for the duration of the project. A participant who had any relationship with an affected company was counted as conflicted (i.e., toward the allowed threshold) regardless of the type or subject of the relationship. Intellectual conflicts, such as a prior publication or presentation on an RA therapeutic, were recognized as important and were required to be disclosed, but because they were ubiquitous, participants with intellectual conflicts were not counted as conflicted (i.e., toward the allowed threshold) based on their intellectual conflict alone.

Participant disclosures were included in the project plan that was posted online for public comment (see description below). In addition, disclosures of all participants were shared with each project participant in writing. At the face-to-face Voting Panel meeting, verbal disclosures were provided before any content discussion. Updated participant disclosures, as well as ACR committee reviewer disclosures, are available online (www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Rheumatoid-Arthritis). Author disclosures are detailed in the footnotes of this article.

Scope and target audience. The Core Leadership Team decided that the guideline would address topics concerning the treatment of RA and not address any topics related to diagnosis, monitoring of disease activity, surgical interventions, or physical therapy interventions. The target audience includes both clinicians and their patients with RA. The ACR plans to develop derivative products in the future, including a pocket card, an app version of this guideline, and a patient education tool to facilitate implementation.

Establishing key principles and PICO (population, intervention, comparator, and outcomes) development. Key principles and provisos, key terms, descriptions, and drug categories used in the guideline development process are shown in Table 1. These key principles were first reviewed by the Content Panel and the Core Leadership Team. The key principles were then provided to the Voting Panel when they reviewed the drafted evidence report, and also when they discussed and voted on each recommendation. The Core Leadership Team collaborated with the Content Panel to develop the initial set of PICO-formatted clinical questions for the guideline (10). We considered clinically relevant interventions and comparators after extensive discussion with the Content Panel and the Core Leadership Team, balancing comprehensiveness with feasibility. These PICO questions were posted for 30 days on the ACR web site for public comment, and revised accordingly. The final set of PICO questions addressed the 6 major topics listed above.

Systematic synthesis of the literature. *Literature searches.* We performed systematic searches of the published literature to identify relevant evidence for the PICO questions (11). Study designs in the literature review included systematic reviews, randomized controlled trials (RCTs), and observational studies (including case series). We searched OVID Medline, PubMed, Embase, and the Cochrane Library (including Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; Cochrane Central Register of Controlled Trials; and Health Technology Assessments) (see Supplementary Appendix 2 available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39480/abstract) (11). The searches were performed using database-specific subject headings and keywords related to the following domains of interest: RA, traditional/conventional DMARDs, tumor necrosis factor inhibitor (TNFi) biologics (adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab), non-TNF biologics (abatacept, rituximab, or tocilizumab), tofacitinib, glucocorticoids, and

Table 1. Key provisos and principles, key terms, definitions, and drug categories for the 2015 ACR recommendations for the treatment of rheumatoid arthritis*

Key provisos and principles
1. Focus on common clinical scenarios, not exceptional cases.
2. Cost is a consideration in these recommendations; however, explicit cost-effectiveness analyses were not conducted.
3. Disease activity measurement using an ACR-recommended measure should be performed in a majority of encounters for RA patients (16).†
4. Functional status assessment using a standardized, validated measure should be performed routinely for RA patients, at least once per year, but more frequently if disease is active. Examples of commonly used functional status measures include Health Assessment Questionnaire, Health Assessment Questionnaire II, Multidimensional Health Assessment Questionnaire, PROMIS (available at https://www.assessmentcenter.net/) Physical Function 10-item, PROMIS Physical Function 20-item, and PROMIS Physical Function Computerized Adaptive Tests (PROPFCAT).
5. If a patient has low RA disease activity or is in clinical remission, switching from one therapy to another should be considered only at the discretion of the treating physician in consultation with the patient. *Arbitrary switching between RA therapies based only on a payer/insurance company policy is not recommended*.
6. A treatment recommendation favoring one medication over another means that the preferred medication would be the recommended first option. However, favoring one medication over the other does not imply that the nonfavored medication is contraindicated for use in that situation; it may still be a potential option under certain conditions.

Key terms	Definitions
Adult RA patient	Adults, ≥18 years, meeting the ACR RA classification criteria (1987 or 2010 revised criteria) (81,82).
Health benefits and harms	Efficacy and safety of treatments including desirable and undesirable effects.
Early RA	RA with duration of disease/symptoms of <6 months, where "duration" denotes the length of time the patient has had symptoms/disease, not the length of time since RA diagnosis.
Established RA	RA with duration of disease/symptoms of ≥6 months or meeting 1987 ACR RA classification criteria (81).‡
Disease activity	Categorized as low, moderate, or high as per validated scales (Table 2) (144–150). Moderate and high disease activity categories were combined based on feedback from the Content Panel, as used previously for the 2012 ACR RA treatment recommendations.
RA remission	A joint ACR/EULAR task force defined remission as a tender joint count, swollen joint count, C-reactive protein level (mg/dl), and patient global assessment of ≤1 each or a Simplified DAS of ≤3.3 (151), 1 of 6 ACR-endorsed disease activity measures.†
Optimal dosing of RA treatments	1) Dosing to achieve a therapeutic target derived from mutual patient-clinician consideration of patient priorities, and 2) given for at least 3 months before therapy escalation or switching.
DMARD failure	Failure of traditional/conventional DMARD(s) due to lack of efficacy/desired response or side effects.
Biologic failure	Failure of biologic(s) due to lack of efficacy/desired response or side effects.
Secondary biologic failure	Biologic was efficacious initially but subsequently became inefficacious.
Active hepatitis B infection	Hepatitis B surface antigen positive, hepatitis B surface antibody negative, hepatitis B core antibody total positive (less important), AST/ALT typically increased, HBV DNA positive (if checked).
Hepatitis C infection	HCV antibody positive, HCV RNA positive, AST/ALT typically increased.
NYHA class III and IV	NYHA class III includes patients with cardiac disease resulting in marked limitation of physical activity with less than ordinary physical activity causing fatigue, palpitation, dyspnea, or angina, but no symptoms at rest. NYHA class IV includes patients with cardiac disease resulting in inability to carry on any physical activity without discomfort, symptoms of heart failure are present even at rest, and discomfort increases if any physical activity is undertaken (152).

Drug category	Descriptions
Methotrexate	Used either oral or subcutaneous (a DMARD).
DMARDs§	Traditional/conventional DMARDs including HCQ, LEF, MTX, or SSZ (excludes azathioprine, cyclosporine, minocycline, and gold), it does not include tofacitinib, which is considered separately.¶
DMARD monotherapy	Most often defined as the use of MTX monotherapy, but may also be SSZ, HCQ, or LEF.
Double DMARD therapy	MTX+SSZ, MTX+HCQ, SSZ+HCQ, or combinations with LEF.

Table 1. *(Cont'd)*

Drug category	Descriptions
Triple DMARD therapy	MTX+SSZ+HCQ.
DMARD combination therapy	Double or triple traditional/conventional DMARD therapy.
Tofacitinib	Oral synthetic small molecule.
Biologics	TNFi biologic or non-TNF biologic (excludes anakinra).§
TNFi biologics	Adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab.
Non-TNF biologics	Abatacept, rituximab, or tocilizumab (excludes anakinra).§
Low-dose glucocorticoid	≤10 mg/day of prednisone (or equivalent).
High-dose glucocorticoid	>10 mg/day of prednisone (or equivalent) and up to 60 mg/day with a rapid taper.#
Short-term glucocorticoid	<3 month treatment.

* ACR = American College of Rheumatology; RA = rheumatoid arthritis; PROMIS = Patient-Reported Outcomes Measurement Information System; EULAR = European League Against Rheumatism; DAS = Disease Activity Score; DMARD = disease-modifying antirheumatic drug; AST = aspartate aminotransferase; ALT = alanine aminotransferase; HBV = hepatitis B virus; HCV = hepatitis C virus; NYHA = New York Heart Association; HCQ = hydroxychloroquine; LEF = leflunomide; MTX = methotrexate; SSZ = sulfasalazine; TNFi = tumor necrosis factor inhibitor; COBRA = Combinatietherapie Bij Reumatoide Artritis.
† Any of the ACR recommended disease activity measures may be chosen, as described in ref. 16.
‡ New classification criteria for RA (ACR/EULAR collaborative initiative) were published in 2010 (82), the definition of established RA is based on the 1987 ACR RA classification criteria, since the 2010 ACR RA classification allows a much earlier diagnosis.
§ Anakinra was considered but not included in these guidelines due to its infrequent use in RA and lack of new data since 2012.
¶ Azathioprine, cyclosporine, minocycline, and gold were considered but not included in these guidelines due to their infrequent use in RA and/or lack of new data since 2012.
# Regimen based on that described in the COBRA study (153).

adverse events. We limited our searches to adults ages ≥18 years and to English language publications. Duplicate references were removed. We excluded narrative reviews, editorials, scientific conference abstracts, and case reports.

The literature related to treatment modalities covered by past ACR RA guidelines (i.e., traditional/conventional DMARDs, TNFi and non-TNF biologics) and tofacitinib was searched to include articles published from January 1, 2009 through March 3, 2014. For other treatment modalities not covered by past ACR RA guidelines (i.e., glucocorticoids), we searched the databases from inception until March 3, 2014. We updated initial literature searches on September 17, 2014. All searches were developed by a medical librarian in collaboration with the Literature Review Team and were peer reviewed by a second medical librarian.

Study selection. The literature search results underwent primary screening in DistillerSR software (Evidence Partners). During primary literature screening, 2 reviewers (various pairs, made from a pool of reviewers including authors MCS, EV, CM, and MO, as well as the medical librarian) independently reviewed the title and abstract of each article for potential eligibility. A third reviewer (RRB) resolved conflicts regarding inclusion versus exclusion. Articles judged as potentially eligible were tagged for electronic matching to specific PICO questions, and subsequently underwent full-text article screening. Each full text was screened by 2 reviewers and independently tagged with PICO-matching criteria. A secondary hand sorting of all randomized studies was conducted to ensure successful matching of relevant evidence to PICO questions (for details on the study selection see Supplementary Appendix 3 available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39480/abstract).

Data extraction and analysis. We extracted study data for each PICO question into RevMan software (12). When determining which data to include, we followed the GRADE methodology that gives preference to RCTs over observational studies as the highest-quality source of evidence. Whenever data from both randomized and observational trials were available, and the RCT was of high quality, we extracted RCT data only (13). A RevMan file was created for each PICO question, and data were pooled and analyzed using this software. Continuous outcome variables were analyzed using the inverse variance method in a random effects model. Continuous outcomes were reported as mean differences with 95% confidence intervals; standardized mean differences (similar in concept to effect sizes) were used when the outcome was measured with different scales. Dichotomous variables were analyzed using the Mantel-Haenszel method in a random effects model. These variables were reported as risk ratios with 95% confidence intervals.

Quality assessment and evidence report formulation. We exported RevMan analyses into GRADEpro software to formulate a GRADE summary of findings table for each PICO question. The quality of evidence, such as the confidence in the effect estimates for each outcome, was evaluated based on GRADE quality assessment criteria. Two independent reviewers (RRB, MCS) performed this GRADE quality assessment in duplicate and discordance was resolved by consensus. This included the risk of bias in included trials, the likelihood of publication bias, inconsistency between trial results, indirectness of the evidence (e.g., differences between populations, interventions, or outcomes of interest in the group to whom the recommendation applies versus those who were included in the studies referenced), and imprecision (wide confidence intervals, usually due to a small number of patients or events, or those situations where clinical decision-making would differ at the extremes of the confidence interval).

The GRADE method distinguishes 4 levels of quality of evidence based on the degree of confidence that the pooled effect estimate lies close to the true effect. Thus, the quality of evidence for each outcome could be rated as high, moderate, low, or very low. The overall evidence quality grade was the lowest quality rating among the individual outcomes deemed critical for the comparison between interventions (14). In the absence of any data, the level of evidence was rated as very low, because it was based on clinical experience only.

	Strong recommendation	*Conditional recommendation*
Patients	**Most people in your situation would want the recommended course of action and only a small proportion would not**	*The majority of people in your situation would want the recommended course of action, but many would not**
Clinicians	**Most patients should receive the recommended course of action**	*Be prepared to help patients to make a decision that is consistent with their own values*
Policy makers	**The recommendation can be adapted as a policy in most situations**	*There is a need for substantial debate and involvement of stakeholders*

Figure 1. Implications of strong and conditional GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology recommendations (154). * = majority means >50% of the people.

We compiled the resulting summary of findings tables in an evidence report (see Supplementary Appendix 1, http://onlinelibrary.wiley.com/doi/10.1002/art.39480/abstract) that was accompanied by a qualitative summary of the evidence for each PICO question. The Content Panel reviewed the drafted evidence report and revised the report to address evidence gaps prior to presentation to the Voting Panel. We referred to other society/organization guidelines for topics that do not exclusively relate to rheumatologic care, such as liver disease (American Association for the Study of Liver Diseases [AASLD]) and TB screening and immunization (Centers for Disease Control and Prevention [CDC]).

Moving from evidence to recommendations. Each recommendation was made based on a consideration of the balance of relative benefits and harms of the treatment options under consideration, the quality of the evidence (i.e., confidence in the effect estimates), and patients' values and preferences, as per GRADE methodology.

A recommendation could be either in favor of or against the proposed intervention and either strong or conditional. According to GRADE, a recommendation is categorized as strong if the panel is very confident that the benefits of an intervention far outweigh the harms (or vice versa) (7–9) (Figure 1). A conditional recommendation denotes uncertainty over the balance of benefits and harms, such as when the evidence quality is low or very low, or when patient preferences or costs are expected to impact the decision. Thus, conditional recommendations refer to decisions where incorporation of patient preferences is an essential element of decision making.

Consensus building. The Voting Panel received the evidence report for review before it met to discuss and decide on the final recommendations. For each PICO question, the Voting Panel heard an oral summary of the evidence and provided votes on the direction and strength of the related recommendation during a face-to-face meeting held on October 5–6, 2014, and subsequent conference calls and e-mails. The voting process was anonymous and conducted using Poll Everywhere software (available at www.polleverywhere.com). We used the 70% consensus threshold, which has been used previously in other similar processes (15) and in previous ACR guidelines (5,6). If 70% consensus was not achieved during an initial vote, the panel members held additional discussions before voting again. In some instances (specifically, DMARD monotherapy failure in early and established RA, hepatitis B, hepatitis C, and previously treated/untreated solid organ cancer), the Voting Panel decided, based on its review of the evidence and its round 1 votes, to combine certain treatment options. They then voted on a new recommendation statement that covered a group of treatment options instead of considering each question separately. In addition, the Voting Panel dropped a number of PICO questions because the clinical scenario was uncommon, irrelevant, or redundant (see Supplementary Appendix 4 available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39480/abstract).

The GRADE methodology contributed a great deal of transparency to the voting process. For example, all of the evidence tables contained detailed descriptions of the criteria upon which the evidence quality was rated (such as estimates of risk of bias or indirectness). As allowed for in GRADE, in some instances, the Voting Panel chose to provide a recommendation in disagreement with the expected strength based on the overall evidence quality (i.e., a strong recommendation despite a low quality rating of evidence). In such cases, a written explanation was provided describing the reasons behind this decision.

Final review and approval of the manuscript by the ACR. In addition to journal peer review, the manuscript was reviewed by the ACR Guideline Subcommittee, ACR Quality of Care Committee, and the ACR Board of Directors, a process that involved over 40 reviewers (details available at www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Rheumatoid-Arthritis). These ACR oversight groups did not mandate that certain recommendations be made within the guideline, but rather, these ACR committees served as peer reviewers.

RESULTS/RECOMMENDATIONS

An abbreviated guideline summary of recommendations for patients with early RA, established RA, and high-risk comorbidities is available (see Executive Summary, Supplementary Appendix 5, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39480/abstract).

Table 2. Instruments to measure rheumatoid arthritis disease activity and to define remission*

Instrument (reference)	Thresholds of disease activity
Patient Activity Scale (PAS) or PASII (range 0–10) (149)	Remission: 0–0.25 Low activity: >0.25–3.7 Moderate activity: >3.7 to <8.0 High activity: ≥8.0
Routine Assessment of Patient Index Data 3 (RAPID-3) (range 0–10) (155)	Remission: 0–1.0 Low activity: >1.0–2.0 Moderate activity: >2.0–4.0 High activity: >4.0—10
Clinical Disease Activity Index (CDAI) (range 0–76.0) (156)	Remission: ≤2.8 Low activity: >2.8–10.0 Moderate activity: >10.0–22.0 High activity: >22
Disease Activity Score 28 (DAS28) erythrocyte sedimentation rate (ESR) (range 0–9.4) (157)	Remission: <2.6 Low activity: ≥2.6 to <3.2 Moderate activity: ≥3.2 to ≤5.1 High activity: >5.1
Simplified Disease Activity Index (SDAI) (range 0–86.0) (158)	Remission: ≤3.3 Low activity: >3.3 to ≤11.0 Moderate activity: >11.0 to ≤26 High activity: >26

* These 6 measures were endorsed by the American College of Rheumatology in 2012 (16). Other measures are now available to clinicians, but they were not included in this guideline because it was beyond the scope of this review. Adapted from ref. 16.

How to interpret the recommendations

1. Strong recommendations are highlighted in green and bolded, and conditional recommendations are highlighted in yellow and italicized in the figures (Figure 1). A strong recommendation means that the panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to most patients, and only a small proportion would not want to follow the recommendation. A conditional recommendation means that the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach.
2. In general, treatment choices are listed in the same order throughout the document (traditional DMARDs, TNFi, non-TNF, tofacitinib), and then alphabetically within each category. When more than one treatment is included as an option, the order does not imply any hierarchy, i.e., each of the treatment options (A or B or C) is recommended equally.

   For each recommendation, details regarding the supportive evidence or conditions (for conditional recommendations, but sometimes also for strong recommendations) are summarized in a section titled "Reasoning underlying the recommendations …." For example, conditions that the panel considered included comorbidities, patient perception of burden of taking medications, side-effect profile, and cost. Additional details including PICO questions and the GRADE evidence tables are available in Supplementary Appendix 1, http://onlinelibrary.wiley.com/doi/10.1002/art.39480/abstract).
3. The Voting Panel members agreed to key principles and provisos, key terms, and descriptions prior to voting on the 2015 ACR RA treatment recommendations. These are explicitly stated in Table 1 and apply to the entire guideline. RA disease activity was defined as low, moderate, or high, as previously described (16) (Table 2).

Recommendations for the treatment of patients with early RA

Recommendations for treatment of early RA (disease duration <6 months) patients are provided in Figures 2 and 3. An executive summary of these recommendations is available in Supplementary Appendix 5, http://onlinelibrary.wiley.com/doi/10.1002/art.39480/abstract.

Reasoning underlying the recommendations for the treatment of early RA. To achieve the above recommendations (Figure 2), the panel discussed several different

Recommendations for patients with symptomatic Early RA	Level of Evidence (evidence reviewed)
1. Regardless of disease activity level, use a treat-to-target strategy rather than a non-targeted approach (PICO A.1).	**Low (17)**
2. If the disease activity is low, in patients who have never taken a DMARD: **• use DMARD monotherapy (MTX preferred) over double therapy (PICO A.2).** **• use DMARD monotherapy (MTX preferred) over triple therapy (PICO A.3).**	**Low (18-21)** **Low (22-25)**
3. If the disease activity is moderate or high, in patients who have never taken a DMARD: *• use DMARD monotherapy over double therapy (PICO A.4).* *• use DMARD monotherapy over triple therapy (PICO A.5).*	*Moderate (18,20,21)* *High (22-25)*
4. If disease activity remains moderate or high despite DMARD monotherapy (with or without glucocorticoids), use combination DMARDs or a TNFi or a non-TNF biologic (all choices with or without MTX, in no particular order of preference), rather than continuing DMARD monotherapy alone (PICO A.7).	**Low (26-28)**
5. If disease activity remains moderate or high despite DMARDs: *• use a TNFi monotherapy over tofacitinib monotherapy (PICO A.8).* *• use a TNFi + MTX over tofacitinib + MTX (PICO A.9).*	*Low (29)* *Low (30)*
6. If disease activity remains moderate or high despite DMARD (PICO A.6) or biologic therapies (PICO A.12), add low-dose glucocorticoids.	*Moderate (31-37)* *Low (31-37)*
7. If disease flares, add short-term glucocorticoids at the lowest possible dose and for the shortest possible duration (PICO A.10, A.11).	*Very low (38-43)*

Figure 2. Summary of 2015 American College of Rheumatology recommendations for the treatment of Early rheumatoid arthritis (RA). Green and bolded = strong recommendation. A strong recommendation means that the panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to most patients, and only a small proportion would not want to follow the recommendation. Yellow and italicized = conditional recommendation: The desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. A treatment recommendation favoring one medication over another means that the preferred medication would be the recommended first option and the nonpreferred medication may be the second option. Favoring one medication over the other does not imply that the nonfavored medication is contraindicated for use; it is still an option. Therapies are listed alphabetically; azathioprine, gold, and cyclosporine were considered but not included. Disease-modifying antirheumatic drugs (DMARDs) include hydroxychloroquine, leflunomide, methotrexate (MTX), and sulfasalazine. PICO = population, intervention, comparator, and outcomes; TNFi = tumor necrosis factor inhibitor. For definitions and descriptions, see Table 1.

PICO questions for early RA. The reasoning underlying the recommendations is described below.

PICO A.1. Despite the low quality evidence, the recommendation is **strong** because the Voting Panel concluded that the improved outcomes experienced by patients with established RA using a targeted approach should be generalizable to those with early RA (Figure 2).

PICOs A.2 and A.3. Despite the low quality evidence, the recommendation is **strong** because 1) there is no evidence in favor of triple therapy in this setting, 2) DMARD monotherapy is generally more acceptable (i.e., easier to take, less cost to the patient) to early RA patients with low disease activity than DMARD combination regimens, and 3) DMARD monotherapy is generally better tolerated than combination DMARD therapy. The panel also voted that methotrexate (MTX) should be the preferred initial DMARD for most early RA patients.

PICOs A.4 and A.5. The recommendation is *conditional* because 1) the evidence is of low quality and the evidence for differences in side effects is imprecise, 2) there is little difference in the benefit of double DMARD therapy over monotherapy, and 3) triple therapy might be preferred by some patients who desire a more rapid short-term benefit (e.g., earlier resumption of work activities) and are willing to assume potential added risk.

PICOs A.6 and A.12. The recommendation is *conditional* because 1) the evidence is of low

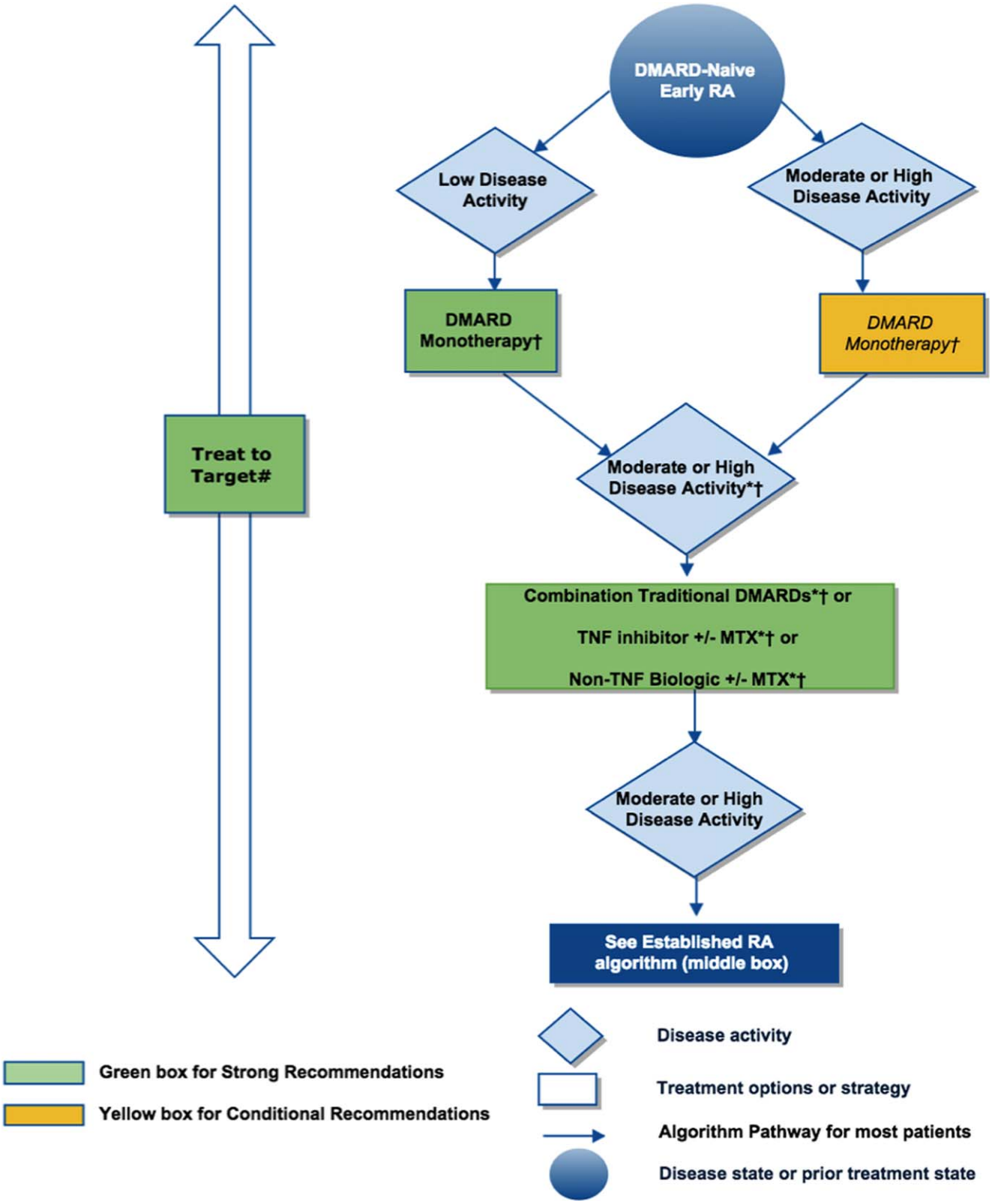

Figure 3. 2015 American College of Rheumatology recommendations for the treatment of Early rheumatoid arthritis (RA), defined as disease duration <6 months. * = consider adding low-dose glucocorticoids (≤10 mg/day of prednisone or equivalent) in patients with moderate or high RA disease activity when starting disease-modifying antirheumatic drugs (DMARDs) and in patients with DMARD failure or biologic failure. † = also consider using short-term glucocorticoids (defined as <3 months treatment) for RA disease flares. Glucocorticoids should be used at the lowest possible dose and for the shortest possible duration to provide the best benefit-risk ratio for the patient. # = treatment target should ideally be low disease activity or remission. For the level of evidence supporting each recommendation, see the related section in the Results. This figure is derived from recommendations based on PICO (population, intervention, comparator, and outcomes) questions A.1 to A.12. For definitions of disease activity (categorized as low, moderate, or high) and descriptions, see Tables 1 and 2. MTX = methotrexate.

quality, and 2) although glucocorticoid therapy is effective as a short-term (i.e., less than 3 months) therapy to "bridge" patients until realizing the benefits of DMARDs, this decision must be balanced by the lack of long-term glucocorticoid safety studies. The risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and the duration of therapy is short.

PICO A.7. The recommendation is **strong** despite the low quality of evidence because, for a patient failing DMARD monotherapy, clinical experience and indirect evidence support the benefits of adding these treatment options, and recommending no additional treatment is not an option. When deciding which therapy to use, considerations may include cost, comorbidities, burden of taking medications (i.e., 1 versus multiple, oral versus other routes) and side-effect profile. The panel also voted that biologic therapy should be used in combination with MTX, when possible, due to superior efficacy of this combination over biologic monotherapy.

PICOs A.8 and A.9. The recommendation is *conditional* because 1) the evidence is low quality, and 2) there are potential longer-term safety concerns related to tofacitinib that need more study, partly related to the shorter experience using tofacitinib.

PICOs A.10 and A.11. The recommendation is *conditional* because the evidence is of low quality because it is indirect, and the risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and duration of therapy is short.

Recommendations for the treatment of patients with established RA

Recommendations for treatment of established RA patients (disease duration ≥6 months), including tapering therapy, are provided in Figures 4 and 5. An executive summary of these recommendations is available in Supplementary Appendix 5, http://onlinelibrary.wiley.com/doi/10.1002/art.39480/abstract.

Reasoning underlying the recommendations for the treatment of established RA

PICO B.1. The recommendation is **strong** because, based on moderate quality evidence, the panel concluded that the benefits far outweigh the risks for patients with established RA treated with a targeted approach compared to a non-targeted approach (Figure 4).

PICO B.2. The recommendation is **strong** despite the low quality of evidence because DMARD monotherapy is available as a less costly first-line therapy that has an extensive safety record with well-documented clinical efficacy, a large body of clinical experience, and familiarity among rheumatologists. The panel also voted that MTX should be the preferred initial DMARD for most patients with established RA who have never taken a DMARD.

PICO B.3. The recommendation is *conditional* despite the published positive tofacitinib efficacy data because the balance of benefit (tofacitinib slightly more efficacious), risk (long-term safety of tofacitinib is currently not well-known versus the well-known long-term safety of MTX), and cost considerations (MTX is less expensive than tofacitinib), favored MTX overall.

PICO B.4. The recommendation is *conditional* because the evidence is of low quality. The evidence supporting an incremental benefit for double DMARD therapy over DMARD monotherapy is indirect, and the evidence for differences in side effects is imprecise.

PICO B.5. The recommendation is **strong** despite moderate to very low quality of evidence because for a patient failing DMARD monotherapy, clinical experience and indirect evidence support the benefits of adding these treatment options, and recommending no treatment is not an option. The panel also voted that biologic therapy should be used in combination with MTX, when possible, due to superior efficacy of this combination over biologic monotherapy.

PICO B.6. The recommendation is **strong** because, compared to TNFi monotherapy, TNFi therapy has superior efficacy when used in combination with MTX, based on high quality evidence.

PICOs B.12 and B.14. The recommendation is *conditional* because 1) there is evidence for rituximab's efficacy in patients who have already received TNFi therapy, and for tocilizumab's superiority over a TNFi in patients already receiving

Recommendations for patients with Established RA[1]	Level of Evidence (evidence reviewed)
1. Regardless of disease activity level, use a treat-to-target strategy rather than a non-targeted approach (PICO B.1).	**Moderate (44-46)**
2. If the disease activity is low, in patients who have never taken a DMARD, use DMARD monotherapy (MTX preferred) over a TNFi (PICO B.2).	**Low (47,48)**
3. *If the disease activity is moderate or high in patients who have never taken a DMARD:* • *use DMARD monotherapy (MTX preferred) over tofacitinib (PICO B.3).* • *use DMARD monotherapy (MTX preferred) over combination DMARD therapy (PICO B.4).*	*High (49)* *Moderate (18,20-25)*
4. **If disease activity remains moderate or high despite DMARD monotherapy, use combination traditional DMARDs *or* add a TNFi *or* a non-TNF biologic *or* tofacitinib (all choices with or without MTX, in no particular order of preference), rather than continuing DMARD monotherapy alone (PICO B.5).**	**Moderate to Very low (23,26,29,30,47,48,50-59)**
5. If disease activity remains moderate or high despite TNFi therapy in patients who are currently not on DMARDs, add one or two DMARDs to TNFi therapy rather than continuing TNFi therapy alone (PICO B.6).	**High (60-65)**
6. *If disease activity remains moderate or high despite use of a single TNFi:* • *use a non-TNF biologic, with or without MTX, over another TNFi with or without MTX (PICO B.12 and B.14).* • *use a non-TNF biologic, with or without MTX, over tofacitinib with or without MTX (PICO B.13 and B.15).*	*Low to Very low (66-72)* *Very low[4]*
7. *If disease activity remains moderate or high despite use of a single non-TNF biologic, use another non-TNF biologic, with or without MTX, over tofacitinib, with or without MTX (PICO B.16 and B.17).*	*Very low[4]*
8. *If disease activity remains moderate or high despite use of multiple (2+) sequential TNFi therapies, first use a non-TNF biologic, with or without MTX, over another TNFi or tofacitinib (with or without MTX) (PICO B.8, B.9, B.10, B.11).*	*Very low (73-75)*
9. *If the disease activity still remains moderate or high despite the use of multiple TNFi therapies, use tofacitinib, with or without MTX, over another TNFi, with or without MTX, if use of a non-TNF biologic is not an option (PICO B.23 and B.24).*	*Low (29,30)*
10. *If disease activity remains moderate or high despite use of at least one TNFi and at least one non-TNF-biologic:* • *first use another non-TNF biologic, with or without MTX, over tofacitinib (PICO B.21 and B.22).* • *If disease activity remains moderate or high, use tofacitinib, with or without MTX, over another TNFi (PICO B.19 and B.20).*	*Very low (29,30)* *Very low (29)*
11. *If disease activity remains moderate or high despite use of DMARD, TNFi, or non-TNF biologic therapy, add short-term, low dose glucocorticoid therapy (PICO B.26 and B.27).*	*High to Moderate (33,41,76,77)*
12. *If disease flares in patients on DMARD, TNFi, or non-TNF biologic therapy, add short-term glucocorticoids at the lowest possible dose and the shortest possible duration (PICO B.28 and B.29).*	*Very low (40-43)*
13. *If the patient is in remission:* • *taper DMARD therapy (PICO B.31)[2].* • *taper TNFi, non-TNF biologic, or tofacitinib (PICO B.33, B.35, B.37) (please also see #15).*	*Low[3] (78)* *Moderate to Very low[3] (79,80)*
14. **If disease activity is low:** • **continue DMARD therapy (PICO B.30).** • **continue TNFi, non-TNF biologic or tofacitinib rather than discontinuing respective medication (PICO B.32, B.34 and B.36).**	**Moderate (78)** **High to Very low (79,80)**
15. **If the patient's disease is in remission, do not discontinue all RA therapies (PICO B.38).**	**Very low[4]**

Figure 4. Summary of 2015 American College of Rheumatology (ACR) recommendations for the treatment of Established rheumatoid arthritis (RA). Green and bolded = strong recommendation. A strong recommendation means that the panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to most patients, and only a small proportion would not want to follow the recommendation. Yellow and italicized = conditional recommendation: The desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. A treatment recommendation favoring one medication over another means that the preferred medication would be the recommended first option and the nonpreferred medication may be the second option. Favoring one medication over the other does not imply that the nonfavored medication is contraindicated for use; it is still an option. Therapies are listed alphabetically; azathioprine, gold, and cyclosporine were considered but not included. Disease-modifying antirheumatic drugs (DMARDs) include hydroxychloroquine, leflunomide, methotrexate (MTX), and sulfasalazine. 1 = definition of established RA is based on the 1987 ACR RA classification criteria (81), since the 2010 ACR/European League Against Rheumatism RA classification allows classification of a much earlier disease state (82). 2 = tapering means scaling back therapy (reducing dose or dosing frequency), not discontinuing it. Tapering should be considered an option and not be mandated. If done, tapering must be conducted slowly and carefully, watching for increased disease activity and flares. Even for patients whose RA is in remission, there is some risk of flare when tapering. 3 = evidence is rated low quality or moderate to very low quality because some evidence reviewed for this recommendation was indirect and included studies with discontinuation rather than tapering of therapy or since studies involved patients achieving low disease activity rather than remission. 4 = no studies were available, leading to very low quality evidence, and the recommendation was based on clinical experience. PICO = population, intervention, comparator, and outcomes; TNFi = tumor necrosis factor inhibitor. For definitions and descriptions, see Table 1.

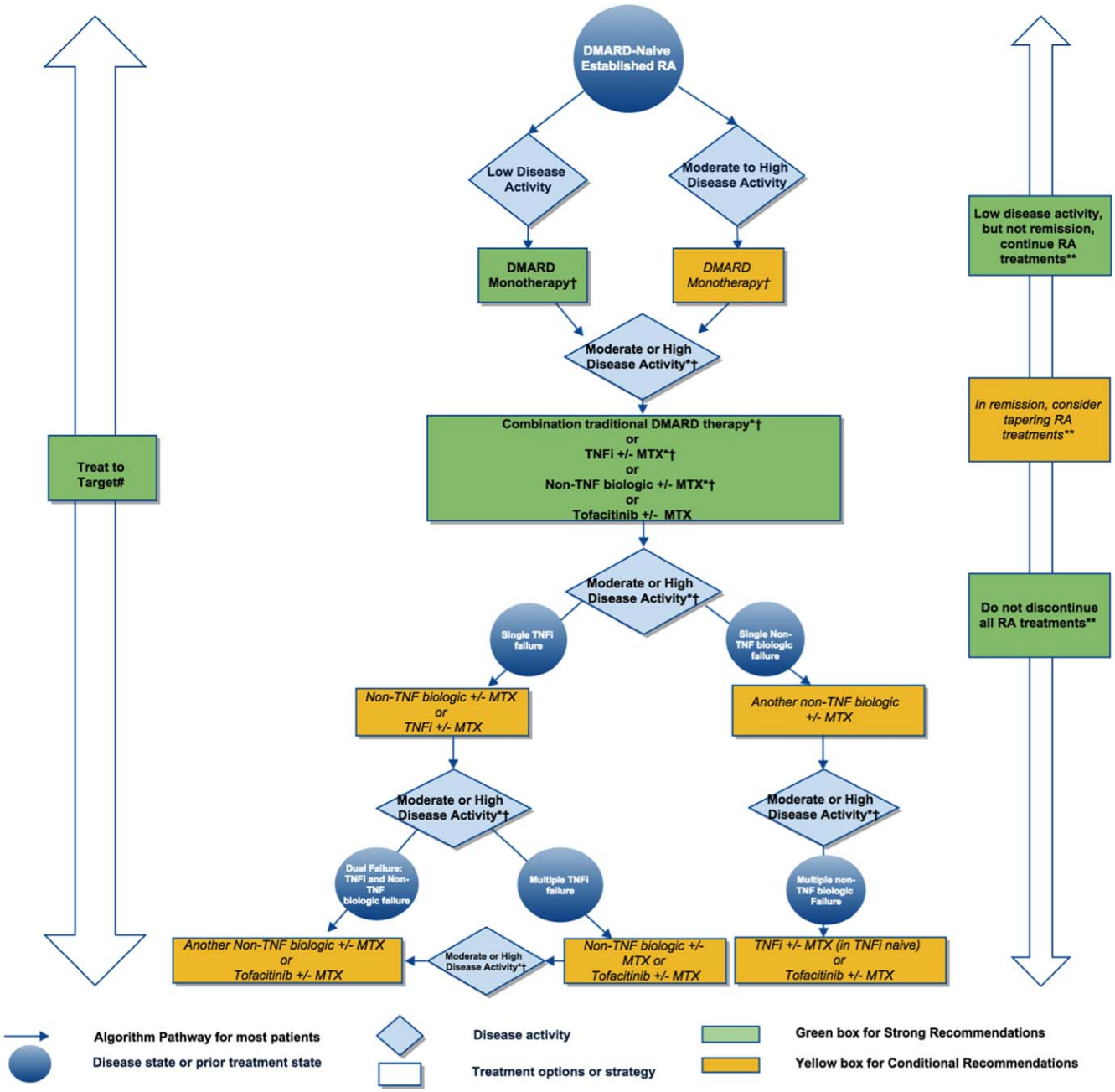

Figure 5. 2015 American College of Rheumatology (ACR) recommendations for the treatment of Established rheumatoid arthritis (RA), defined as disease duration ≥6 months, or meeting the 1987 ACR classification criteria (81). Due to complexity of management of established RA, not all clinical situations and choices could be depicted in this flow chart, and therefore we show the key recommendations. For a complete list of recommendations, please refer to the Results. * = consider adding low-dose glucocorticoids (≤10 mg/day of prednisone or equivalent) in patients with moderate or high RA disease activity when starting traditional disease-modifying antirheumatic drugs (DMARDs) and in patients with DMARD failure or biologic failure. † = also consider using short-term glucocorticoids (defined as <3 months treatment) for RA disease flares. Glucocorticoids should be used at the lowest possible dose and for the shortest possible duration to provide the best benefit-risk ratio for the patient. # = treatment target should ideally be low disease activity or remission. ** = tapering denotes scaling back therapy (reducing dose or dosing frequency), not discontinuing it and if done, must be conducted slowly and carefully. For the level of evidence supporting each recommendation, see the related section in the Results. This figure is derived from recommendations based on PICO (population, intervention, comparator, and outcomes) questions B.1 to B.38. For definitions of disease activity (categorized as low, moderate, or high) and descriptions, see Tables 1 and 2. MTX = methotrexate; TNFi = tumor-necrosis factor inhibitor.

MTX/DMARDs, and 2) there is evidence for efficacy of tocilizumab monotherapy.

PICOs B.13 and B.15. The recommendation is *conditional* because 1) the evidence is of very low quality, and 2) there is not enough difference in efficacy between non-TNF biologics and tofacitinib to outweigh the long-term safety data and the amount of experience associated with non-TNF biologics.

PICOs B.16 and B.17. The recommendation is *conditional* because 1) the evidence is of very low quality, 2) non-TNF biologics have longer-term safety data compared to tofacitinib, 3) there is greater long-term clinical experience with non-TNF biologics compared to tofacitinib, 4) there is not enough difference in efficacy between non-TNF biologics and tofacitinib to outweigh the longer-term safety data and greater amount of experience with non-TNF biologics, and 5) the fact that other non-TNF biologics with different mechanisms of action may be efficacious and worth trying.

PICOs B.8, B.9, B.10, and B.11. The recommendation is *conditional* because 1) the evidence is of very low quality, and 2) there is limited evidence, especially for the long-term safety data for tofacitinib.

PICOs B.23 and B.24. The recommendation is *conditional* because 1) the evidence is of very low quality, 2) improvement in outcomes as measured by the Health Assessment Questionnaire is numerically higher for patients randomized to tofacitinib compared to TNFi in an RCT; however, long-term safety data for tofacitinib are not yet available, and 3) some patients may prefer an oral formulation over an injection.

PICOs B.21 and B.22. The recommendation is *conditional* for the same reasons as cited above for PICOs B.16 and B.17 (except reason 2).

PICOs B.19 and B.20. The recommendation is *conditional* for the same reasons as cited above for PICOs B.23 and B.24.

PICOs B.26 and B.27. The recommendation is *conditional* because the risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and duration of therapy is short.

PICOs B.28 and B.29. The recommendation is *conditional* because 1) the evidence is of very low quality, and 2) the risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and duration of therapy is short.

The panel also made several recommendations related to tapering therapy, with the following general caveats: 1) "Tapering" is defined as scaling back therapy 1 medication at a time (reducing dose or dosing frequency), 2) Patients' values and preferences should drive decisions related to tapering, 3) A comprehensive plan to monitor disease activity and address possible flares is implemented, and 4) Prior to tapering, RA patients, including those in sustained remission, are informed of the risk of flare.

PICOs B.31, B.33, B.35, and B.37. The recommendation is *conditional* because 1) the evidence is of low quality, 2) while tapering carries a risk of flare, minimizing therapy may decrease toxicity and/or cost, and lowers the risk of treating patients unnecessarily.

PICOs B.30, B.32, B.34, and B.36. The recommendation is **strong** because based on clinical observations and experience only a small minority of patients with low disease activity (not remission) is able to successfully discontinue all RA therapy.

PICO B.38. The recommendation is **strong** despite very low quality of evidence because based on clinical experience, the risk of RA flare and the need for resumption of therapy are high, if all RA therapies are discontinued.

The Voting Panel also voted on 2 additional PICO questions (B.7 and B.18) to fill the remaining gaps in the treatment algorithm after the initial voting (Figure 5). Both compare therapy with no therapy. We followed the GRADE methodology and the same process for these PICO questions.

PICO B.7. If disease activity remains moderate or high despite the use of a single TNFi, the recommendation is *conditional* for using another TNFi rather than not using a TNFi. The recommendation is *conditional* because both evidence from TNFi studies and clinical experience support response to a second TNFi in a significant proportion of patients, especially in the presence of secondary failure (i.e., a TNFi worked initially and then stopped working). For additional recommendations related to this patient population, see PICOs B.12, B.15, B.23, and B.24.

Table 3. Recommendations for optimal followup laboratory monitoring intervals for complete blood cell count, liver transaminase levels, and serum creatinine levels for patients with rheumatoid arthritis receiving disease-modifying antirheumatic drugs*

	Monitoring interval based on duration of therapy‡		
Therapeutic agents†	<3 months	3–6 months	>6 months
Hydroxychloroquine	None after baseline§	None	None
Leflunomide	2–4 weeks	8–12 weeks	12 weeks
Methotrexate	2–4 weeks	8–12 weeks	12 weeks
Sulfasalazine	2–4 weeks	8–12 weeks	12 weeks

* More frequent monitoring is recommended within the first 3 months of therapy or after increasing the dose, and the outer bound of the monitoring interval is recommended beyond 6 months of therapy. Adapted from ref. 6.
† Listed alphabetically.
‡ The panel indicated that patients with comorbidities, abnormal laboratory results, and/or multiple therapies may require more frequent laboratory testing than what is generally recommended laboratory monitoring for disease-modifying antirheumatic drugs as shown in the table.
§ See ref. 6 for baseline monitoring recommendations.

PICO B.18. If disease activity remains moderate or high despite the use of multiple non-TNF biologics and the patient is TNFi-naive, the recommendation is *conditional* for using TNFi rather than not using TNFi. The recommendation is *conditional* because the evidence is of very low quality. Although there are no trials of patients with multiple non-TNF biologic failures, if non-TNF biologics have not been effective and TNFi therapy has not yet been given, then TNFi therapy should be tried, unless there are contraindications for its use.

Recommendations for laboratory monitoring for DMARDs and TB screening in patients receiving biologics or tofacitinib

The panel endorsed the recommendations previously published in the 2008 recommendations and in the 2012 update to be included in the 2015 recommendations (Table 3 and Figure 6). The panel indicated that in the absence of significant new knowledge, development of an alternate recommendation was not warranted with one exception: the Voting Panel recommended that the same TB screening algorithm as described for biologics should be followed for patients receiving tofacitinib. For additional details (including baseline laboratory monitoring), please see the 2008 and 2012 guidelines (5,6).

Recommendations in RA patients with high-risk comorbidities

Recommendations are provided in Figure 7. An executive summary of these recommendations is available in Supplementary Appendix 5, http://onlinelibrary.wiley.com/doi/10.1002/art.39480/abstract.

Congestive heart failure

PICOs C.1, C.2, C.3, C.4, C.5, and C.6. The recommendations are *conditional* because the evidence is of very low quality. The Voting Panel noted that there are no reports of exacerbation of heart failure using non-TNF biologics and the US Food and Drug Administration (FDA) warns against using TNFi in this population based on worsening of congestive heart failure with TNFi in the Adverse Event Reporting System database. A TNFi should only be used if there are no other reasonable options, and then, perhaps, only in compensated heart failure (83,84) (Figure 7).

Hepatitis B

To address hepatitis B, the AASLD practice guidelines were reviewed (85,86). These guidelines suggest that immunosuppressive therapy can be safely utilized when prophylactic antiviral therapy is prescribed concomitantly.

PICO D.1. The recommendation is **strong** despite very low evidence (85–92) because clinical experience supports the benefits of treating these RA patients with active disease, and an absence of additional harms, if patients are receiving concomitant effective antiviral treatment. The Voting Panel further specified that for a patient with natural immunity from prior exposure to hepatitis B (i.e., hepatitis B core antibody positive, normal liver function tests,

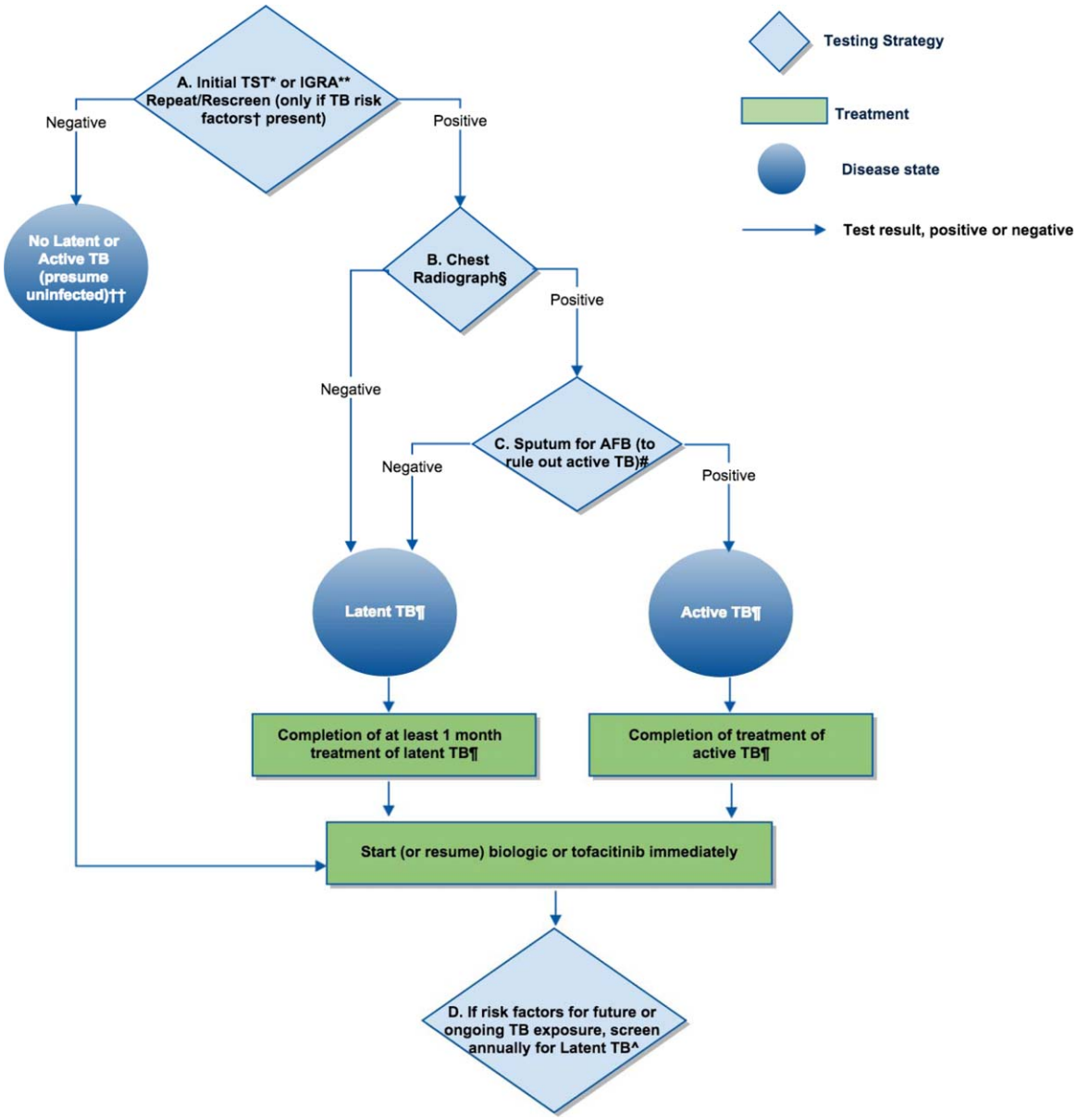

Figure 6. Tuberculosis (TB) screening algorithm for biologics or tofacitinib (endorsed and modified from the 2012 American College of Rheumatology RA treatment recommendations). The Voting Panel reviewed and endorsed the 2012 TB screening algorithm with 1 change, that tofacitinib should be included alongside biologics. * = anergy panel testing is not recommended. ** = interferon-gamma release assay (IGRA) is preferred if patient has a history of BCG vaccination. † = risk factors for TB exposure are defined based on a publication from the US Centers for Disease Control and Prevention as: close contacts of persons known or suspected to have active TB, foreign-born persons from areas that have a high incidence of active TB (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia), persons who visit areas with a high prevalence of active TB, especially if visits are frequent or prolonged, residents and employees of congregate settings whose clients are at increased risk for active TB (e.g., correctional facilities, long-term care facilities, and homeless shelters), health care workers who serve clients who are at increased risk for active TB, populations defined locally as having an increased incidence of latent *Mycobacterium tuberculosis* infection or active TB, possibly including medically underserved, low-income populations, or persons who abuse drugs or alcohol, and infants, children, and adolescents exposed to adults who are at increased risk for latent *M tuberculosis* infection or active tuberculosis (159,160). †† = if patient is immunosuppressed and false-negative results more likely, consider repeating screening test(s) with tuberculin skin test (TST) or IGRA. § = chest radiography may also be considered when clinically indicated in patients with risk factors, even with a negative result on repeat TST or IGRA. # = obtain respiratory (e.g., sputum, bronchoalveolar lavage) or other samples as clinically appropriate for acid-fast bacilli (AFB) smear and culture. Consider referral to TB specialist for further evaluation and treatment. ¶ = in a patient diagnosed as having latent or active TB, consider referral to a specialist for the recommended treatment. ^ = patients who test positive for TST or IGRA at baseline (pretreatment) often remain positive for these tests even after successful treatment of TB. These patients need monitoring for clinical signs and symptoms of recurrent TB disease, since repeating tests will not allow help in diagnosis of recurrent TB. The level of evidence supporting each recommendation for TB reactivation was derived from consensus opinion of experts, case studies, or standards of care. The level of evidence for initiation of biologics in patients being treated for latent TB infection was higher, with data derived from a single randomized trial or nonrandomized studies. Adapted from ref. 5.

High-risk condition	Recommendation	Level of Evidence (evidence reviewed)
Congestive heart failure[1]		
CHF	*Use combination DMARDs or non-TNF biologic or tofacitinib over TNFi (PICO C.1, C.2 and C.3).*	*Moderate to Very low (83,84)*
CHF worsening on current TNFi therapy	*Use combination DMARDs or non-TNF biologic or tofacitinib over another TNFi (PICO C.4, C.5 and C.6).*	*Very low[7]*
Hepatitis B[2]		
Active Hepatitis B infection and receiving/received effective antiviral treatment	**Same recommendations as in patients without this condition (PICO D.1).**	**Very low (85-92)**
Hepatitis C[2]		
Hepatitis C infection and receiving/received effective antiviral treatment	*Same recommendations as in patients without this condition (PICO E.1).*	*Very low (92-103)*
Hepatitis C infection and not receiving or requiring effective antiviral treatment	*Use DMARDs over TNFi (PICO E.2)[3].*	*Very low (92-103)*
Past history of treated or untreated malignancy[4]		
Previously treated or untreated skin cancer (non-melanoma or melanoma)	*Use DMARDs over biologics in melanoma (PICO F.1).* *Use DMARDs over tofacitinib in melanoma (PICO F.2).* *Use DMARDs over biologics in non-melanoma (PICO F.3).* *Use DMARDs over tofacitinib in non-melanoma (PICO F.4).*	*Very low (104-106)*
Previously treated lymphoproliferative disorder	**Use rituximab over TNFi (PICO G.1).**	**Very low (105,107)**
Previously treated lymphoproliferative disorder	*Use combination DMARD or abatacept or tocilizumab over TNFi* (PICO G.2, G.3 and G.4).	*Very low (105,107)*
Previously treated solid organ malignancy	*Same recommendations as in patients without this condition (PICO H.1).*	*Very low (105,108)*
Previous Serious Infection(s)[5]		
Previous Serious infection(s)	*Use combination DMARD over TNFi (PICO I.1)[5].* *Use abatacept over TNFi (PICO I.2)[6].*	*Very low (109-116)*

Figure 7. Summary of 2015 American College of Rheumatology recommendations for high-risk patients with established rheumatoid arthritis with moderate or high disease activity and congestive heart failure (CHF), hepatitis B or C, past history of malignancy, or serious infection(s). Green and bolded = strong recommendation. A strong recommendation means that the panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to most patients, and only a small proportion would not want to follow the recommendation. Yellow and italicized = conditional recommendation. The desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. A treatment recommendation favoring one medication over another means that the preferred medication would be the recommended first option and the nonpreferred medication may be the second option. Favoring one medication over the other does not imply that the nonfavored medication is contraindicated for use; it is still an option. 1 = conditional recommendations supported by evidence level ranging from moderate level to no evidence, supported by clinical experience and the Food and Drug Administration safety warning with tumor necrosis factor inhibitors (TNFi). 2 = strong recommendations for Hepatitis B were largely based upon the recent American Association for the Study of Liver Diseases practice guidelines (85,86) and clinical experience; conditional recommendations for Hepatitis C were largely supported by very low level evidence based upon case series and clinical experience. 3 = consider using DMARDs other than methotrexate or leflunomide, such as sulfasalazine *or* hydroxychloroquine. 4 = conditional recommendations supported by level of evidence ranging from very low to no evidence, are largely based upon expert opinion and clinical experience. 5 = conditional recommendation was supported by very low level evidence. 6 = there was no consensus for making recommendations regarding the use of rituximab over TNFi or the use of tocilizumab over TNFi in this setting, due to indirect evidence (e.g., no comparison to TNFi or including patients with tuberculosis) and differences of opinion. In 1 study, compared to patients who restarted their previous TNFi following hospitalized infections, patients who switched to abatacept exhibited lower risk of subsequent hospitalized infections among the therapies examined. 7 = no studies were available, leading to very low quality evidence, and the recommendation was based on clinical experience. DMARDs = disease-modifying antirheumatic drugs; PICO = population, intervention, comparator, and outcomes.

and hepatitis B surface [HBs] antibody positive and HBs antigen negative), RA treatment should be the same as that of unexposed patients, as long as the patient's viral load is monitored regularly (117,118), conservatively, every 6–12 months. For patients with chronic hepatitis B who are untreated, referral for antiviral therapy is appropriate prior to immunosuppressive therapy (88,119–124). A recent review summarized this evidence (125).

Hepatitis C

PICO E.1. The recommendation is *conditional* because the evidence is of very low quality, i.e., indirect evidence from patient populations other than RA (92–103). The evidence suggests that these RA patients with hepatitis C virus (HCV) infection should *not* be treated differently than RA patients who do not have hepatitis C. The Voting Panel recommended that rheumatologists collaborate with gastroenterologists and/or hepatologists to monitor patients receiving antiviral therapy. This is important considering the recent availability of highly effective therapy for HCV, which might lead to a greater number of HCV patients being treated successfully.

PICO E.2. The recommendation is *conditional* because the evidence is of very low quality. For patients with HCV infection or exposure, the safety of biologic therapy was addressed indirectly by 2 RCTs and a variety of small observational studies including case series (92–103). Much of this research was not confined to individuals with RA. This very low-level evidence suggests that TNFi therapy can be safely administered in HCV-positive patients, if treatment with antiviral therapy is used. One small, long-term observational study of HCV-positive individuals receiving TNFi immunosuppression found that increased HCV activity was associated with the absence of concomitant antiviral therapy (93). In a small RCT of HCV-positive individuals with RA who did not require antiviral therapy, neither patients treated with MTX nor patients treated with TNFi therapy demonstrated significant change in viral load (98). The Voting Panel recommended that rheumatologists collaborate with gastroenterologists and/or hepatologists in recommending individualized treatment based on other comorbidities, reason(s) for not receiving HCV treatment, and the need to minimize immunosuppression, and consider using DMARDs other than MTX or leflunomide, such as sulfasalazine *or* hydroxychloroquine.

Malignancy

Previous melanoma and non-melanoma skin cancer. Separate PICO questions addressed melanoma and non-melanoma skin cancer, but the recommendations were similar, and therefore were combined.

PICOs F.1, F.2, F.3, and F.4. The recommendation is *conditional* because 1) the evidence is of very low quality, 2) due to potentially lower risk of recurrence of skin cancer with DMARDs versus other therapies based on clinical experience and 2 retrospective studies (104,105), and 3) a lack of data and knowledge about some of the mechanisms of action of biologics and tofacitinib, which may potentially contribute to an increased cancer risk. DMARDs were considered less immunosuppressive than biologics. The Voting Panel also stated that host factors may vary and may influence the risk of recurrence of skin cancer. Even though biologics were not the first option, several Voting Panel members indicated that if the joint disease was moderately or highly active in the setting of a low-grade melanoma or non-melanoma skin cancer that had been previously treated, biologics would be an acceptable option with close skin surveillance in conjunction with a dermatologist.

It is important to note that although the panel voting on PICO F.3 (using a DMARD rather than a biologic for patients with a prior history of non-melanoma skin cancer) achieved the necessary 70% threshold for consensus, there was 1 Voting Panel member with a dissenting view that the risk difference between DMARDs and biologics in RA patients with a previously treated or untreated non-melanoma skin cancer may be insignificant, and 2 other Voting Panel members also shared some of these concerns but voted conditionally in favor of DMARDs.

Previous lymphoproliferative disorders

PICO G.1. The recommendation is **strong** despite very low quality evidence because rituximab is an approved treatment for some of these disorders and the best available clinical trial data suggest that there is a signal in clinical trials of induction and/or an increased risk of lymphoma in patients treated with TNFi (105,107).

	Killed vaccines			Recombinant vaccine	Live attenuated vaccine
	Pneumococcal[1]	Influenza (intramuscular)	Hepatitis B[2]	Human Papilloma	Herpes Zoster[3]
Before initiating therapy					
DMARD monotherapy	✓	✓	✓	✓	✓
Combination DMARDs	✓	✓	✓	✓	✓
TNFi biologics	✓	✓	✓	✓	✓ *(PICO J.1)*[5]
Non-TNF biologics	✓	✓	✓	✓	✓ *(PICO J.1)*[5]
While already taking therapy					
DMARD monotherapy	✓	✓	✓	✓	✓
Combination DMARDs	✓	✓	✓	✓	✓
TNFi biologics	✓	✓	✓ **(PICO J.4, J.5)**[6]	✓	*Not recommended (PICO J.2, J.3)*[7]
Non-TNF biologics[4]	✓	✓	✓ **(PICO J.4, J.5)**[6]	✓	*Not recommended (PICO J.2, J.3)*[7]

Figure 8. 2015 American College of Rheumatology (ACR) recommendations update regarding the use of vaccines in patients with rheumatoid arthritis (RA) starting or currently receiving disease-modifying antirheumatic drugs (DMARDs) or biologics. ✓ = recommend vaccination when indicated (based on age and risk). Red indicates vaccinations not recommended. The panel endorsed all 2012 RA treatment recommendations for vaccination with 1 exception (see footnote 6), and re-voted only for certain immunization recommendations in patients receiving biologics. All recommendations were *conditional*, except that the panel strongly recommended (in green) using appropriately indicated killed/inactivated vaccines in patients with early or established RA who are currently receiving biologics. Evidence level was very low for recommendations based on population, intervention, comparator, and outcomes (PICOs) J.1, J.2, J.3, J.4, and J.5. Evidence level for the remaining recommendations that were endorsed from the 2012 ACR RA treatment guideline was similar (on a different scale). 1 = the Centers for Disease Control and Prevention (CDC) also recommends a one-time pneumococcal revaccination after 5 years for persons with chronic conditions such as RA. The CDC recommends pneumococcal conjugate vaccine(PCV13 or Prevnar 13) for all children younger than 5 years of age, all adults ≥65 years, and persons 6−64 years of age with certain medical conditions. Pneumovax is a 23-valent pneumococcal polysaccharide vaccine (PPSV23) that is currently recommended for use in all adults ≥65 years old and for persons who are ≥2 years old and at high risk for pneumococcal disease (e.g., those with sickle cell disease, HIV infection, or other immunocompromising conditions). PPSV23 is also recommended for use in adults 19 − 64 years of age who smoke cigarettes or who have asthma (http://www.cdc.gov/vaccines/vpd-vac/pneumo/default.htm?s_cid=cs_797). 2 = if hepatitis B risk factors are present (e.g., intravenous drug abuse, multiple sex partners in the previous 6 months, health care personnel). 3 = the panel conditionally recommended that in RA patients ages ≥50 years, the herpes zoster vaccine should be given before the patient receives biologic therapy or tofacitinib for their RA. 4 = response to certain killed vaccines may be reduced after rituximab therapy. 5 = the panel conditionally recommended giving the herpes zoster vaccine before the patient receives biologic therapy or tofacitinib for their RA in both early or established RA patients ages ≥50 years (PICO J.1). The panel also voted that after giving the herpes zoster vaccine, there should be a 2-week waiting period before starting biologics. 6 = the panel strongly recommended that in patients with early or established RA who are currently receiving biologics, appropriately indicated killed/inactivated vaccines should be used (PICOs J.4 and J.5). 7 = the panel conditionally recommended that in early or established RA patients who are currently receiving biologics, live attenuated vaccines such as the herpes zoster (shingles) vaccine should not be used (PICOs J.2 and J.3). TNFi = tumor necrosis factor inhibitor. For definitions and descriptions, see Table 1. Adapted from ref. 5.

PICOs G.2, G.3, and G.4. The recommendation is *conditional* because 1) the evidence is of very low quality (105,107), 2) there is a lack of evidence for combination DMARD therapy versus TNFi (PICO G.2), and 3) as described in PICO G.1, there is a possible increased risk of lymphoma associated with TNFi, but there is no evidence that abatacept or tocilizumab increases this risk (PICOs G.3 and G.4).

Previous solid organ cancer

PICO H.1. The recommendation is *conditional* because the evidence is of very low quality (105,108).

Serious infections

PICOs I.1 and I.2. The recommendation is *conditional* because 1) the evidence is of very low quality (indirect), as most trials excluded patient groups with a high risk of serious infections, and 2) rheumatologists have greater experience with DMARDs compared to TNFi in patients with previous serious infections. The recommendation regarding abatacept is conditional because the evidence is very low quality. In one study, compared to patients who restarted their previous TNFi following hospitalized infections, patients who switched to abatacept exhibited the lowest risk of subsequent hospitalized infection among the therapies examined (109).

Recommendations for use of vaccines in RA patients receiving DMARD and/or biologic therapy

Recommendations for use of vaccines in RA patients on DMARD and/or biologic therapy are provided in Figure 8.

PICO J.1. The recommendation is *conditional* because the evidence is of very low quality. The CDC has recommended the herpes zoster vaccine for people ages ≥60 years in the general population, but not for adults ages 50–59 years, even though the FDA approved the vaccine in adults ≥50 years. The CDC reconsidered the use of vaccination in people 50–59 years in 2013 and decided not to change its current recommendation for the general population, but did not vote (126). Our Voting Panel considered these recommendations and, because the immune systems of RA patients are compromised by the disease or by medications, the panel agreed that patients with RA ages ≥50 years should be vaccinated before receiving biologic or tofacitinib therapy because the benefits of doing so likely outweigh the risks in this population.

PICOs J.2 and J.3. The recommendation is *conditional* because 1) the evidence is of very low quality (127,128), and 2) there is a safety warning about the use of live vaccines in patients receiving biologics (127,128) (see Zostavax packet insert available at https://www.merck.com/product/usa/pi_circulars/z/zostavax/zostavax_pi2.pdf).

PICOs J.4 and J.5. The recommendation is **strong** despite very low quality of evidence (129–135) because of the documented benefit of killed vaccines in adults and no significant concerns of harm in RA patients receiving biologics, as per the general guidance from the CDC. Clinicians should consult the CDC recommendations for killed vaccines (136–140). Responses to some killed vaccines may be reduced after rituximab therapy (141) and possibly after MTX therapy. Whenever possible, vaccines should be given *prior to* receiving therapy.

In addition to these recommendations, the Voting Panel endorsed the vaccination recommendations made in 2012, with the 1 exception mentioned above, i.e., responses to certain killed vaccines may be reduced after rituximab therapy (141) (Figure 8).

DISCUSSION

The 2015 ACR RA treatment guideline addresses the use of DMARDs, biologics, tofacitinib, and glucocorticoids in early and established RA and the use of various treatment approaches in frequently encountered clinical scenarios, including treat-to-target, switching between therapies, tapering of therapy, the use of biologics and DMARDs in high-risk RA patients, vaccination in patients with RA receiving DMARDs or biologics, TB screening with biologics or tofacitinib, and laboratory monitoring with DMARDs. The recommendations aim to provide guidance for clinicians and patients in an era of rapid advances in the treatment of RA. These recommendations were developed using scientific evidence, a rigorous, well-defined guideline development methodology, and a group consensus process. Compared to earlier treatment guidelines, there were several differences in the development of the 2015 RA treatment recommendations.

First, we used the GRADE methodology because it provides an internationally accepted systematic approach to guideline development. PICO questions were developed with the intended patient populations and outcomes explicitly listed. Before beginning the evidence synthesis, we posted the PICO questions online and solicited feedback and comments from the ACR membership. We also noted dissenting views. An example is the dissenting view related to the conditional recommendation for DMARDs over biologics for RA patients with previously treated or untreated non-melanoma skin cancer. Even though the panel reached consensus with 90% voting in favor, 1 panel member had a dissenting opinion and voted for biologic therapy over DMARD therapy in this situation. It should be noted that melanoma and non-melanoma were considered and voted on separately by the panel but that the final recommendations were similar for both situations and, therefore, are presented as a single recommendation.

Unlike previous ACR RA guidelines, the panel decided to base these new recommendations only on patients' disease activity level rather than including both disease activity and prognosis. The justification for this approach was that adding another variable (prognosis) to the PICO questions would have made the project much less feasible. Also, the Content Panel and the Voting Panel agreed that disease prognosis was largely captured in the concept of disease activity and that information regarding prognosis was unlikely to further contribute to decision-making.

Recommendations related to immunization and treatment in patients with RA and coexistent viral hepatitis B or C were informed primarily by the CDC (138) and the AASLD guidelines (85,86), respectively, and

require further explanation. The panel made a *conditional* recommendation to use herpes zoster immunization at age 50 and older prior to starting biologics, considering the higher infection risk due to RA and its treatments. This is consonant with the FDA approval for the use of herpes zoster vaccine in adults ages ≥50 years, and despite current CDC recommendations to use the vaccine in the general population (i.e., not RA patients) at ages ≥60 years. The panel also stated that as long as RA patients with viral hepatitis were started on the appropriate antiviral treatments for hepatitis B and C prior to initiation of RA therapy, they could be treated similarly to RA patients without these chronic viral infections. Case reports, case series, and small observational studies of RA patients with hepatitis B or C who have been treated with medications for RA provided additional supportive evidence. However, the data are limited in these clinical settings, and close monitoring of such patients and consultation with the appropriate specialists is advised.

The Voting Panel strongly recommended the use of combination traditional DMARDs *or* addition of a TNFi *or* a non-TNF biologic *or* tofacitinib for patients with established RA with moderate or high disease activity despite DMARD monotherapy. After carefully considering the evidence, the panel concluded that the limited direct comparative evidence for these therapies in this clinical situation precluded recommending a ranking of these treatment options.

Due to rapidly evolving knowledge for the treatment of RA, some recommendations may be outdated by the time they are published due to the emergence of new evidence. Examples include new data on tapering and discontinuation of therapies in early RA (142) and treat-to-target (143). The short half-life of treatment recommendations is also related to the rigorous and time-consuming process of guideline development used by the ACR, which complies with guidance from the National Academy of Medicine (formerly the Institute of Medicine) and the Council for Medical Subspecialty Societies. Additional time is also required for review and endorsement of each guideline document by ACR committees, journal reviewers and editors, and the ACR Board of Directors. However, the ACR regularly updates RA guidelines and strives to shorten the time between the end of the literature review and the publication of guidelines, to make them as relevant and current as possible.

The panel provided "conditions" when making a conditional recommendation. The listed conditions were not necessarily exhaustive for each recommendation, but included those factors that were most important in determining the final panel vote. This process ensured that conditions were a direct reflection of the Voting Panel members' discussion and agreements. Although we used 70% as the agreement threshold, for 80% of the recommendations there was 90% consensus (of which 50% of the recommendations had 100% consensus). We noted that 77% of the recommendations were conditional and the remaining 23% were strong. This was partially due to the lack of evidence for common clinical situations, and our a priori decision that PICO questions should be based on what is important for a clinician and patient to know, not based on the presence or absence of the highest level of evidence. This indicates that more evidence is needed to derive strong RA recommendations in the future. A number of recommendations were strong despite low quality evidence, which is allowed according to GRADE methodology, and the Voting Panel provided justification for these recommendations.

Several important aspects of RA care were not addressed due to resource limitations, including the use of nonpharmacologic interventions (e.g., physical therapy, occupational therapy, assistive devices), use of biologics and DMARDs in other less-common conditions (e.g., new diagnosis of cancer, family history of cancer or multiple sclerosis, new diagnosis of hepatitis while receiving successful RA therapy). The Voting Panel considered the dosing issues related to glucocorticoids and MTX and believed strongly that it was not within its charge to mandate dosing. Recommendations for individual medications (e.g., various DMARDs, TNFi, non-TNF biologics) were not made, since an a priori decision was made to examine these as categories for feasibility reasons. Although we recognize that other disease activity measures have become available since the ACR endorsed 6 measures in its 2012 paper (16), it was outside the scope of this guideline effort to reevaluate measures and recommend to the ACR an updated list for possible endorsement.

A targeted literature search was performed for biosimilars, but there was too little evidence for the panel to provide recommendations on this complex issue at present. In addition, at the time of panel voting, biosimilars for RA were not yet approved for use in the US. The ACR has published a position statement on biosimilars (available at http://www.rheumatology.org/Practice-Quality/Administrative-Support/Position-Statements) that may provide some guidance for interested readers. The team recommended that biosimilars in RA therapy should be considered for future research agendas and RA guideline efforts.

The team also discussed the following topics and recommended that they be targeted for future research: use of biologics and DMARDs during the period of conception, pregnancy, and breastfeeding; treatment of RA with interstitial lung disease; laboratory monitoring for biologics/tofacitinib; and biomarker testing.

The 2015 ACR RA treatment recommendations apply to common clinical situations, since the panel considered issues common to most patients, not exceptions. In an effort to standardize terminology, the ACR has asked that the term "guideline" be used when referring to a guideline paper and the term "recommendation" when referring to an individual recommendation statement within the guideline paper. The use of the term "guideline" should not be construed as a mandate that every clinician/patient should follow the recommendations made in every clinical situation. These recommendations are not proscriptive and should be used by clinicians and patients as a guide for discussion related to RA treatments. Only a clinician's assessment, an active patient-physician dialogue, and collaborative decision-making will result in the optimal risk/benefit analysis. The best treatment decisions will be made by clinicians incorporating patients' values and preferences. Thus, the choice of the best treatment in some cases may be other options in the algorithm/recommendation rather than the first option in the treatment recommendation algorithm.

These recommendations are not intended to support payment or insurance decisions and should not be used for denial of treatments to patients. These recommendations cannot adequately convey all uncertainties and nuances of patient care in the real world. For example, a listing of all conditions entertained in each conditional recommendation is not feasible. We also noted that for newer drugs (e.g., tofacitinib), long-term experience and safety data are usually lacking, and additional data are needed to increase the confidence of clinicians in utilizing such medications.

In conclusion, the 2015 ACR RA pharmacologic treatment guideline is comprehensive and provides guidance to clinicians and patients regarding the treatment of RA. Using state-of-the-art methodology (GRADE) and a well-defined group-consensus technique, our guideline development process was systematic, explicit, and transparent. Periodic updates of this guideline, as required by the ACR for all of its guidelines, will ensure that this RA treatment guideline remains current and usable for patients and physicians for treatment decision-making in RA. Finally, the 2015 ACR RA treatment guideline is a useful tool not only to guide treatment in clinical practice but also to facilitate discussion about individualized treatment decision-making between patients and their clinicians.

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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 published. Dr. Singh 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. Singh, Saag, Bridges, Akl, Bannuru, Sullivan, Vaysbrot, McNaughton, Osani, Shmerling, Curtis, Furst, Parks, Kavanaugh, O'Dell, King, Leong, Matteson, Schousboe, Drevlow, Ginsberg, Grober, St.Clair, Tindall, Miller, McAlindon.

Acquisition of data. Singh, Saag, Bridges, Akl, Bannuru, Sullivan, Vaysbrot, McNaughton, Osani, Shmerling, Curtis, Furst, Parks, Kavanaugh, O'Dell, King, Leong, Matteson, Schousboe, Drevlow, Ginsberg, Grober, St.Clair, Tindall, Miller, McAlindon.

Analysis and interpretation of data. Singh, Saag, Bridges, Akl, Bannuru, Sullivan, Vaysbrot, McNaughton, Osani, Shmerling, Curtis, Furst, Parks, Kavanaugh, O'Dell, King, Leong, Matteson, Schousboe, Drevlow, Ginsberg, Grober, St.Clair, Tindall, Miller, McAlindon.

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APPENDIX A: PANEL AND TEAM MEMBERS

Voting Panel: Arthur Kavanaugh, MD, James O'Dell, MD, Charles King, MD, Amye Leong, MBA, Eric L. Matteson, MD, MPH, John T. Schousboe, MD, PhD, Barbara Drevlow, MD, Seth Ginsberg, BSc, James Grober, MD, E. William St.Clair, MD, Elizabeth Tindall, MD.

Core Leadership Team: Jasvinder A. Singh, MBBS, MPH (Project Principal Investigator), Kenneth G. Saag, MD, MSc, S. Louis Bridges Jr., MD, PhD, Elie A. Akl, MD, MPH, PhD, Timothy McAlindon, MD, MPH.

Literature Review Team: Timothy McAlindon, MD, MPH (Literature Review Team Principal Investigator), Raveendhara R. Bannuru, MD, PhD, Matthew C. Sullivan, BA, Elizaveta Vaysbrot, MD, MS, Christine McNaughton, BS, Mikala Osani, BA, Janet Joyce, MLS, (Librarian, Ottawa, Ontario, Canada).

Content Panel: Robert H. Shmerling, MD, Jeffrey R. Curtis, MD, MS, MPH, Daniel E. Furst, MD, Deborah Parks, MD.