Pan American League of Associations for Rheumatology recommendations for the management of rheumatoid arthritis

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The Pan American League of Associations for Rheumatology has developed evidence-based recommendations for the pharmacological management of rheumatoid arthritis in Latin America. A panel of rheumatoid arthritis experts from Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Mexico, Panama, Peru, Uruguay, and Venezuela formulated clinically relevant questions in the population, intervention, comparator, outcome format. Systematic literature reviews were done following the Grading of Recommendations Assessment, Development and Evaluation method. Recommendations were formulated based on evidence quality and expert consensus, which required at least 70% agreement among the voting members to be included in the guidelines. Ten recommendations and a treatment algorithm were developed. Key topics include early initiation of conventional synthetic disease-modifying antirheumatic drugs (DMARDs), particularly methotrexate, parenteral methotrexate for intolerance, cautious glucocorticoid use, switching mechanisms of action after unsuccessful biological or targeted synthetic DMARD treatment, tapering in remission, and guidance for rheumatoid arthritis-associated interstitial lung disease and vasculitis. Special attention is given to cost-effectiveness and accessibility considering the socioeconomic characteristics of Latin America. These recommendations aim to support clinicians in Latin America by providing a practical, evidence-based, and contextually relevant framework that addresses the unique challenges faced in the region.

Introduction

Rheumatoid arthritis is a prevalent autoimmune disease in Latin America that substantially reduces the quality of life for patients and affects physical, emotional, occupational, social, and economic aspects of their lives.[1] The regional prevalence of rheumatoid arthritis ranges from 0·8% to 1·6%, with an incidence rate of 18·5 cases per 100 000 person-years (95% CI 16·7–20·4) and a high prevalence in individuals born in Latin America whose ancestry is also Latin American.[2–7] Managing this condition poses considerable challenges, including disparities in access to health care, medication shortages, and few rheumatologists.[2,8,9] These challenges, combined with socioeconomic inequalities and the increasing prevalence of rheumatoid arthritis, underscore the urgent need for tailored strategies to improve patient outcomes.

In the past decade, efforts to better understand rheumatoid arthritis dynamics in Latin America have revealed specific barriers, such as fragmented health-care systems, geographical inequities, and the under-representation of regional experts in the development of global rheumatoid arthritis guidelines.[3] Although international guidelines, such as those from the American College of Rheumatology and the European Alliance of Associations for Rheumatology (EULAR), offer valuable recommendations, they often do not fully address the unique challenges faced by Latin American countries.[10,11] These challenges include little access to biological therapies, inconsistent disease monitoring, and cultural factors that affect treatment adherence.[6] Barriers to optimal rheumatoid arthritis care vary in different regions and include availability (eg, regulatory approval and local supply of drugs), affordability (eg, drug pricing, payer models, and public *vs* private coverage), and acceptability issues (eg, patient awareness, cultural attitudes towards treatment, and trust in the health-care system). These challenges are particularly pronounced in Latin America, where health-care systems are highly heterogeneous and often under-resourced compared with those in high-income countries.[12] To address these gaps, the Pan American League of Associations for Rheumatology (PANLAR) developed a special group for the accreditation of centres of excellence in rheumatoid arthritis, an initiative set up to overcome barriers to rheumatoid arthritis care and treatment. This programme establishes the minimum standards of care that participating centres can gradually implement and improve, fostering better outcomes for patients with rheumatoid arthritis. Additionally, PANLAR has introduced an accreditation process to ensure that these standards are consistently met.[13,14]

In the past 5 years, PANLAR generated recommendations for the management of different prevalent diseases,[15–18] with the conviction to generate common guidelines through evidence-based recommendations

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See Online for appendix

For more on the **GRADE method** see www.gradeworkinggroup.org

For more on **Rayyan software** see https://rayyan-prod.qcri.org/

For more on **PANLAR** see https://www.panlar.org/

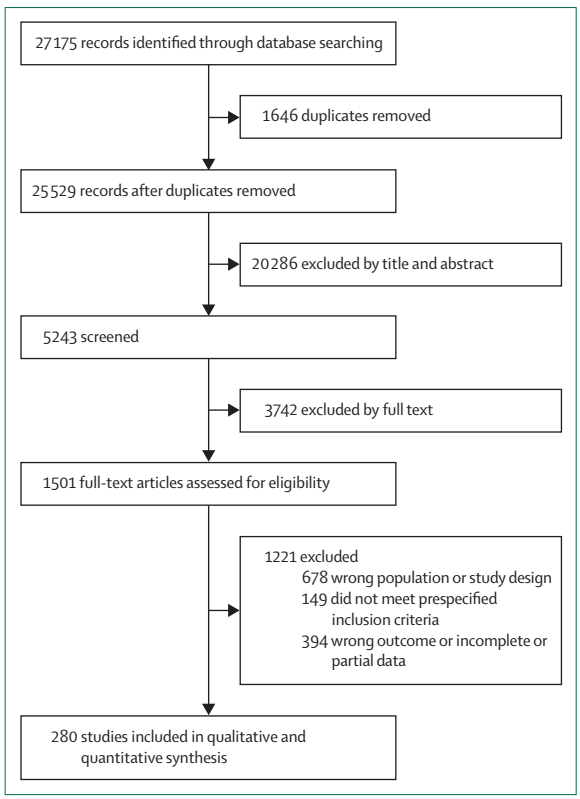

Figure 1: **Study selection**

that, while considering the particularities of the region, make homogenisation of management practices in Latin America possible.

Conversely, many PANLAR member countries have few rheumatologists with specific clinical or research expertise in rheumatoid arthritis. The few local experts might not be sufficient to develop country-specific guidelines—these countries could benefit from regional recommendations formulated by experts from both neighbouring nations and their own.

PANLAR published guidelines for the management of rheumatoid arthritis in 2006.[19] Since then, major changes have occurred in the management of rheumatoid arthritis, many new drugs and mechanisms of action have been incorporated into the treatment of this disease, and new long-term information on older drugs has become available.

This Review serves as a call to action, presenting recommendations tailored to the unique context of Latin America. It aims to address not only the medical complexities of rheumatoid arthritis but also socioeconomic factors that influence patient care and quality of life. Therefore, the differentiation from the American College of Rheumatology and EULAR guidelines is not merely intended to create a region-specific consensus, but to address concrete differences in treatment access, such as the unavailability of particular biologics in public formularies, restricted use of agents such as rituximab or Janus kinase (JAK) inhibitors in some countries, and high out-of-pocket costs that reduce patient adherence. These recommendations aim to bridge the gap between global evidence and local feasibility to support realistic and effective implementation in Latin America. Moreover, they aim to offer an evidence-based framework for health-care professionals treating patients with rheumatoid arthritis in Latin America. They specifically focus on the use of conventional synthetic and biological and targeted synthetic disease-modifying antirheumatic drugs (DMARDs).

Methods

The complete methodological details are included in the appendix (pp 12–16). These guidelines have been made and endorsed by PANLAR, and were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[20] method and abide by the Appraisal of Guidelines, Research and Evaluation (AGREE) reporting checklist to ensure transparency and completeness of reporting. The working group was divided into two teams: a team of four methodologists and a team of rheumatologists with expertise in the care of patients with rheumatoid arthritis. The rheumatologist team consisted of 21 experts from Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Mexico, Panama, Peru, Uruguay, and Venezuela. Rheumatoid arthritis experts defined the scope of these guidelines, generated questions in the population, intervention, comparator, outcome (PICO) format, and voted. The guidelines were then reviewed by four PANLAR reviewers with internationally recognised expertise and leadership in rheumatoid arthritis. Patients with rheumatoid arthritis were actively involved in the guideline development process with a dedicated meeting, as detailed in the appendix (pp 59–65). These patients are members of Grupo Juntos, a PANLAR-led initiative that brings together patients and health-care professionals to promote patient-centred care in rheumatology. Their perspectives, including suggestions, concerns, preferences, fears, uncertainties, and negative experiences with treatment, were presented to the full expert panel and discussed before the voting sessions.

Evidence was searched for in MEDLINE and PubMed, the Cochrane Library, and the Latin American and Caribbean Health Sciences Literature (appendix pp 43–57). Grey literature was also evaluated. Rayyan software was used to screen the literature search results. Two independent reviewers screened the titles and abstracts for duplicates, with a third reviewer resolving conflicts. Two independent reviewers screened the eligible articles.

Data extraction and statistical analyses were done with RevMan software (version 5.4.1) and study quality was assessed with the Cochrane risk-of-bias tool. RevMan files were exported to GRADEpro GDT

software to generate GRADE profiles for every PICO question. Two independent reviewers assessed the quality of evidence for every outcome based on the GRADE criteria. Disagreements between reviewers were resolved by discussion and, when necessary, consultation with a third independent reviewer. The GRADE system classifies evidence into four levels (high, moderate, low, and very low) according to an estimate of the confidence in the effect. Expert consensus-based recommendations, in the absence of evidence, were rated as very low quality.

The rheumatoid arthritis expert panel developed the recommendations based on clinical questions, which required 70% agreement at the voting stage. The voting process was anonymous and completed online. If the voting on a particular PICO question did not reach a consensus of 70% agreement in the first instance, the members held a discussion before voting again. Voting was allowed only three times. If there was no agreement among at least 70% of the voting members after three attempts, the recommendation was considered ungraded. Every recommendation considered the risk-to-benefit ratio and the available evidence quality. A recommendation could be either in favour of or against a proposed intervention. Recommendations were classified as either strong or conditional. Strong recommendations reflected high confidence that the intervention favourably balanced benefits and risks for most patients. Conditional recommendations indicated less confidence, often because of low-quality evidence. Conditional recommendations also arose from uncertainty regarding the benefits and risks of an intervention.

Relevant conflicts of interest were those occurring within 36 months before and during the development of these guidelines. Individuals whose primary employment (>51% of work time and effort) was with a company that manufactured or sold therapeutics or diagnostics were not eligible to participate. Diagnosis and other important aspects of the management of patients with rheumatoid arthritis (eg, immunisations, clinical monitoring, and imaging) are not addressed in these guidelines. However, interstitial lung disease and vasculitis associated with rheumatoid arthritis have been reviewed as two of the most common serious clinical complications.

The target audience for these recommendations is health-care providers and stakeholders involved in managing patients with rheumatoid arthritis, including—but not limited to—rheumatologists, neurologists, ophthalmologists, geriatricians, internists, primary care providers, general practitioners, specialty pharmacists, and physicians from other specialties. Patients with rheumatoid arthritis might also benefit from these recommendations. Information regarding these guidelines is available on the PANLAR website and materials for patients will be developed and made

***Panel 1*: PANLAR rheumatoid arthritis guidelines—definitions and common terms**

Active disease

Active disease is defined as a state of persistent and clinically evident inflammation in the joints, characterised by symptoms such as joint pain, swelling, protracted morning stiffness, and elevated inflammatory markers (eg, C-reactive protein and erythrocyte sedimentation rate). This active inflammatory process can lead to progressive joint damage and functional impairment if not adequately controlled.[20–22] High or moderate disease activity is defined by criteria, as follows:

- Disease activity score in 28 joints: moderate activity (>3·2 to ≤5·1) or high activity (>5·1)
- Simple disease activity index: moderate activity (>11 to ≤26) or high activity (>26)
- Clinical disease activity index: moderate activity (>10 to ≤22) or high activity (>22)

Inactive disease

Inactive disease is defined as a state in which inflammatory activity is not clinically detectable, characterised by the absence of swollen or tender joints, minimal or no morning stiffness, and typical or near-typical inflammatory markers. This state often corresponds to clinical remission.[20,21,23]

- Disease activity score in 28 joints: remission (≤2·6)
- Simple disease activity index: remission (≤3·3)
- Clinical disease activity index: remission (≤2·8)

Sustained remission

Remission for at least 6–12 months.

Primary treatment failure

No initial response to biological disease-modifying antirheumatic drug (DMARD) or targeted synthetic DMARD treatment. This classification indicates that the patient has not had a significant clinical improvement since starting treatment.

Secondary treatment failure

Refers to the loss of response to a biological DMARD or targeted synthetic DMARD treatment that was previously effective, characterised by an adequate response not being maintained after a recommended treatment period of at least 3 months or 6 months—ie, although the patient initially responded to the treatment, they subsequently stopped benefiting from it.

Conventional synthetic DMARDs

Conventional synthetic DMARDs are commonly used in rheumatoid arthritis treatment, including leflunomide, methotrexate, hydroxychloroquine, and sulfasalazine. Conventional synthetic DMARDs aim to slow down the progression of the disease and alleviate symptoms.

Targeted synthetic DMARDs

DMARDs that specifically target particular molecules that are involved in the inflammatory process. In rheumatoid arthritis, Janus kinase inhibitors such as tofacitinib, baricitinib, filgotinib, and upadacitinib are examples of targeted synthetic DMARDs.

Biological DMARDs

Biologically derived medications that target specific components of the immune system involved in the inflammatory response. TNF inhibitors include adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. IL-6 receptor inhibitors include sarilumab and tocilizumab. Co-stimulation inhibitors include abatacept. B-cell depleting therapies (CD20) include rituximab.

Biosimilar

According to PANLAR consensus, a biosimilar is a biological product that is highly similar to an existing approved reference product and has no clinically meaningful differences, and is equivalent in efficacy and comparable in safety to its reference biologic.[24]

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(Panel 1 continued from previous page)

Difficult-to-treat
Unsuccessful treatment with two or more biological or targeted synthetic DMARDs of different mechanism of action, unless restricted by access to treatment due to socioeconomic factors and other issues. Refers to a challenging nature in managing rheumatoid arthritis due to factors such as no response to treatments or complexities in reaching therapeutic goals.[25,26]

Switching
Change from one treatment to another due to various factors, such as little efficacy, side-effects, or changes in patient preferences.

Cycling
Switching to a different biological DMARD or targeted synthetic DMARD with the same mechanism of action.[26]

Swapping
Switching to a biological DMARD or targeted synthetic DMARD with a different mechanism of action.

Treat-to-target
Treatment strategy aiming to reach and maintain specific predefined targets, such as remission or low disease activity.[27]

Centres of excellence
Specialised centres that provide high-quality medical care and are focused on treatment targets, education, and research for a specific disease—in this case, rheumatoid arthritis.[11]

Rheumatoid arthritis-associated interstitial lung disease
A serious and common pulmonary complication of rheumatoid arthritis, characterised by inflammation and fibrosis of the lung parenchyma. Typically diagnosed with high-resolution CT and classified into radiological patterns, such as usual interstitial pneumonia and non-specific interstitial pneumonia.[28]

Rheumatoid vasculitis
A rare but serious complication of rheumatoid arthritis, characterised by inflammation of blood vessels that can affect multiple organs, including the skin, peripheral nerves, and, in severe cases, internal organs such as the heart and lungs. This condition is typically associated with long-standing rheumatoid arthritis and high disease activity.[29]

available there. PANLAR plans to update these guidelines regularly.

Results

A total of 100 PICO questions were generated (appendix pp 17–42). The literature review initially identified 27 175 manuscripts, 280 of which were considered for the evidence report (figure 1; appendix p 58). Input from patients, gathered in a dedicated meeting with patient representatives, was reviewed and discussed with the full expert panel before the voting sessions. Patient suggestions, concerns, and preferences were thus considered during the formulation of every recommendation to ensure alignment with their priorities.

Panel 1 presents the terminology definitions of the disease concepts. Nine general principles were developed, presented in panel 2, all of which were 100% agreed upon. Treatment recommendations are listed in the table. An algorithm for the pharmacological management of patients with rheumatoid arthritis is shown in figure 2. The different drugs and their suggested doses are presented in the appendix (pp 431–432).

Recommendation 1: for patients with rheumatoid arthritis and active disease who are naive to DMARD treatment, we strongly recommend starting therapy with conventional synthetic DMARDs

Conventional synthetic DMARDs are widely used for the treatment of rheumatoid arthritis. Therapy should be initiated as soon as a rheumatoid arthritis diagnosis is established. Methotrexate remains the preferred choice of conventional synthetic DMARD, owing to its efficacy and safety profile.[21–23] Leflunomide has a similar clinical efficacy to methotrexate in both established and early rheumatoid arthritis, and is equally effective in slowing radiographic damage. By contrast, sulfasalazine and antimalarials (chloroquine and hydroxychloroquine) might be less efficacious than both leflunomide and methotrexate in the long term.[21] Patients with rheumatoid arthritis with moderate or high disease activity who were treated with methotrexate, alone or in combination with other DMARDs under the treat-to-target strategy, showed a decrease in the severity of disease activity in 80% of patients.[27] When methotrexate monotherapy is ineffective, adding triple conventional synthetic therapy (methotrexate plus sulfasalazine plus hydroxychloroquine) can help control symptoms in about one-third of patients.[24] The panel especially recommends this strategy for patients without poor prognostic factors.

Recommendation 2: we strongly recommend considering glucocorticoids only when initiating or changing conventional synthetic DMARDs, with glucocorticoid therapy tapered and discontinued as quickly as possible

The use of glucocorticoids for rheumatoid arthritis management presents substantial challenges in Latin America, where approximately 60% of patients are treated with these medications.[25]

In general, current recommendations for the use of glucocorticoids in the management of rheumatoid arthritis are suboptimal. Short-term glucocorticoids are frequently necessary to alleviate symptoms before the onset of action of DMARDs. Glucocorticoid treatment should be limited to the lowest effective dose for the shortest possible duration. The toxicity associated with glucocorticoids was judged to outweigh their potential benefits.[9] Nevertheless, glucocorticoids in combination with DMARDs help control disease activity and inhibit radiographic progression, especially in the short-to-medium term and in rheumatoid arthritis onset.[26] Intra-articular glucocorticoids are strongly recommended to treat monoarticular or oligoarticular flares. The chronic use of glucocorticoids

has been suggested as an option to control disease activity in countries with low health-care resources, such as Latin America. Protracted glucocorticoid therapy at low doses is still highly prevalent in clinical practice: the GLORIA study suggests that withdrawal of low-dose prednisolone is feasible and safe after 2 years of administration, although with increased risk of fractures and infections.[27]

Recommendation 3: the use of parenteral methotrexate over oral methotrexate is strongly recommended in patients with gastrointestinal intolerance to the oral form

The use of methotrexate should be optimised with subcutaneous administration in cases of intolerance to oral administration.[30] Studies have suggested that, compared with the standard oral formulation, the subcutaneous form reduces gastrointestinal intolerance.[31] Additionally, although evidence is poor, an open-label, randomised sequence, three-way crossover study suggested that subcutaneous methotrexate has higher bioavailability than the oral form, potentially offering some advantages in its use.[28] Moreover, a meta-analysis showed that treatment with parenteral methotrexate was significantly more likely to reduce disease activity than the oral form. This finding suggests that parenteral methotrexate is more effective than oral methotrexate.[29] Changing from oral methotrexate to subcutaneous methotrexate has also been shown to improve adherence, rheumatoid arthritis control, and quality of life, independent of changes in dose.[30]

Recommendation 4: for patients with active rheumatoid arthritis who are naive to methotrexate or conventional synthetic DMARDs and who have contraindications to conventional synthetic DMARDs, we strongly recommend starting treatment with TNF inhibitors, IL-6 inhibitors, abatacept, rituximab, or JAK inhibitors

This recommendation is intended for patients in whom conventional synthetic DMARDs cannot be used due to clinical contraindications (eg, hepatic toxicity, lung disease, pregnancy, or previous severe intolerance).[32] Although conventional synthetic DMARDs, particularly methotrexate, are the preferred first-line agents in most guidelines, patients who cannot receive them require alternative treatment strategies to avoid delays in disease control and progression of joint damage.

This recommendation is supported by evidence from clinical trials and observational studies showing the efficacy and safety of biological or targeted synthetic DMARDs in rheumatoid arthritis. The panel acknowledges that initiating advanced therapies as first-line treatment is highly unusual in routine care and might face approval or reimbursement challenges, especially in settings with low resources. Therefore, this approach should be reserved for well justified clinical scenarios, with decisions tailored to individual patient needs and aligned with the regulatory and health-care system contexts in each country. For example, in some Latin American countries, rituximab can only be used after unsuccessful TNF inhibitor treatment.[2,10]

Panel 2: General principles for the PANLAR recommendations for the management of rheumatoid arthritis

Comprehensive care
The management of rheumatoid arthritis should adopt a holistic approach that addresses not only the clinical manifestations of the disease but also its psychosocial impact, including emotional, occupational, and social dimensions

Equitable access
Efforts should be made to ensure that all patients, regardless of geographical location, socioeconomic status, or health-care system, have equitable access to timely diagnosis, appropriate treatment, and ongoing care

Active patient participation
Rheumatologists should promote patient involvement by emphasising patient education, adherence, empowerment, and self-management strategies to enhance quality of life

Early access and prioritisation of methotrexate
- We recommend initiation of disease-modifying antirheumatic drug (DMARD) therapy as soon as possible after the diagnosis of rheumatoid arthritis
- Methotrexate is the preferred initial treatment, in line with international recommendations and regional experience

Regular monitoring and treatment goals
Treating physicians should establish therapeutic goals aimed at reaching remission or low disease activity when remission is not possible. They should engage in shared decision making with patients and establish protocols for regular monitoring of disease activity with validated indices

Adjuvant therapy
- If the disease cannot be controlled with conventional synthetic DMARDs, targeted synthetic DMARDs, or biological DMARDs, adjuvant therapy such as glucocorticoids could be considered
- Therapy should be considered on a case-by-case basis
- These therapies should follow accepted principles, emphasising short durations and the lowest possible doses

Non-pharmacological management
Non-pharmacological interventions, such as physical activity, patient education, and psychological support, should be integrated into the comprehensive care of patients with rheumatoid arthritis

Risk-based treatment selection
Treatment choices should consider individual comorbidities and risk factors to optimise safety and therapeutic outcomes

Immunisations
Patients with rheumatoid arthritis should receive recommended vaccinations, ideally before starting immunosuppressive therapy, to reduce the risk of preventable infections

Biosimilars and generic drugs
The use of biosimilars and the practice of switching from originator biologics to approved biosimilars or generic drugs are supported to enhance treatment access and reduce costs, provided they meet established standards of quality, efficacy, and safety, and are guided by appropriate regulatory frameworks

		Recommendation strength	Level of evidence	Level of agreement
1	For patients with rheumatoid arthritis and active disease who are naive to DMARD treatment, we recommend starting therapy with conventional DMARDs (methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine); methotrexate is the preferred initial treatment	Strong	Low to moderate	100%
2	We recommend considering glucocorticoids only when initiating or changing conventional synthetic DMARDs to rapidly improve symptoms; glucocorticoid therapy should be tapered and discontinued as quickly as possible; intra-articular glucocorticoids are recommended for treating monoarticular or oligoarticular flares	Strong	Low	94%
3	The use of parenteral methotrexate over oral methotrexate is recommended for patients with gastrointestinal intolerance to the oral form	Strong	Low	71%
4	For patients with active rheumatoid arthritis naive to methotrexate or conventional synthetic DMARDs who cannot receive conventional synthetic DMARDs, we recommend treatment with TNF inhibitors, IL-6 inhibitors, abatacept, rituximab, or JAK inhibitors	Strong	Moderate to high	88%
5	In patients with active rheumatoid arthritis and intolerance or inadequate response to conventional synthetic DMARDs, we recommended starting TNF inhibitor, abatacept, IL-6 inhibitor, rituximab, or JAK inhibitor. In patients 65 years or older with a history of smoking or risk factors for cardiovascular disease or malignancy, JAK inhibitors are conditionally recommended after unsuccessful conventional synthetic DMARD treatment or intolerance, and when biological DMARDs are contraindicated or unavailable	Strong	Moderate to high	100%
6	Combining biological DMARDs and targeted synthetic DMARDs with conventional synthetic DMARDs is recommended; IL-6 inhibitors and targeted synthetic DMARDs are recommended over other biological DMARDs when biological DMARDs cannot be combined with conventional synthetic DMARDs as co-medication	Strong	Moderate to high	88%
7	Switching to another biological DMARD or targeted synthetic DMARD of a different mechanism of action (swapping) or to other biological DMARDs or targeted synthetic DMARD of the same mechanism of action (cycling) is recommended in active rheumatoid arthritis and intolerance or incomplete response (primary or secondary failure) to biological DMARDs or targeted synthetic DMARDs	Strong	Moderate to high	94%
8 (a)	For patients who have been in remission for more than 6–12 months, we recommend gradually reducing the dose of biological DMARD instead of discontinuing the medication altogether	Strong	Low to moderate	93%
8 (b)	For patients who are on combination therapy and have been in remission for more than 6–12 months, we conditionally recommend reducing the dose of biological DMARDs or targeted synthetic DMARDs first, followed by reducing the dose of conventional synthetic DMARDs	Conditional	Moderate to high	90%
9 (a)	In patients with rheumatoid arthritis-associated interstitial lung disease, we conditionally recommend treatment with methotrexate, rituximab, abatacept, or targeted synthetic DMARDs	Conditional	Low	76%
9 (b)	In patients with progressive rheumatoid arthritis-associated interstitial lung disease, we conditionally recommend the use of the antifibrotic drugs pirferidone or nintedanib	Conditional	Low	86%
10	For patients with rheumatoid arthritis and rheumatoid vasculitis, we conditionally recommend treatment with rituximab	Conditional	Low	86%

DMARD=disease-modifying antirheumatic drug. JAK=Janus kinase.

Table: **PANLAR recommendations for treatment of rheumatoid arthritis**

Recommendation 5: in patients with active rheumatoid arthritis and intolerance or inadequate response to conventional synthetic DMARDs, we strongly recommend starting a TNF inhibitor, abatacept, IL-6 inhibitor, rituximab, or JAK inhibitor; in patients 65 years or older with a history of smoking or risk factors for cardiovascular disease or malignancy, JAK inhibitors are conditionally recommended after conventional synthetic DMARD intolerance or unsuccessful treatment and when biological DMARDs are contraindicated or unavailable

In clinical trials and observational studies, TNF inhibitors, abatacept, IL-6 inhibitors, rituximab, and JAK inhibitors were shown to be effective and safe in treating patients with rheumatoid arthritis who have had an inadequate response or intolerance to conventional synthetic DMARDs. Additionally, these treatments have shown favourable long-term safety.[10,11] Despite some head-to-head comparisons of biological DMARDs after unsuccessful conventional synthetic DMARD treatment, the panel did not endorse one agent over another.[33–35] Several studies have shown better results with JAK inhibitors (upadacitinib and baricitinib) than with TNF inhibitors in patients who did not respond to conventional synthetic DMARDs.[36–38]

In light of the findings from the ORAL Surveillance study, which showed an increased risk of major adverse cardiovascular events and cancer with tofacitinib versus TNF inhibitors, the panel had an in-depth discussion, carefully weighing the risks and benefits of JAK inhibitors. Considering the warnings issued by regulatory agencies for all JAK inhibitors, caution is advised when prescribing these therapies to patients 65 years or older with a history of smoking or cardiovascular or malignancy

risk factors.[39] Additionally, adverse events of special interest were reported to be generally less frequent in Latin American patients than in non-Latin American patients, likely reflecting differences in baseline characteristics. However, adverse events remained higher with tofacitinib than with TNF inhibitors in both cohorts, consistent with the overall findings of the ORAL Surveillance study. These results highlight the importance of assessing individual risk factors to guide benefit–risk evaluations and optimise treatment decisions.[40]

Recommendation 6: combining biological DMARDs and targeted synthetic DMARDs with conventional synthetic DMARDs is strongly recommended

Strong evidence suggests that most biological DMARDs are more effective and confer increased survival rates when used in combination with conventional synthetic DMARDs, particularly methotrexate.[41] Therefore, the expert panel strongly recommends combination therapy, unless the patient is unable to tolerate conventional synthetic DMARDs. However, for individuals for whom combination therapy is not possible, strong evidence from randomised control trials suggests the efficacy of IL-6 inhibitors or JAK inhibitors for use as monotherapy.[42–46] Therefore, IL-6 inhibitors and targeted synthetic DMARDs are strongly recommended over other biological DMARDs when biological DMARDs cannot be used with conventional synthetic DMARDs as co-medication.

Recommendation 7: switching to another biological DMARD or to targeted synthetic DMARDs with different mechanism of actions (swapping), or to other biological or targeted synthetic DMARDs with the same mechanism of action (cycling) is strongly recommended in active rheumatoid arthritis and intolerance or incomplete response to biological DMARDs or targeted synthetic DMARDs

In patients who are unsuccessfully treated with TNF inhibitors, the available evidence—largely based on clinical trials—supports the use of agents with alternative mechanisms of action (eg, rituximab, abatacept, IL-6 inhibitors, or JAK inhibitors).[47–50] Evidence supporting the use of a second TNF inhibitor after unsuccessful treatment is scarce. One Argentinian registry[51] and one clinical trial (GO-AFTER)[52] showed that golimumab can offer clinical benefit in patients who had previous unsuccessful TNF inhibitor treatment. Another trial showed that switching to a second TNF inhibitor without a washout period after unsuccessful primary treatment with a first TNF inhibitor was both effective and safe.[35] However, insufficient evidence exists to establish whether swapping to a different mechanism of action is more effective than the use of another TNF inhibitor (cycling) in the context of unsuccessful TNF inhibitor treatment. A post-hoc analysis of the SELECT-COMPARE study

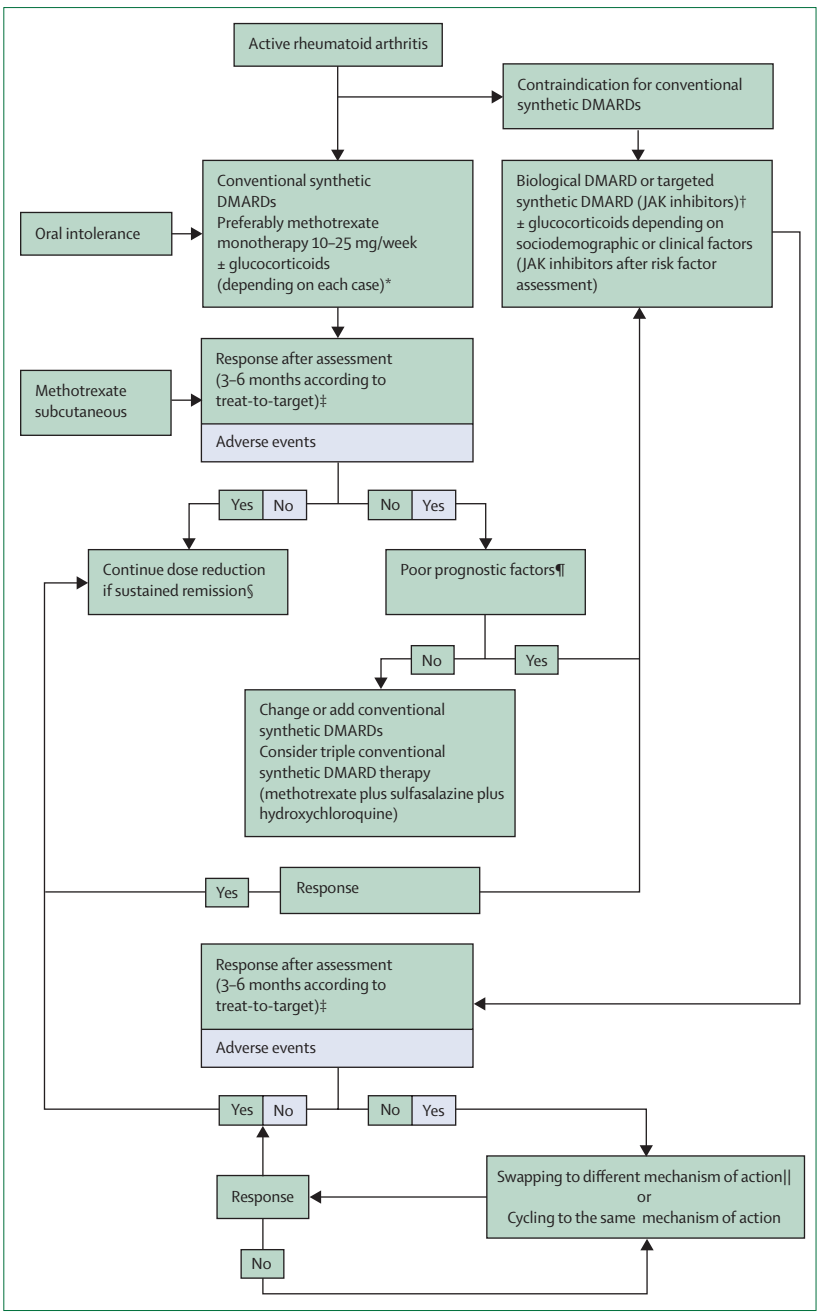

Figure 2: **Recommendations for the treatment of rheumatoid arthritis in Latin America**
Special situations: in rheumatoid vasculitis, rituximab is recommended. In rheumatoid arthritis with interstitial lung disease, avoiding the use of TNF inhibitors is recommended. DMARD=disease-modifying antirheumatic drugs. JAK=Janus kinase. *Short term glucocorticoids are frequently necessary to alleviate symptoms before the onset of action of DMARDs. Glucocorticoid treatment should be limited to the lowest effective dose for the shortest possible duration. †In patients 65 years or older with a history of heavy smoking or risk factors for cardiovascular disease or malignancy, JAK inhibitors are conditionally recommended after conventional synthetic DMARD or biological DMARD intolerance or failure, and when biological DMARDs are contraindicated or unavailable. ‡Treatment strategy aiming to reach and maintain specific predefined targets, such as remission or low disease activity. PANLAR encourages rheumatologists from Latin American to care for and treat rheumatoid arthritis with multidisciplinary centre of excellence-type teams. §Remission of at least 6–12 months at the same dose. ¶Poor prognostic factors include persistent high disease activity, high rheumatoid factor or anti-citrullinated protein antibody positivity, and early joint damage. ||In case of primary failure to first anti-TNF, only swap. In all other cases, swap or cycle.

showed that patients who were unsuccessfully treated with adalimumab and were switched to upadacitinib had better outcomes than those who were unsuccessfully treated with upadacitinib and were switched to adalimumab.[53] Registry studies and the pragmatic ROC study suggest increased benefits with a change in the mechanism of action following unsuccessful TNF inhibitor treatment.[54]

When a patient is unsuccessfully treated with any mechanism of action other than TNF inhibitors, little evidence is available regarding whether to cycle within the same mechanism of action (eg, tocilizumab to sarilumab) or to switch to a different mechanism of action (eg, tocilizumab to abatacept), or even to a TNF inhibitor. The SELECT-CHOICE study showed that upadacitinib is superior to abatacept in patients who were unsuccessfully treated with at least one biological therapy.[55] Experts recommend tailoring the treatment decision for every patient, considering the characteristics of the disease, comorbidities, and potential side-effects associated with every drug. Patients who have had multiple unsuccessful treatments might fall under the EULAR definition of difficult-to-treat rheumatoid arthritis. In these individuals, following the proposed guidelines for managing difficult-to-treat rheumatoid arthritis is recommended.[25,26]

Recommendation 8 (a): for patients on monotherapy who have been in remission for more than 6–12 months, we strongly recommend gradually reducing the dose of the biological DMARD instead of discontinuing the medication altogether

Recommendation 8 (b): for patients on combination therapy who have been in remission for more than 6–12 months, we conditionally recommend reducing the dose of biological DMARDs or targeted synthetic DMARDs first, followed by reducing the dose of conventional synthetic DMARDs

When patients are in sustained clinical remission, establishing a tapering strategy is recommended rather than suspending or stopping treatment, as tapering significantly reduces the risk of relapse. The tapering strategy can involve either gradually reducing the dose or extending the dosing interval.[56] The panel recommends considering a tapering strategy for biological or targeted synthetic DMARD treatment in most cases of prolonged clinical remission, as costs will be substantially reduced. In Latin America, the economic impact of advanced treatments is particularly relevant.

Customising the tapering strategy for every patient is important: some might have poor prognostic factors, a history of unsuccessful treatment with biologics, or delayed diagnosis. For these patients, tapering medication should be done carefully since the risk of relapse can increase, and even if treatment is reinstated, the previous state of remission might not be reached.

Recommendation 9 (a): in patients with rheumatoid arthritis-associated interstitial lung disease, we conditionally recommend treatment with methotrexate, rituximab, abatacept, or targeted synthetic DMARDs

Recommendation 9 (b): in patients with progressive rheumatoid arthritis-associated interstitial lung disease, we conditionally recommend the use of antifibrotic drugs, such as pirfenidone or nintedanib

Studies on rheumatoid arthritis-associated interstitial lung disease have not differentiated between various types of interstitial lung disease, such as usual interstitial pneumonia and non-specific interstitial pneumonia. Consequently, the panel did not provide specific recommendations for different types of interstitial lung disease. The quality of evidence is generally poor, and studies show considerable heterogeneity. Regarding TNF inhibitors, the evidence is mixed: although some patients might benefit, other treatment options are available with more reliable evidence. Little evidence exists for IL-6 inhibitors; therefore, no treatment recommendation was issued in relation to this mechanism of action.

Evidence from observational and registry studies supports the efficacy of methotrexate, rituximab, abatacept, and targeted synthetic DMARDs, which are conditionally recommended in these guidelines. Abatacept had the strongest evidence.[57–59] Although mycophenolate mofetil has been suggested for the treatment of rheumatoid arthritis-associated interstitial lung disease in other guidelines, its use is supported by little evidence and data from randomised controlled trials is absent. Additionally, it does not improve joint manifestations, hindering its utility in rheumatoid arthritis. Therefore, it was not included in the current recommendations.

Little evidence suggests that JAK inhibitors might be beneficial for patients with rheumatoid arthritis-associated interstitial lung disease. This evidence comes from post-hoc analyses of tofacitinib clinical trials and observational studies.[60] A comprehensive study in patients with rheumatoid arthritis without primary associated interstitial lung disease showed that tofacitinib reduces the incidence of developing this extra-articular manifestation.[61,62] No considerable differences exist in the evidence supporting pirfenidone and nintedanib. However, data for nintedanib, primarily derived from subanalyses of clinical trials (INBUILD), are more robust. Given the substantial financial impact of these medications in the region, cost-effectiveness should be a key consideration in treatment selection. However, the scarcity of long-term effectiveness data reduces the ability to do robust long-term cost-effectiveness analyses.

Recommendation 10: for patients with rheumatoid arthritis and rheumatoid vasculitis, we conditionally recommend rituximab treatment

Rheumatoid vasculitis is a rare but serious extra-articular manifestation of rheumatoid arthritis, often associated

with high disease activity and seropositivity (rheumatoid factor and anti-citrullinated protein antibodies). The evidence supporting the use of rituximab in this context comes from two observational cohort studies[63,64] and multiple published case series and case reports. These studies suggest that rituximab can be effective in inducing remission and reducing relapse rates in patients with rheumatoid vasculitis, particularly those with severe systemic involvement.[64]

Although no randomised controlled trials have specifically evaluated rituximab for rheumatoid vasculitis, its mechanism of action and efficacy in other systemic vasculitis conditions (eg, antineutrophil cytoplasmic antibody-associated vasculitis) provide further biological plausibility. Based on this partial but supportive evidence and clinical experience, the panel issued a conditional recommendation in favour of rituximab for this indication.

Discussion

The recommendations outlined herein provide a comprehensive, evidence-based framework for managing rheumatoid arthritis in the Pan American region, with special emphasis on challenges unique to Latin America. Disparities in health-care access, medication shortages, and socioeconomic inequalities substantially impact both the quality of care and patient outcomes. These recommendations bridge the gap between global guidelines and the specific needs of the region by offering tailored strategies to optimise rheumatoid arthritis management.[2,8] The GRADE approach was applied based on the consensus of a multidisciplinary panel of experts from various Latin American countries, who identified key priority areas relevant to the region. To support these recommendations, we did a systematic review of the literature. Additionally, the AGREE reporting checklist was used to ensure transparency and comprehensiveness in the development of the clinical guidelines for rheumatoid arthritis management.

This process involves formulating evidence-based recommendations and adapting them to Latin American contexts, where the aforementioned factors might hamper the effective implementation of the recommendations. Thus, particular aspects of the recommendations sparked extensive discussion among the expert panel and might also generate debate among readers. Notable examples include the use of triple therapy with conventional synthetic DMARDs, chronic use of glucocorticoids, and a preference for subcutaneous methotrexate.

The evidence was synthesised in a series of key questions addressing therapeutic goals, the efficacy and safety of various treatment options (both as monotherapy and in combination), strategies for managing non-response, and optimisation approaches once therapeutic goals are reached. A glossary was developed to define relevant terms, parameters, and measurement tools (panel 1). Additionally, the perspective of patients was incorporated with discussions on therapeutic goals, pharmacological management, non-pharmacological management, and follow-up care.

A strong recommendation is made for initiating treatment with conventional synthetic DMARDs, particularly methotrexate. This approach aligns with global guidelines, while emphasising cost-effectiveness and accessibility in Latin America. Methotrexate remains the cornerstone of rheumatoid arthritis treatment due to its proven efficacy, safety, and affordability.[28,65] For patients with gastrointestinal intolerance, switching to parenteral methotrexate is advised.[28–30] The high bioavailability and reduced gastrointestinal side-effects of subcutaneous methotrexate enhance adherence and therapeutic efficacy, reinforcing the importance of optimising methotrexate therapy before considering more expensive biological or targeted synthetic DMARDs.

In resource-limited settings, triple therapy with conventional synthetic DMARDs (methotrexate plus sulfasalazine plus hydroxychloroquine) is recommended for patients who have an inadequate response to methotrexate monotherapy. This step-up approach not only improves disease control but also reduces health-care costs, a particularly practical strategy in the region.[66,67] Notably, the broad availability of biosimilars and generic versions of targeted synthetic DMARDs, such as tofacitinib, has led to a significant reduction in treatment costs in the region. This increased availability has improved access to advanced therapies for many patients who previously could not afford or obtain originator biologics. In Latin America, biosimilars have played a crucial role in expanding treatment options within constrained health-care budgets. However, differences in regulatory oversight, pharmacovigilance systems, and procurement policies in different countries continue to affect their adoption. Ensuring quality, interchangeability, and clinician and patient confidence in biosimilars remains essential for maximising their benefit in clinical practice. This recommendation contrasts with the EULAR guidelines, which generally recommend methotrexate monotherapy combined with glucocorticoids.

The use of glucocorticoids in rheumatoid arthritis management remains controversial, especially in Latin America, where they are widely used. Although glucocorticoids offer rapid symptom relief, their long-term use is associated with considerable toxicity. Consequently, we recommend limiting the use of glucocorticoids to the lowest effective dose for the shortest possible duration. For localised flares, intra-articular glucocorticoids are strongly advised, providing targeted relief that minimises systemic exposure.[26,27] Although these guidelines align with those of EULAR for short-term glucocorticoid use, we recognise the challenges of rapid tapering and discontinuation in regions with little access to alternative therapies.

The early use of biological or targeted synthetic DMARDs is strongly recommended for patients with contraindications to conventional synthetic DMARDs. This strategy is supported by growing evidence that early, aggressive treatment can prevent joint damage and improve long-term outcomes.[32] However, the panel recognises the challenges associated with accessing these therapies in Latin America and stresses the need for strong justification to secure approval from payers and health-care systems.

Managing unsuccessful treatment requires an individualised approach. We recommend swapping to a different mechanism of action after the unsuccessful use of a biological or targeted synthetic DMARD, as evidence suggests improved outcomes with this strategy. Although cycling within the same mechanism of action is less supported, careful consideration of patient-specific factors, including comorbidities and potential side-effects, is essential. Both the 2022 EULAR guidelines and these Pan American recommendations support dose reduction rather than complete discontinuation in patients who reach sustained remission.[10] This strategy is particularly relevant in Latin America, where the economic burden of biological therapies is substantial. We emphasise that tapering strategies should be customised based on individual patient factors, such as poor prognostic features or a history of unsuccessful treatment.

Regarding JAK inhibitors, these guidelines align with those of EULAR in recognising their efficacy in rheumatoid arthritis management, while emphasising the importance of careful risk stratification, particularly in light of safety concerns highlighted by the ORAL Surveillance trial. While EULAR adopts a more restrictive approach, favouring biological DMARDs over JAK inhibitors in high-risk populations, these recommendations offer a pragmatic perspective, recognising that access to biological DMARDs might be hindered in some regions. In such cases, JAK inhibitors, particularly the more affordable generic versions of tofacitinib, might serve as viable alternatives.

Search strategy and selection criteria

References for the present guidelines were identified with searches of MEDLINE, PubMed, Latin American and Caribbean Health Sciences Literature, and Cochrane Library databases from database inception to Feb 29, 2024. Grey literature was also included. The following terms were searched: "Arthritis, Rheumatoid", "Rheumatoid Arthritis", and different pharmacological agents as other relevant key words, according to the PICO questions (appendix pp 17–42). Only published randomised controlled trials, non-randomised trials, cohort studies, post-hoc analyses, and pooled analyses in English, Portuguese, or Spanish were selected (appendix pp 43–57). Case reports, reviews, letters to editors, animal studies, editorials, commentaries, duplicates, studies re-analysing identical data previously published, and studies in languages other than English, Portuguese, or Spanish were excluded. The strength of recommendations and the quality of evidence of each statement were evaluated based on the Grading of Recommendations Assessment, Development, and Evaluation method (appendix pp 73–430).

The conditional recommendations for managing rheumatoid arthritis-associated interstitial lung disease and rheumatoid vasculitis reflect the paucity of evidence available for these complex conditions. EULAR and the European Respiratory Society have published recommendations[68] on the management of interstitial lung disease in rheumatic diseases, suggesting the use of immunosuppressive treatments in patients with rheumatoid arhritis-associated interstitial lung disease, which aligns with our recommendations. Rituximab remains the preferred treatment option for rheumatoid vasculitis. The panel underscores the need for further research to clarify the efficacy and safety of these treatments in such patient populations, while offering a pragmatic, cost-effective approach based on current evidence.

Cost considerations remain a crucial factor in treatment decision making in Latin America, where health-care budgets are low and drug pricing varies substantially. Although oral agents such as JAK inhibitors might reduce administration-related costs compared with infused or injectable therapies, a comprehensive cost-effectiveness assessment should also account for factors such as monitoring requirements, risk of complications, and long-term outcomes. These types of analyses are still scarce in the region. Additionally, the increasing availability of biosimilars and generic versions of targeted synthetic DMARDs is contributing to a progressive reduction in treatment costs in many Latin American countries.

Rheumatoid arthritis not only affects physical health but also the psychosocial and economic wellbeing of patients. Therefore, multidisciplinary comprehensive care models and educational interventions for patients, based on shared decisions and integrative approaches, can improve not only clinical outcomes but also the quality of life of patients, especially when considering sociodemographic and cultural particularities and resource limitations. PANLAR has developed the Centres of Excellence programme in rheumatoid arthritis in the past 8 years, creating a regulatory framework for implementation and accreditation, and being a global rheumatology association pioneer in this field.[12,13] Patients played an active role in the development of these guidelines by contributing real-world perspectives on treatment priorities, expectations, and barriers to care. Their input was integrated into the decision-making process and helped shape the recommendations to better support patient-centred care and shared decision making.

We should acknowledge some limitations of these guidelines. Although a panel of rheumatologists developed this consensus, we acknowledge the key role of other health-care professionals—nurses, pharmacists, and physical and occupational therapists—in the multidisciplinary management of rheumatoid arthritis. These guidelines are intended to support all professionals involved in rheumatoid arthritis care, and future updates

should strive to incorporate their perspectives further to enhance the relevance and implementation of the recommendations.

Non-pharmacological management was raised by patients during this process but was not included in the PICO questions or recommendations. This exclusion represents a limitation and highlights the need for future guidelines to address this important aspect of rheumatoid arthritis care. Another important limitation of these guidelines is the absence of specific recommendations for the management of rheumatoid arthritis in patients with active or previous malignancy, a topic that requires dedicated a systematic review and that will be addressed in a future update.

In summary, these recommendations represent a substantial step forward in addressing the unique challenges in rheumatoid arthritis management in Latin America. By integrating evidence-based strategies with a focus on accessibility and cost-effectiveness, we aimed to improve patient outcomes and reduce the overall burden of rheumatoid arthritis in the region. While these recommendations share many similarities with the EULAR guidelines, such as the early use of conventional synthetic DMARDs, cautious glucocorticoid use, and strategic deployment of biological and targeted synthetic DMARDs, they also address the distinct challenges faced in Latin America, including little access to biologics, economic constraints, and a high prevalence of comorbidities. Successful implementation will require sustained efforts to overcome systemic barriers, including health-care disparities, medication shortages, and the need for enhanced rheumatology expertise with the enhancement of the rheumatoid arthritis Centres of Excellence programme. Future research should prioritise the generation of region-specific data to further refine these recommendations and ensure that they remain relevant in the evolving landscape of rheumatoid arthritis management in Latin America.

Contributors

PSM, RGS, CVCU, MLB, and ERS conceptualised this Review. All the authors defined the scope of the guidelines, generated the PICO questions, and voted on and elaborated recommendations. The methodology, including the systematic literature search, formal analysis of the literature, and grading of the evidence quality, was done by MLB, NMMZ, LRB, and NZ. The initial draft of the manuscript was written by PSM, RGS, CVCU, MLB, and ERS. Internal review and editing of the manuscript were done by CETG, MHCR, GC, EM, and RX. PSM, RGS, CVCU, MLB, NMMZ, and ERS were involved in the critical review and editing of the manuscript. No other PANLAR committee member was involved in the writing of the manuscript. All authors approved the final manuscript.

Declaration of interests

Several authors of these guidelines, including voting members, have interacted with the pharmaceutical industry, including the manufacturers of some of the drugs mentioned in these recommendations. However, none of the authors received any support or fees directly or indirectly related to, or influencing, the development of these guidelines. DGFA, MLB, NMMZ, GF, and LRB are part of PANLAR Research Unit. NZ is one of the methodologists. Methodologists received support from PANLAR. The rheumatoid arthritis experts did not receive support from PANLAR or any other funding source, including pharmaceutical companies or other agencies, to participate in this work. DGFA, MLB, GF, and NMMZ are part of PANLAR committees. None of the authors received financial support for this project from any entity. CVCU reports research support from Pfizer; speaker fees from Pfizer, Lilly, Jansen, AbbVie, and Amgen; support from Amgen to attend EULAR; and is editor in chief of the *Global Rheumatology* journal from PANLAR. SC reports speaker fees from Boehringer Ingelheim; and grants for attending meetings from Pfizer, AbbVie, Adium, Boehringer Ingelheim, and FAPASA. MHCR reports speaker fees from AbbVie. GC reports consulting fees from AbbVie, Bago, Biosidus, Bristol Myers Squibb, GSK, Johnson & Johnson, Pfizer, Raffo, and Sandoz; and research support from Pfizer and Johnson & Johnson. DGFA reports speaker fees from AbbVie, Pfizer, Janssen, Boehringer Ingelheim, Lilly, Geoden Richter, and Pharmalab; grants for attending meetings from Pfizer, Boehringer Ingelheim, and Janssen; and sits on advisory boards for GSK, Janssen, Lilly, and AbbVie. RGS reports speaker fees from AbbVie, Novartis, Janssen, Pfizer, Lilly, and Sandoz; and consulting fees from AbbVie and Janssen. AMK reports speaker fees from Organon, AbbVie, Janssen, Lilly, Sandoz, Pfizer, and UCB; and support for attending meetings from Organon, AbbVie, and UCB. YFM reports speaker fees from Janssen. EM reports consulting fees from GSK, Hi Bio, AnaptysBio, Alpine Immunology, AbbVie, Pfizer, Bristol Myers Squibb, Johnson & Johnson, Biogen, and AstraZeneca; speaker fees from AbbVie, MRK Serono, Sanofi, Novartis, Pfizer, GSK, and AstraZeneca; and research support from Roche, AbbVie, Pfizer, GSK, and Lilly. AR reports speaker fees and support for attending meetings from AbbVie. PSM reports research support from Pfizer, Novartis, and Bristol Myers Squibb; speaker fees from Novartis, Amgen, and Janssen; support for attending meetings from Steincare Pharmalab, AbbVie, and Janssen; and sits on advisory boards for Bristol Myers Squibb, Amgen, Biopas, and UCB. ERS reports consulting fees from AbbVie, Amgen, Bristol Myers Squibb, Janssen, Lilly, Novartis, Pfizer, Roche, Sandoz, and UCB; speaker fees from AbbVie, Amgen, Janssen, Lilly, Novartis, Pfizer, Sandoz, and UCB; and support for attending meetings from AbbVie, Amgen, and Pfizer. LS reports speaker fees from Pfizer, AbbVie, Novartis, and Roche. CETG reports consulting fees from AstraZeneca and Janssen; and speaker fees from AbbVie, AstraZeneca, Biopas, Janssen, Pharmalab, and UCB. SV reports speaker fees from Boehringer Ingelheim. RX reports consulting fees from AbbVie, Fresenius Kabi, Hypera, and Janssen; and speaker fees from AbbVie, Janssen, UCB, GSK, AstraZeneca, Lilly, and Pfizer. All other authors declare no competing interests.

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