Best Practice & Research Clinical Rheumatology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

Global RA treatment recommendations: An update from the various international societies

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ARTICLE INFO

Keywords:
Rheumatoid arthritis
Treatment
Recommendations
Guidelines
Healthcare disparities
Early recognition
Global health
Shared decision-making

ABSTRACT

Rheumatoid arthritis is a chronic inflammatory arthritis with many extra-articular manifestations and is associated with an increased risk of morbidity and mortality. This review attempts to provide an update on the treatment recommendations from various global societies and discuss some of the challenges and solutions to caring for people with rheumatoid arthritis across the world.

A search was conducted on PubMed, Google Scholar, and EMBASE from 2000 to 2024 using rheumatoid arthritis, treatment, recommendations, guidelines, management, disparities, and access as the search terms. Emphasis was placed on pertinent recommendations published in the last five years. Recent available recommendations of the American College of Rheumatology (ACR), European Alliance of Associations for Rheumatology (EULAR), Asia-Pacific League of Associations for Rheumatology (APLAR), Pan-American League of Rheumatology (PANLAR) and African League of Associations for Rheumatology (AFLAR) were concentrated on. The latest recommendations from various societies are discussed.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that affects the joints with a variety of extra-articular manifestations and is associated with multiple comorbidities. Joint involvement is usually progressive, peripheral, and symmetrical, and if left untreated, results in irreversible damage and disability [1–4]. In poorly treated RA patients, there is a risk of increased morbidity and mortality [3,4]. Early diagnosis and immediate institution of appropriate therapy are key to better outcomes with a greater chance of attaining remission or low disease activity [5] (see Tables 3–5).

The published prevalence of RA varies greatly in different regions of the world, ranging from as low as 0.24% to as high as 2% [3,6–8]. The variability in reported prevalence is multifactorial, including different data collection methods, various diagnostic and classification criteria, selection bias, and socio-economic differences worldwide [2,4]. There appears to be a higher prevalence of RA in urban areas and resource-replete countries than in rural and resource-poor countries, which is suspected to be related in part to environmental exposures, as well as improved detection rates [4,9]. According to the Global Burden of Disease study in 2019, the global incidence and prevalence of RA is rising, with some regional variation in trends [8–10]. Importantly, although the rates of RA appear to be increasing from 1990 to 2019, the age-standardized disability-adjusted life years (DALY) in higher-income countries have decreased, which may indicate an improvement in early detection and effective treatment [6]. Our understanding of the actual global

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https://doi.org/10.1016/j.berh.2024.102019
Received 1 October 2024; Received in revised form 27 October 2024; Accepted 28 October 2024

Please cite this article as: Charles Cubberley, Ajesh Maharaj, *Best Practice & Research Clinical Rheumatology*, https://doi.org/10.1016/j.berh.2024.102019

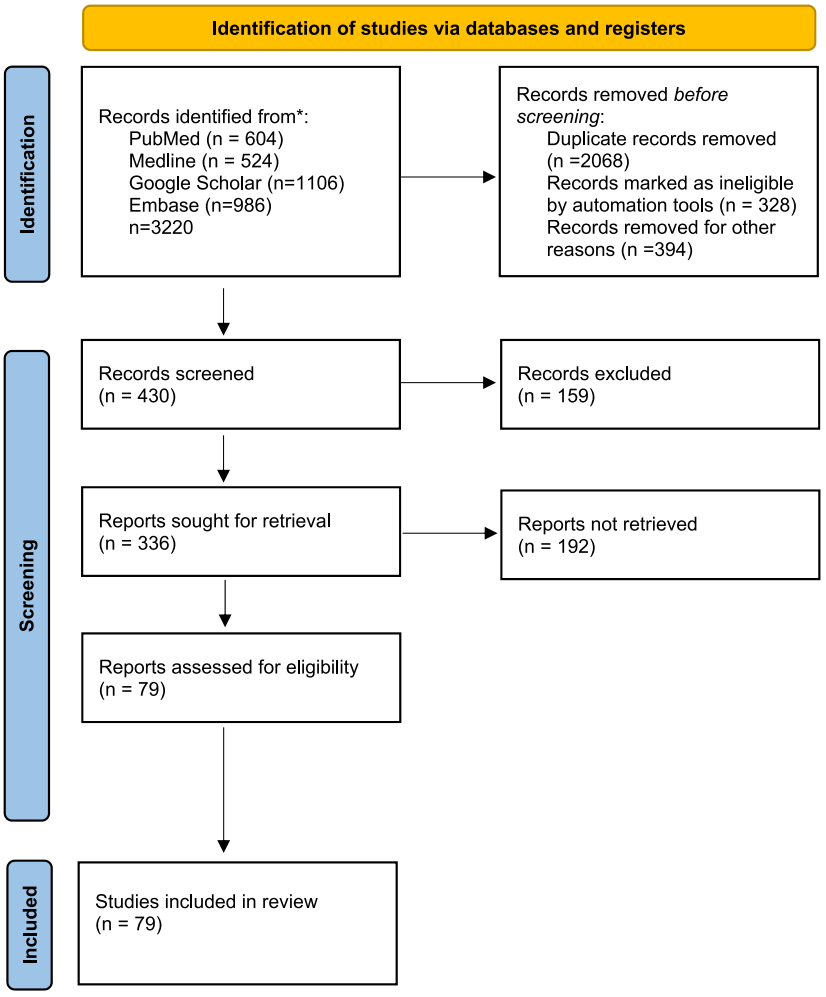
disease burden of rheumatoid arthritis remains imperfect due to a multitude of factors, including variance in disease phenotype, genetic predisposition to develop RA, environmental risk factors (such as tobacco smoking), provider familiarity with RA and detection rates, delays in presentation, the prevalence of mimicking infectious diseases (such as viral hepatitis or HIV), amongst others [4,7–10]. In resource-poor regions, the misperception of low disease prevalence due to poor detection, under-recognition of the socioeconomic impact of untreated disease, and patient and provider knowledge of the disease all contribute to the treatment of rheumatoid arthritis oftentimes not being prioritised over other illnesses [11].

The treatment of RA has evolved dramatically in the last two decades with the advent of advanced therapies, including biological disease-modifying agents (bDMARDs) and targeted synthetic disease-modifying agents (tsDMARDs) [12]. The addition of tumour necrosis factor inhibitors (TNFi) to our armamentarium at the turn of the century has revolutionised the treatment of RA [13]. After the discovery of TNFi, various other biological therapies with different modes of action, including tocilizumab (TCZ), an interleukin-6 (IL-6) inhibitor, rituximab (RTX), a CD-20 monoclonal antibody, and abatacept (ABT), a co-stimulatory molecule inhibitor were introduced in the treatment landscape [14]. More recently, the tsDMARDs, including the Janus kinase inhibitors (JAKi), have given us more firepower to manage this aggressive disease [15]. The recent introduction of biosimilars has made these drugs more available and affordable in resource-poor countries [16–18]. Given the advancements in treatment, management recommendations needed to be updated urgently to include early diagnosis and treatment of RA to improve outcomes. Various published studies show that the earlier the disease is treated, the greater the chances of remission or low disease activity and the retardation of damage [19]. The change from the 1987 ACR classification criteria to the 2010 classification criteria, making it easier to diagnose patients early in the disease course and inclusion in clinical studies, as well as updated EULAR recommendations, are steps in the right direction [20–22].

2. Methods

PubMed, Google Scholar, and EMBASE searches using “rheumatoid arthritis treatment recommendations” as the keyword was carried out. Other keywords, including early diagnosis, early institution therapy, classification criteria, management, comorbidities, and clinical practice guidelines, were included in the advanced tool PubMed. A more focused literature review was then conducted on key topics identified. Language restriction was limited to research articles published in English. The search was for the period from 2000 to 2024. Emphasis was placed on recent recommendations of ACR, EULAR, PANLAR, APLAR and AFLAR, where available, using 2015 as a cut-off for guideline publication. 3220 articles were identified, of which 2790 were excluded due to duplication, ineligibility, and non-English articles. Of the remaining 430, 159 articles were excluded as they did not fulfil the inclusion criteria. 192 articles were excluded as full texts were not retrieved electronically. 79 articles were assessed for eligibility and included in the study. Articles were cross-referenced and included wherever applicable. Medline, Google Scholar, and Embase databases were searched separately.

3. Results



4. International clinical practice guideline recommendations on the treatment of RA

4.1. General considerations and approach to management

This review focuses on the pharmacologic treatment recommendations for RA. However, it is important to acknowledge that the treatment of RA is a multimodal one, where the patient also benefits greatly from non-pharmacologic means to slow the development of disability and maintain quality of life.

Although this review does not focus on the diagnosis of RA, there is widespread consensus regarding the importance of early recognition and intervention in this disease [23]. Early diagnosis, referral to a rheumatologist, and initiating treatment within the first months of disease can significantly improve outcomes and limit long-term disability, though it follows that the exact timeframe is not uniformly defined and may include a "pre-RA" or prevention window [24,25]. There is consensus among international societies that treating RA early with disease-modifying anti-rheumatic drugs (DMARDs) is essential to effective care.

There also exists an emphasis on a joint patient-physician shared decision-making (SDM) approach in selecting the appropriate treatment strategy to balance benefits and risks of this complex disease in the international clinical practice guidelines (CPGs). A study in the United States found the patient-reported rate of suboptimal SDM communication in RA care to be as high as one in three [26]. One recent review article of RA treatment in resource-poor countries enumerated the challenges in implementing SDM in these areas, including clinicians' lack of knowledge of the benefits of SDM, patients' lack of knowledge about RA and treatment, literacy or numeracy, preferences to not be involved in decision making, and a shared lack of confidence in how to engage in SDM conversations between patient and provider alike [9]. The introduction of shared decision-making "toolkits" in the care of multilingual RA patients with low formal educational achievement in the United States is an example of how decisional conflict in this complex disease is being addressed, although this topic remains an area for improvement globally, and meaningful change will take years of intentional change and education to achieve [26].

4.2. Initial treatment approach

Conventional synthetic disease-modifying agents (csDMARDS), including methotrexate, hydroxychloroquine, sulphasalazine and leflunomide, are generally recommended as first-line therapy upon the diagnosis of rheumatoid arthritis as part of the ACR, EULAR, and APLAR recommendations (see Fig. 1).

The 2021 ACR RA CPG's initial treatment approach takes the step of stratifying patients into "high" or "low" disease activity, whereafter recommendations for medication (e.g. methotrexate (MTX) vs. hydroxychloroquine (HCQ) monotherapy) diverge respectively (Fig. 2) [27]. This change from the ACR's previous treatment guidelines was influenced in part by the inclusion of a patient panel in guideline development, who expressed interest in medication options with fewer potential side effects in low disease activity

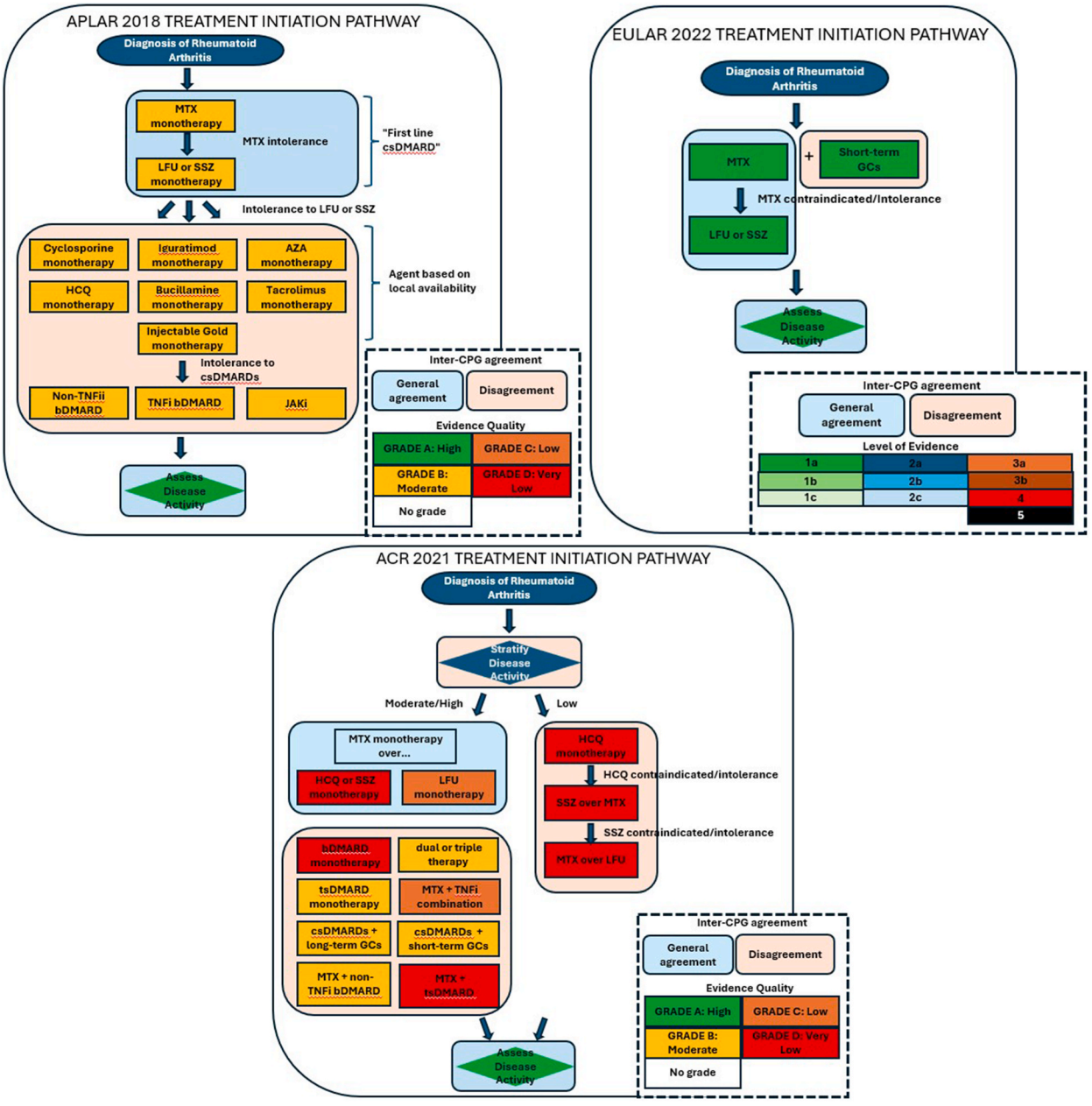


Fig. 1. APLAR, EULAR and ACR treatment pathways with levels of evidence and inter-guideline agreement of recommendations. APLAR: Asia Pacific League of Rheumatology; EULAR; European League of Associations of Rheumatology; ACR: American College of Rheumatology; MTX: methotrexate; LFU: leflunomide; HCQ: hydroxychloroquine; SSZ: sulfasalazine; GC: glucocorticoids; TNFi: tumour necrosis factor inhibitors; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; tsDMARDs: target synthetic disease-modifying anti-rheumatic drugs [22,27,28].

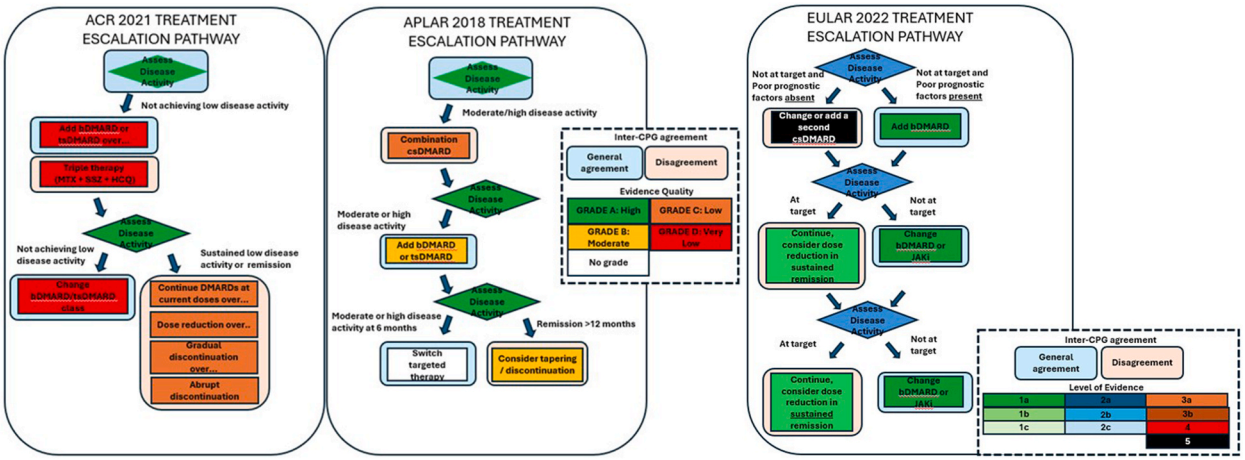


Fig. 2. Pathways for escalation and de-escalation of therapies of EULAR, ACR, and PANLAR CPGs with level of evidence and inter-guideline agreement [22,27,28].

states. In contrast, the EULAR 2022 and APLAR 2018 CPGs do not make this distinction but rather recommend treatment initiation with MTX if tolerated [22,28]. This divergence likely reflects an effort to streamline or simplify early treatment choices into a single, highly effective monotherapy to avoid undertreating early disease and risking progression should HCQ be construed as a "replacement" for MTX in early RA. MTX is regarded across CPGs as a highly effective csDMARD that should be considered a cornerstone of treatment [20–22,27,28]. The ACR mentions the lower cost of MTX over leflunomide (LFU), as well as its value as an "anchor" DMARD in a combination regimen should treatment escalation be required [27]. The efficacy of MTX, its lower cost, and its safety profile were cited as the reasons for MTX monotherapy over tsDMARD or bDMARD monotherapy at the outset of the disease. The familiarity of rheumatologists with this medication and ease of dose adjustment also make this an attractive option to many practitioners.

The ACR recommends monotherapy over combination therapy due to the burdens of higher cost, polypharmacy, and potential toxicities. This set of recommendations, however, was conditional on the basis that some patients and providers may prefer more aggressive initial treatment to achieve earlier disease remission. EULAR's recommendation of MTX being "part of" the initial treatment strategy recognises that some practitioners still use triple therapy (MTX + HCQ + sulfasalazine (SSZ)) in their initial approach, though the MTX monotherapy in combination with short-term glucocorticoids (GCs) is the primary recommendation [22]. APLAR's guidelines caution against combination therapy at disease outset due to increased toxicity and a lack of data demonstrating clear benefits over MTX monotherapy but acknowledge that active and progressive disease may require the use of combination therapy, especially in Asian-Pacific countries where the use of bDMARD or tsDMARD therapies may be prohibitively expensive [28].

In the arena of DMARD intolerance or contraindication for patients recently diagnosed with RA, there is relative agreement amongst international societies for the use of other effective csDMARDs, such as LFU or SSZ, given their high level of efficacy.

4.3. Treatment escalation in rheumatoid arthritis

Once the diagnosis of RA is established, the patient is usually commenced on therapy, initiating with a conventional synthetic disease-modifying (csDMARD) agent as monotherapy. At the initiation of therapy, a treatment approach is established with defined targets at the end of three to six months. Frequent monitoring and re-assessment of disease activity is uniformly recommended, with consensus around re-assessment at the three-month mark [22,27,28]. At three months, improvement should be noted, and the target should be reached within six months. Treatment is usually escalated if the target is not reached at the end of six months. Treatment escalation should be done through SDM to empower the patient in making decisions and improve adherence while accounting for comorbidities and poor prognostic features.

Poor prognostic features are generally agreed upon, including.

- Persistently moderate or high disease activity (after csDMARD therapy) according to composite measures, despite csDMARD therapy
- High acute phase reactant levels (ESR and CRP)
- High swollen joint count
- Presence of rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA), especially at high levels
- Presence of early erosions
- Failure of 2 or more csDMARDs

Most recommendations dictate that if there are no poor prognostic features, a second conventional synthetic disease-modifying agent should be added to the therapy or replaced by the initial csDMARDs.

If poor prognostic features are present and the initial csDMARDs response is inadequate, a biologic DMARD should be added to the treatment regimen. The patient should be reassessed after three months to note if there is an improvement, and if the target is met at six months, treatment should be continued. If the target is not met at six months, the bDMARD should be changed, the bDMARD should be changed, or a targeted synthetic disease-modifying agent (tsDMARD) should be added. When adding a JAK inhibitor, comorbidities and risk factor assessment should be done prior to the addition of this class of drugs.

4.4. Glucocorticoid use

As the body of literature about the side effects and dangers of glucocorticoids continues to grow, international societies' guidelines have primarily aligned with minimising their use to the lowest possible dose for the shortest period [22,27–29]. As a note, the 2015 APLAR guidelines address glucocorticoid use, whereas the 2018 guidelines did not provide an update to these recommendations and will thus be discussed in this section.

4.5. At initiation of RA treatment

Wherein the ACR recommends against the use of short-term GCs in the initiation of treatment in their most current guidelines [27], EULAR has updated the language in their guidelines to specify tapering short-term GCs (less than 3 months duration) should be done to drug discontinuation [22]. The discussion of this point in the EULAR guidelines additionally suggests that the efficacy of using GCs in combination therapy in achieving low disease activity has been demonstrated in clinical trials (NORD-STAR), and thus, this is maintained as part of their recommendations [30]. APLAR and EULAR guidelines agree with the use of either parenteral or oral GCs at low doses (<7.5 mg prednisolone/day) in combination with DMARD therapy at disease outset as a therapeutic bridge until steroid-sparing medications reach effect [22, 28 29,]. This was based on the consensus of low-dose GCs slowing radiographic progression in early RA at two years. Where the APLAR guidelines suggest discontinuation by six months, the more recent EULAR recommendations shorten this taper to three months.

The APLAR and EULAR CPGs recommend against using GCs when switching from csDMARD therapy to bDMARD or tsDMARD due to the higher risk of infection with bDMARD in combination with GCs [22,29]. When GCs are required to maintain remission on the current therapy, the ACR recommends switching classes of medications rather than continuing GC therapy [27].

4.6. Management of flares

The most current EULAR and APLAR CPGs agree on using short-term GCs to manage flares [22,28]. However, it is important to note that while glucocorticoids can alleviate symptoms in these scenarios, they do not obviate the need for long-term DMARD therapy. Flares, particularly polyarticular ones, are a junction where disease control with the current therapy must be addressed.

4.7. Intra-articular glucocorticoids

The utility of intra-articular GCs, particularly in the setting of monoarticular or oligoarticular disease flares, is generally accepted between guidelines. However, the ACR's recommendation does make the distinction that using intra-articular GCs to treat patients who are not at target does not replace the strategy of optimising DMARD therapy. There remains a value in intra-articular GCs, particularly where a patient may prefer to maintain his or her current DMARD regimen due to otherwise well-controlled disease. The APLAR 2015 guidelines advise caution when performing short-interval (less than three months apart) repeat injections in the same joint and more than three times in the same joint per year.

4.8. Chronic glucocorticoid use

Chronic use of GCs in RA is widely discouraged for the multitude of side effects they confer. If no alternative therapy is available, it is a viable option, however, a detailed discussion about the risks of this strategy through a SDM process is recommended by the 2015 APLAR CPGs. The toxicity of the cumulative dose of steroids and over what time they are given are areas of interest under investigation.

4.9. International practice variation

The ability to minimise GC use, unfortunately, is likely one of the more prominent ways that practice patterns diverge in resource-poor countries with more limited access to the wide variety of DMARDs. EULAR specifically acknowledges this care gap in their guidelines [22], and APLAR cautions against the widespread over-the-counter availability of GCs in many Asian-Pacific countries, as well as against monotherapy for treating RA [28]. A cross-sectional study of treatment patterns in the Middle East and North African reported ever use of glucocorticoids in about 80% of patients. This number was enriched particularly in patients with low educational attainment, which was used as a proxy for socioeconomic status [8].

5. Treatment escalation

5.1. Treat-to-Target in RA

The treatment of rheumatoid arthritis has undergone great changes in the last decade [31]. Recent recommendations have emphasized the need for a treat-to-target strategy in the decision-making process. The target is usually defined as low disease activity or remission, depending on the circumstances and available human and financial resources (Table 2) [22,27,28]. Although the treat-to-target strategy is ideal, this is not always attained in real-world settings due to several compounding factors [32]. The target is usually identified using one of the composite disease activity indices, and the clinician attempts to reach the target within three to six months of therapy (Table 1) [21]. If the target is not reached, therapies are escalated. Various studies have shown the benefit of a treat-to-target strategy as compared to usual therapy [32]. The treat-to-target approach generally requires more aggressive therapy with more frequent monitoring than usual care [33]. Due to improved disease control, drug survival and patient adherence are improved and the more intensive treat-to-target approach rather than usual therapy, even though the frequency of monitoring is increased [34]. Studies using the treat-to-target approach have shown better outcomes and a decrease in long-term morbidity and mortality in patients with rheumatoid arthritis [34]. The risk of usual care is patients are left in moderate disease activity with progression of disease and more erosive disease [31,34]. The treat-to-target paradigms commencing with conventional synthetic disease-modifying (csDMARDs) agents and aggressively escalating therapy whenever needed may also reduce the need for biological disease-modifying agents, especially in resource-poor countries (Fig. 3) [33].

5.2. Remission versus low disease activity as a target

Once the clinician and the patient have agreed upon the target through a SDM process, it is important to ensure that the target is reached within a specified period. The main aim should be the attainment of the lowest possible disease activity, depending on the therapies available. The various composite indices that are used between societies include the DAS, DAS28, SDAI, RAPID3, and CDAI [37,38].

To attain the target, the composite index chosen should be measured at each clinic visit. When using the DAS28, the ESR or CRP can be used; however, consensus dictates that the CRP is more predictable with less variability as compared to the ESR and is the preferred measure in patients treated with csDMARDs [39].

5.3. Frequency of monitoring

The frequency of monitoring is dictated to by the circumstances in which the patient is in as well as the stage of treatment.

(1) On initiation of therapy during active disease, as part of the treat-to-target paradigm.
(2) Once the patient has achieved the treatment target, using the composite index chosen at the initial visit.
(3) Once remission or low disease activity is achieved and maintained, and the patient is considered to be well controlled.

A consensus has been reached that during the initial stages of treatment, as part of the treat-to-target strategy, the patients should be monitored monthly until the target is reached. Once the target is attained, the frequency of visits can be quarterly. Once remission or low disease activity is maintained, the frequency of monitoring can be extended to six to twelve months [27,28].

5.4. Patients with poor prognostic features

Consensus has been reached that patients with poor prognostic features should be monitored no differently from patients without poor prognostic features as long as a treat-to-target strategy is employed and maintained [27].

Table 1
Initial therapies across the various recommendations.

Medication	ACR Recommendations	EULAR Recommendations	APLAR Recommendations
Methotrexate	First-line treatment in most, particularly for moderate to severe RA.	First-line DMARD, particularly in patients with moderate to high disease activity.	Recommended as a first-line DMARD for all RA patients.
Sulfasalazine	Considered if there are contraindications to methotrexate, or in combination therapy.	Can be considered as a second-line agent or in combination if an inadequate response to MTX.	Used as second-line therapy or in combination with methotrexate.
Hydroxychloroquine	Generally used in mild RA or with moderate to high disease activity, often considered in combination with other DMARDs.	Can be used, especially in mild disease or early RA; typically as a part of combination therapy.	Recommended for mild cases; not recommended as monotherapy in established disease.
Leflunomide	Considered in patients for whom methotrexate is contraindicated or not tolerated.	Can be used as a second-line agent especially if MTX is not effective or tolerated.	Suggested as an option for those who cannot use methotrexate; often used in combination.

Table: 2
DAS.

SCORE	DISEASE ACTIVITY SCORE MEASURE
<2.6	Remission
2.6-3.19	Low disease activity
3.2–5.1	Moderate disease activity
>5.1	High disease activity

	Category	Original definition	New proposed definition
DAS	Remission	<1.6	
	Mild activity	<2.4	
	Moderate activity	2.4-<3.7	
	High activity	>3.7	
DAS28	Remission	<2.6	<2.4
	Mild activity	<3.2	<3.6
	Moderate activity	3.2-<5.1	3.6-<5.5
	High activity	>5.1	>5.5

Cut-offs for the activity categories according to DAS & DAS 28.
Abbreviations: DAS, disease activity score, DAS28 disease activity score using the twenty-eight joint count.
Source: Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995 Jan; 38(1):44-8. https://doi.org/10.1002/art.1780380107. PMID: 7818570.

Table: 3
EULAR Response criteria using DAS & DAS28.

Disease activity level	DAS @ end point	DAS28 @ end point	Improvement; >1.2	>0.5-≤1.2	≤0.6
Low	≤2.4	≤3.2	Good		
Moderate	>2.4 ≤ 3.7	>3.2 & ≤ 5.1		Moderate	
High	>3.7	>5.1			None

SDAI/CDAI Remission.
- SDAI = 28 TJC +28 SJC + MDGA + PtGA + CRP.
- CDAI = 28TJC +28 SJC + MDGA + PtGA.
- SDAI remission: ≤3.3.
- CDAI remission: ≤2.8.

developing patient profile exercises and validated an observational datasets.
abbreviations: EULAR; European Alliance of Associations of Rheumatology; DAS; Disease Activity Score; DAS28: DAS 28 joint count; SDAI: Simplified Disease Activity Score; CDAI: Clinical Disease Activity Index; TJC: tender joint count; SJC: swollen joint count; MDGA: Physician Global Assessment; PtGA: patient global assessment; CRP; c-reactive protein [35,36].

Table 4
ACR/EULAR composite disease activity indices.

Index	Disease activity State	Original Definition	Newly proposed definition
SDAI	Remission	<5	≤3.3
	Low disease activity	≤20	≤11
	Moderate disease activity	≤40	≤26
	High disease activity	>40	>26
CDAI	Remission	–	≤2.8
	Low disease activity	–	≤10
	Moderate disease activity	–	≤22
	High disease activity	–	>22
DAS28	Remission	≤2.6	≤2.4
	Low disease activity	≤3.2	≤3.6
	Moderate disease activity	≤5.1	≤5.5
	High disease activity	>5.1	>5.5

Table 5
Comparison of the various global recommendations.

Intervention	EULAR Recommendations	ACR Guidelines	APLAR Recommendations
Initial treatment	DMARDs (disease-modifying anti-rheumatic drugs) are encouraged.	Early DMARD treatment, especially methotrexate, is prioritised.	Methotrexate is the first-line csDMARD.
Biologics	Consider biotherapies when csDMARDs fail or in cases of severe RA.	Biologics are recommended for moderate to severe RA if csDMARDs are inadequate.	Biologics may be used when csDMARDs are inadequate.
Targeted synthetic DMARDs	Tofacitinib and other JAK inhibitors can be considered.	Targeted synthetic agents (like JAK inhibitors) are recommended in specific circumstances.	Tofacitinib and similar agents may be used in certain cases.
Monitoring	Regular monitoring of disease activity and treatment responses.	Continuous assessment of disease activity and potential side effects of medications.	Regular monitoring for disease activity and medication responses.
Patient involvement	Shared decision-making with patients is emphasized.	Patient preferences should be considered in treatment decisions.	Patient involvement and education are encouraged in treatment plans.
Non-pharmacological measures	Rehabilitation and lifestyle modifications are important.	Incorporation of physical therapy and lifestyle interventions.	Emphasis on non-drug interventions along with pharmacotherapy.
Surgery	Consider surgical options if appropriate.	Surgical intervention may be warranted in certain cases of joint damage.	Surgical options should be considered in advanced cases.

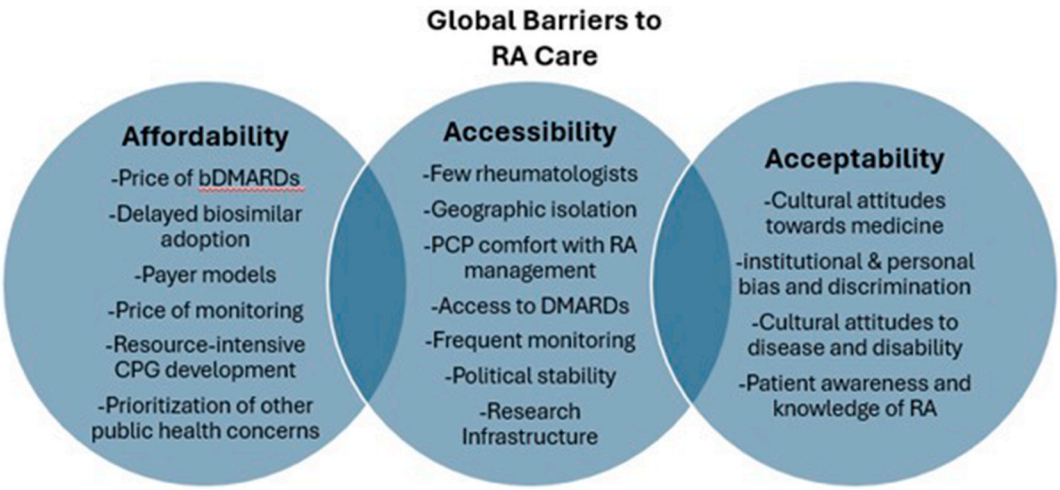


Fig. 3. Global barriers to RA care.

5.5. *Cost-effectiveness of treat-to-target*

Data from the CAMERA trial with a subgroup analysis of cost-effectiveness showed that the treat-to-target strategy was cost-effective, with less utilisation of medical resources, compared to usual care. The TICORA RCT trial found similar findings [40,41]. It is generally accepted that the treat-to-target approach is more beneficial in terms of cost-effectiveness compared to usual care [41].

5.6. *Challenges in adopting the treat-to-target strategy in resource-poor countries*

Late presentation of patients with rheumatoid arthritis in resource-poor countries is well documented [9]. This results in patients presenting with a high disease burden that may be less responsive to csDMARDS that many of these countries are limited to. Also, the lack of both financial and human resources is a limiting factor for regular follow-ups during the intensive phase of therapy, as many patients must travel long distances to see a rheumatologist [9]. The frequency of visits is often delayed, resulting in poor outcomes and greater chances of failure of the treat-to-target strategy. The availability of bDMARDs or tsDMARDs is generally limited in resource-poor countries, and therefore, escalation of therapy in patients who have failed csDMARDs is often difficult. Oftentimes, these patients have to be maintained on dual or triple therapy with csDMARDs and a combination of glucocorticoids for prolonged periods, which is not ideal. Apart from the high cost of bDMARDs, the high prevalence of infections, especially tuberculosis, hepatitis B infections, and HIV, is another limiting factor.

5.7. *De-escalation of therapy in rheumatoid arthritis*

The treatment of rheumatoid arthritis has evolved greatly in the last two decades [42]. The addition of newer advanced therapies to our armamentarium has increased the chances of patients reaching remission or low disease activity. Another factor that has contributed to this is early diagnosis, early institution of treatment and the treat-to-target strategy. The often-asked and

difficult-to-answer question in patients who have been doing well in the treatment of rheumatoid arthritis is when de-escalating therapy or tapering DMARDs is a possibility. There are many benefits of tapering therapy, including fewer adverse events and drug toxicity, financial benefits, and greater adherence to therapy. Whenever one considers de-escalation or tapering of therapy, one has to balance the risk of flares, risk of radiographic progression, maintenance of remission or low disease activity and whether the attainment of the pre-de-escalation phase can easily be attained if a flare does occur.

When discussing the reduction or tapering of therapy, one has to consider the reduction/tapering along the following lines.

- Tapering/stopping csDMARDS
- Tapering/stopping bDMARDS.
- Tapering/stopping t/sDMARDS

Various studies have looked at tapering of cs DMARDs in patients in remission or with low disease activity. In a study by Luis et al. which evaluated the tapering of methotrexate and compared to dosing regimens, the methotrexate every other week versus weekly, flare rates of taking methotrexate was noted to be 8% at twenty-four weeks and 42% and thirty-two weeks [43]. In another study, ten Wolde et al. documented a flare rate of 38% in one year [44].

5.8. Risk of flare with TNF inhibitors tapering

Various studies have looked at the tapering of stopping biological DMARDs in patients in remission of low disease activity in rheumatoid arthritis. In the PRESERVE study, evaluating patients on etanercept 50 mg weekly, 25 mg weekly, and placebo with methotrexate and looking at radiographic progression, less radiographic progression was seen in the full-dose etanercept as compared to the half-dose or placebo groups [45]. The change in the modified total SHARP score was significantly higher in the lower doses of those patients who stopped etanercept.

5.9. Tocilizumab

In the DREAM study, patients who were in remission/LDA stopped TCZ, and were monitored 4 weekly for 52 weeks, the study reported an 87% flare at one year for patients with low disease activity stopping tocilizumab [46]. In the RESTORE study, 88% of patients achieved DAS28 remission within twelve weeks after restarting tocilizumab [47].

5.10. Abatacept

In the AVERT study, patients with early active rheumatoid arthritis with low disease activity at one-year patients (Disease Activity Score (DAS)28 (C reactive protein (CRP)) <3.2) at month 12 entered a 12-month period of withdrawal of all RA therapy [47]. At six months, flare rates were 75% and 72% off all treatments for patients on abatacept + methotrexate and abatacept monotherapy, respectively [48].

Despite the heterogeneity of various studies, overall results suggest that approximately 33% of patients with low disease activity on csDMARDs do not experience a flare within the first year. Limited data on radiographic progression is available.

5.11. Special populations

Increasing emphasis has been placed on treatment strategies for commonly encountered patient populations with rheumatoid arthritis. The 2021 ACR clinical practice guidelines provided recommendations for a number of these groups [27]. Depending on the area where a clinician is practicing special considerations for concurrent diseases need to be made. For example, awareness of tuberculosis in endemic regions, areas with higher rates of viral hepatitides, or lung disease prevalence all shape the treatment strategies of providers. We review some of these populations below, as well as some other comorbidities encountered globally.

5.11.1. Pulmonary disease

The subject of lung disease in RA includes a heterogeneous array of different pathologies that range broadly. Untreated lung disease carries the risk of serious morbidity and mortality, and the implications of inadequate management has become a topic of increasing attention. Pre-existing parenchymal pulmonary and airway disease increase the risk for methotrexate-induced pneumonitis [49]. However, the degree of risk that is associated with this disease is unknown. The ACR's recommendations point out that other DMARDs are associated with pneumonitis, and thus given the efficacy, safety, and availability of methotrexate, it remains the medication of choice in this population [27]. Resource-poor countries also contend with overall higher rates of tobacco use and respiratory pathogens from industrial and occupational exposures, which may further increase the incidence of methotrexate-induced pneumonitis [50]. Even in relatively resource-replete countries, regular monitoring for lung disease through pulmonary function testing, CT scans, or access to a pulmonologist can be limited [51]. Recently, the ACR has published screening & monitoring and treatment guidelines for ILD in several autoimmune diseases, including RA, and we are hopeful that increasing awareness of this topic globally will have a sizeable impact on outcomes in patients with RA [52].

5.11.2. Heart failure

As with pulmonary disease, resource-poor countries are disproportionately affected by an increased incidence, morbidity, and mortality of heart failure from various causes [53]. This disparity is also widened by limited access to cardiologists, advanced imaging and monitoring, and the array of medications that make up the backbone of heart failure care. TNFi are associated with worsening heart failure [54]. Unfortunately, as the first class of bDMARDs for RA, it is also one of the most widely available and *relatively* affordable options for many patients and rheumatologists globally. The ACR currently recommends that TNFi therapy should be used cautiously or avoided in patient at risk for class III or IV cardiac failure due to the increase the risk of hospitalisation and mortality especially in those patients with an ejection fraction of less than 40%. The ACR has conditionally recommended that alternative bDMARDs or tsDMARDs be sought in the case of incident or worsening heart failure [55].

5.11.3. Metabolic dysfunction-associated steatotic liver disease (MASLD)

The ACR recommends that patients with MASLD (formerly non-alcoholic fatty liver disease, NAFLD) and moderate-to-high disease activity may be treated with MTX with the caveats that they are more frequently monitored, have normal liver enzymes, do not have evidence of liver fibrosis, and a gastroenterologist or hepatologist is consulted [55,56]. As with pulmonary disease and heart failure, adding another specialist to patient care may pose a barrier in more resource-poor countries.

5.12. Infectious diseases

5.12.1. Mycobacterial lung infections

The ACR recommends that an infectious disease provider be involved in patient care with non-tuberculous mycobacterial lung infections of infection due to the heterogeneity of these infections. Glucocorticoid use should be minimized/avoided, and use of csDMARDs over tsDMARDs or bDMARDS is recommended due to the risk of worsening infection [27]. In the case of tuberculosis, preference is given to abatacept over other bDMARDs because of its lower rates of infection. There is consensus amongst the international CPGs that all patients should be screened for latent tuberculosis prior to the commencement bDMARDs or tsDMARDS. EULAR recommends the use of the interferon gamma release assay (IGRA) as it performs better than the tuberculin skin test (TST) and is less affected by glucocorticoid use, together with the chest radiograph [57]. Given the low level of agreement between the IGRA and TST, EULAR recommends that both be used for screening in cases of high suspicion/high-risk individuals for latent tuberculosis [22]. Prophylactic treatments regimens should be aligned with local/national guidelines. Close monitoring of liver function tests should be done for patients on hepatotoxic tuberculostatic therapy and methotrexate. In addition, the pharmacokinetics and pharmacodynamics of JAKi and glucocorticoids may be affected by concomitant use of rifampicin. APLAR's approach to tuberculous mycobacterial infections leaves the treatment regimen for this infection up to the guidelines of the local country, likely emphasising the importance of region-specific knowledge in available therapies, resistance rates, and infectious disease providers [28]. As an example of this region-specific variation, the recently published South African Rheumatism and Arthritis Association (SARAA) guidelines for b/tsDMARD use risk stratify most patients at intermediate to high risk of TB exposure due to the local prevalence of disease, recommend screening with a chest radiograph, tuberculin skin test or interferon-gamma release assay for all patients initiating b/tsDMARD therapy, provide treatment options for patients identified as having a latent TB infection, provide guidance regarding choice of b/tsDMARD for patients with very high risk for TB infection, and discuss next steps for a patient with active tuberculosis [58].

5.12.2. Hepatitis B and hepatitis C

In general, there is consensus amongst international CPGs regarding routine screening for hepatitis B (HBV) and hepatitis C virus (HCV) prior to initiation of DMARD therapy. Given the increased risk for reactivation, both the ACR and APLAR guidelines pay special attention to rituximab in this population [27,28]. Both societies recommend prophylactic antiviral treatment over frequent monitoring in hepatitis B (HBV) core positive patients prior to receiving RTX regardless of surface antigen status. EULAR recommends that patients should be screened for Hepatitis B surface antigen (HBsAg) and hepatitis C [22]. If patients are positive, prophylactic antiviral therapies are recommended [57]. It is also recommended that these patients be referred to a hepatologist as part of the multidisciplinary team approach.

ACR, APLAR, and EULAR also agree to treat patients with HBsAg and core antibody positivity in the setting of initiating any other DMARD, though make the distinction that core antibody positive, surface antigen negative patients should be monitored rather than initiating treatment in the case of all DMARDs except RTX [22,27,28]. The ACR recommendation also follows that a hepatologist should be involved in co-management of these patients, which may be unattainable in the setting of resource-poor countries. APLAR's recommendations concur on the use of prophylactic antiviral therapy, though specify that surface antigen positive patients who plan to initiate DMARD therapy should be treated with antiviral prophylaxis during and after treatment [28].

5.12.3. HIV

The global prevalence of HIV and implications on RA care a topic that is covered in the APLAR 2018 CPG [28]. In the 2022 EULAR recommendations for the screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases, it is advised that all patients starting on csDMARDS or bDMARDS should be screened for HIV infection and appropriate HIV care be instituted whenever necessary [22]. Though both the incidence and mortality rates of HIV are declining due to increased awareness, knowledge of prevention, and high-quality treatment options, this disease presents unique challenges in the realm of RA globally. A 2022 review paper on the topic highlighted the complexities of care for individuals with HIV, from the relatively high prevalence of MSK manifestations (5–12%, depending on the region) which may mimic RA, the variable impact of HIV

on RA disease activity (IE immune-reconstitution syndrome), confounding factors in monitoring treatment response, and the challenges of treatment from both an immunosuppression and drug interaction perspective [23].

6. E. Healthcare disparities

The topic of global rheumatoid arthritis treatment strategies cannot be addressed without acknowledging the impact of healthcare access disparities. There is an ever-growing body of literature which explores the multitude of ways that healthcare policy is shaped within a country or region based on access to care [59]. Although by no means exclusive, the diagnosis and management of autoimmune conditions, such as RA, is disproportionately impacted by the many complex and interacting factors that limit healthcare access. A three-dimensional model of care access proposed includes the availability of care (such as the presence of rheumatologists in a geographic region), the affordability of care (with particular attention to cost differences between medication classes and the emergence of biosimilars), and the acceptability of treatment in the cultural/traditional context of the community which care is offered (Fig. 3) [58,60].

6.1. Availability of care

Rheumatoid arthritis management requires regular access to a subspecialist with additional years of medical training for diagnosis, disease activity measurement, medication safety monitoring, and management strategies with attention to pertinent comorbid conditions. EULAR has recommended that a rheumatologist is the primary provider that should be responsible for the management of RA, though acknowledges that in areas with few rheumatologists, the monitoring of disease may fall to experienced non-physicians and non-rheumatologist healthcare professionals. In areas where there is not regular access to providers knowledgeable in the identification and management of RA, unabated and irreversible disease progression leading to loss of independence, disability, and economic power is a real risk. The ability to start treatment in a timely manner because of delays in referral is an acknowledged barrier to care in the APLAR 2015 guidelines [29]. A 2016 observational study in Saudi Arabia reported patients with RA symptoms saw an average of 4 physicians before diagnosis and time from symptom-onset to diagnosis was 30.2±16 months [61]. This problem is exacerbated by the clustering of specialists in urban areas, furthering the divide in care availability for rurally dwelling patients [62]. A 2013 study in the United States showed that 7% of practicing rheumatologists in the ACR database were practicing in a rural region [63]. In some regions throughout the world, this disparity is addressed through deputising local providers and nurses to carry out the duties of the rheumatologist [64]. A 2021 review article about nursing-led care (NLC) of rheumatoid arthritis in Africa and the Middle East reported the benefits of NLC include increased access, improved patient-reported self-efficacy, patient satisfaction, and comparable disease activity scores at two years to patients under the care of a rheumatologist [65]. The same review described a consistent cost saving when NLC was implemented (up to 13% less than physician-led care) [65]. Although NLC provides a tangible way to improve RA care in this area, the challenges of providing additional training, funding, and nurse scarcity in resource-poor areas still exist, though perhaps in a less pronounced way.

The knowledge of current medications, difficult-to-treat cases, ability to manage medically complex multimorbid patients, and medication safety that a rheumatologist brings may not be a realistic expectation for a busy local primary care provider. Several studies demonstrated wide variability in CPG adherence by practicing rheumatologists, and it would be unreasonable to expect that busy non-rheumatology practitioners would routinely be following treatment guidelines more closely [66,67]. Telehealth is an emerging strategy for addressing the gap in access to rheumatologists. Even within resource-rich countries, geographically remote regions, limited access to private or public transportation, physical disability, lack of social support, amongst many other factors, are barriers to regular in-person visits [68], A pilot project in the Gilgit-Baltistan region of Pakistan demonstrated an estimated average of nearly 800 km and 15hrs of travel time saved over 500 rheumatology consultations with the implementation of a “telerheumatology” program rather than traveling to a tertiary care center in Islamabad [69].

6.2. Affordability of care

The expanding arsenal of targeted biological therapies has reshaped the way that rheumatoid arthritis is treated. Where disease progression to disability was once an eventuality, this outcome in a resource-replete area is now considered a potentially avoidable tragedy. Unfortunately, with the cornucopia of new medications also comes a very real cost burden, which, without insurance or governmental support, is essentially unaffordable to all but the most affluent members of society. Several studies have suggested that RA disease activity is inversely correlated to access to bDMARDs [59,70]. The price of new medications places a strain on both individuals and the healthcare system and minimising cost while providing good healthcare outcomes is a universal goal. In the Middle East and North Africa region, fewer than 2% of RA patients are receiving treatment with TNFi vs. 40% of patients in the USA [68]. However, access to biologics in the United States is also fraught with challenges due to cost. The Centers for Medicare & Medicaid Services (CMS) recently bargained for a 67% reduction in the price of etanercept, a medication which came to market in 1998 from a 30-day supply costing $7106 USD to a new price of $2355 [71].

Although payer structures and healthcare administration policies vary widely throughout the world, the cost of new biologic medications greatly influences what treatments are feasible. A 2014 epidemiologic study of 46 European described an alarming 22% of countries did not reimburse for bDMARDs and that year of treatment with a bDMARD would exceed the GDP per capita in over half of the countries studied [72].

With the development of biosimilars, there may be new opportunities for access to treatments that previously were unobtainable

due to cost, both due to the likely decrease in originator cost after loss of market exclusivity and the oftentimes lower cost of the biosimilar. Despite these potential cost savings, barriers such as lack of guidance from governmental or professional societies, mistrust of comparative efficacy, and unknown side effects may explain the slow uptake of biosimilars [16–18]. The role of biosimilars in the treatment of RA will likely be a point of discussion in future international CPGs given the potential to transform the economic landscape globally, and both international and national professional societies have begun to publish consensus statements and regarding their use [16–18]. Instituting national registries or databases for biosimilar safety monitoring, switching or substituting bDMARDs to biosimilars, the role of intended copies, and the price of biosimilars are all important topics to be addressed while navigating this new landscape.

6.3. Acceptability of care

The profound and nuanced ways in which any group's culture impacts how healthcare is delivered and received is hard to overstate. From historical and current bias and discrimination based any perceptible difference between the institution of healthcare or healthcare provider and the patient, differences in healthcare outcomes exist. Although the prevalence of autoimmune disease based on genetic predisposition plays a role in certain groups being disproportionately affected by RA, it is also clear that marginalised groups and minorities bear a much greater burden of disease morbidity and mortality than others due to symptom minimisation from providers, increased rates of poverty, poor trust in the medical system, and loss to follow-up, amongst others. For example, Indigenous North American populations (INA) with rheumatoid arthritis had fewer rheumatologist visits than non-INA populations, were seen less frequently, were more likely to be lost to follow-up, had more interrupted treatment courses, and used more steroids [68].

7. Limitations

Global RA treatment is a large topic which spans from an individual patient to national and international healthcare policy. As such, we have focused on several key points for the practicing provider to consider regarding the consensus of international guidelines from different parts of the world.

International clinical practice guidelines (CPGs) are written intentionally for commonly encountered clinical scenarios and cannot reasonably be expected to address every possible barrier to care. A recent systematic review of thirteen international and national clinical practice guidelines (CPGs) compared management recommendations and provided a helpful "should do", "could do", or "do not do" framework for several broad aspects of RA management [73]. However, comparing each individual national or regional CPG would likely not provide a practical body of information and would rather dilute the nuances that each guideline may provide for tailored treatment strategies in their respective regions. The limitations of evaluating a broad topic such as this are similar-we rely on practitioners' knowledge of local guidelines and region-specific needs and limitations when making treatment decisions. Where large international rheumatology societies agree on general treatment strategies and there is a high likelihood these will be successful in treating RA an individual area, a local practitioner must be able to adapt these guidelines to suit the needs of their patients and the resources available to a country. On the other side of this coin, however, the development of CPGs is a laborious process that requires a great deal of resources. Country- or region-specific practice guidelines which draw on the groundwork of international CPGs have the advantage of foregoing some of the cost while adding valuable local knowledge. In 2012 a group of expert rheumatologists representing the Middle East and Northern Africa (MENA) region and South Africa convened to do just this-analyse the 2010 EULAR RA CPGs and their applicability to local practice [11]. Although newer international CPGs have been developed since the publication of this paper, common barriers to regional implementation such as access to biologic therapy, institution of early aggressive therapy, and frequent monitoring of disease activity were cited and remain critically important to delivering effective RA care [11]. As of the writing of this review, the South African Rheumatism and Arthritis Association (SARAA) has recently published CPGs for the treatment of RA, which synthesise elements of international CPGs while adding valuable local practice insight to the practicing rheumatologist [74].

Modern international guidelines are formulated based on the best available evidence for each guideline item. The ACR and APLAR follow the GRADE outline for each recommendation, whereas EULAR follows the Oxford level of evidence paradigm. An important consideration of each recommendation is the population of interest from which these recommendations are derived. Certainly, there is a large degree to which the best available evidence for each recommendation is drawn from between guidelines (for example, the comparative efficacy for MTX over other csDMARDs in early disease). In countries and regions where research infrastructure is underdeveloped or non-existent, there follows a paucity of data on populations who live there (Fig. 4). This leaves data derived from a different population to serve for best practices for a population not originally studied [8]. This is not to diminish the quality of the evidence that international guidelines use, as the process for developing these recommendations goes through a rigorous literature search and review, as well as committee review from representatives of each member country (in the case of APLAR and EULAR) but simply to show that where research has not been performed, there may be unknown differences.

All guidelines do not specifically mention the route and dose of medications, and it is important that a practicing clinician is knowledgeable about what is available and on the formulary in his or her region.

As with all medicine, rheumatology care is one which is constantly progressing and evolving to encompass the latest data and refine treatment recommendations upon this. As such, each set of clinical practice guidelines depends on a committee to constantly be appraising the available literature and deciding when there is enough meaningful new information that an updated guideline is available. This means that the burden of knowing the latest CPG updates again falls upon the individual to integrate these best practices into his or her daily work. Although our paper outlines some fundamental treatment recommendations that are not likely to rapidly or drastically change, it is important to acknowledge the importance of constantly refreshing practice.

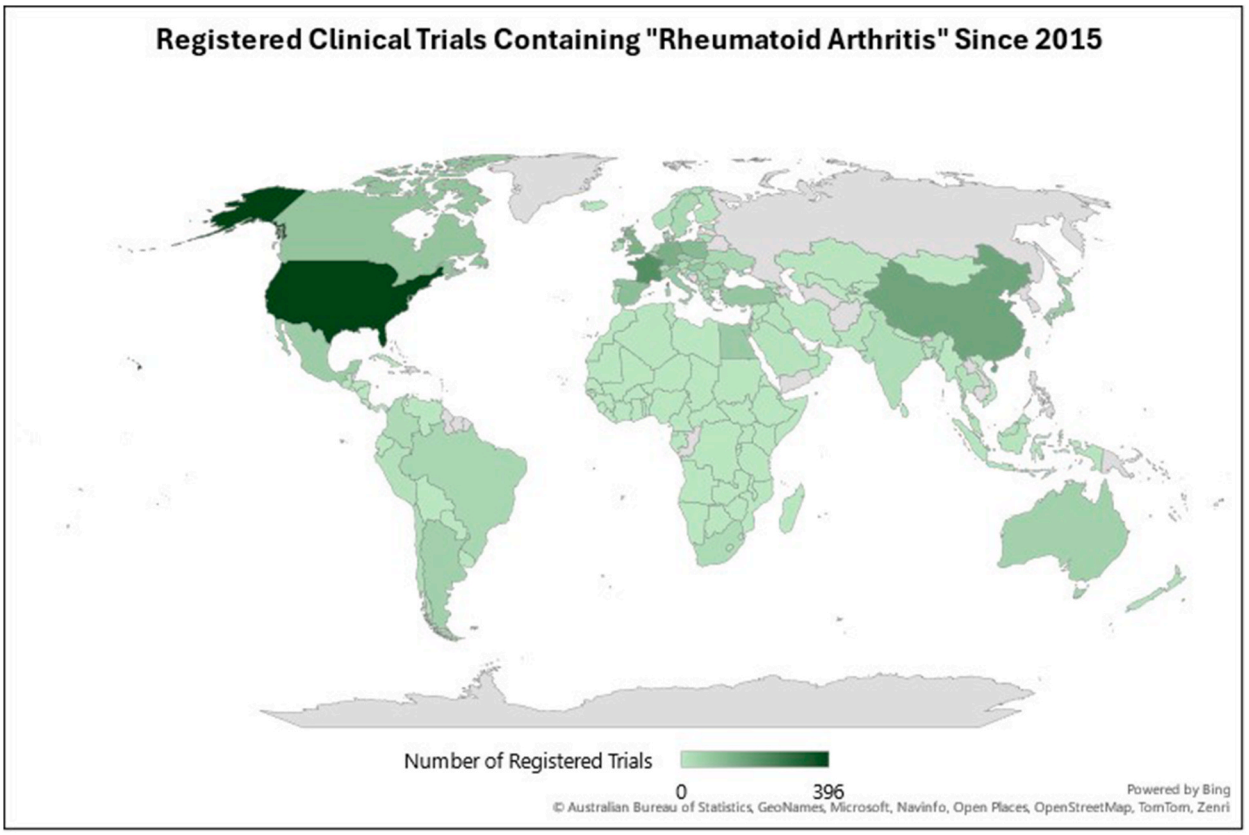


Fig. 4. Heat map of trials containing "rheumatoid arthritis" registered at clinicaltrials.gov since 2015 of member countries of ACR, EULAR, APLAR, PANLAR, or AFLAR.

We have not addressed pregnancy and perinatal recommendations in this review. This topic is very broad and the access to medical care during pregnancy globally is another focus of improving healthcare throughout the globe.

Practice points

1. Early diagnosis and institution of appropriate therapy are important for better outcomes with less disability.
2. The treat-to-target approach should be encouraged, and failure to achieve the pre-determined targets should result in therapy escalation.
3. The algorithms of professional rheumatology societies should be followed while tailoring treatment strategies to maximise patient outcomes based on available resources in various areas of the world.
4. Therapy escalation and de-escalation are important practice points in the clinical setting, and they benefit from shared decision-making.
5. Corticosteroid use varies greatly across the globe, and attention should be paid to the multitude of negative side effects from their long-term use.
6. Healthcare disparities have an undeniably large impact on the provision of guideline-directed care for people with rheumatoid arthritis. A better understanding of these compounding barriers is an area of opportunity for practicing rheumatologists, guideline writers, and policymakers alike to facilitate better outcomes for patients across the globe.

Research agenda

I. Global collaborative efforts to standardise therapy in all world regions.
II. There is a conspicuous dearth of published literature from the African continent, which needs to be addressed at the global level.
III. Impact and availability of biosimilars in changing the treatment landscape and enhancing access in resource-poor countries.
IV. Improving shared decision-making utilisation strategies worldwide to enhance RA care.
V. Implementing robust telehealth programs in rural areas to improve RA treatment.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Charles Cubberley: Writing – review & editing, Writing – original draft, Conceptualization. **Ajesh Maharaj:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Funding

No funding was received for this manuscript.

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