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Rheumatoid Arthritis (Y Yazici, Section Editor)

Treatment Guidelines in Rheumatoid Arthritis—Optimizing the Best of Both Worlds

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Abstract

Purpose of review Rheumatoid arthritis (RA) leads to significant joint damage and systemic complications. Available treatment options for RA has made it possible to achieve a good control over disease activity and improve patient outcomes. In this review, we discuss management guidelines for RA and their practical application by discussing clinical scenarios commonly encountered in rheumatology practice.
Recent findings European League Against Rheumatism recently updated treatment recommendations for management of RA. The general fundamentals of these recommendations are similar to those of the 2015 American College of Rheumatology guidelines for the treatment of RA but with some key distinctions. We discuss three RA cases to illustrate key aspects of treatment guidelines. New data show increased cardiovascular risk in patients with RA that is possibly related to associated systemic inflammation.
Summary While several questions about RA remain unanswered, the clinical outcomes have improved in recent years. A strategic approach to manage RA is recommended which involves early diagnosis and treatment and escalating treatments to achieve a therapeutic target. In addition to treating RA disease activity, management of comorbid conditions is imperative to prevent long-term systemic damage.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory condition that causes joint damage and increases morbidity and mortality via systemic complications [1]. The treatment paradigm of RA has shifted markedly over the past three decades with the development of new therapeutics enabling a tighter control of the disease activity and improvement in outcomes. This strategy, referred to as *treat to target*, aims to achieve low disease activity or remission and requires frequent measurement of disease activity at clinic visits, and treatment adjustment/titration to achieve the target. Instruments such as clinical disease activity index (CDAI), simple disease activity index (SDAI), and disease activity score (DAS) 28 which utilizes readily available clinical and/or laboratory parameters are commonly being used in clinical practice already (Table 1). These measures assess RA disease activity quantitatively as high, moderate, low, and remission, and RA therapy is then adjusted in order to target low disease activity or remission.

Table 1. Instruments to measure disease activity in rheumatoid arthritis (RA) for clinical care*

Instrument	Scale	Threshold for disease activity	Components
Patient Activity Scale (PAS) or PAS II	0–10	Remission: 0–0.25 Low activity: 0.26–3.7 Moderate activity: 3.71–7.99 High activity: 8.0–10	Health Assessment Questionnaire (HAQ) Pain VAS: 0–10 Pt Global VAS: 0–10
Clinical Disease Activity Index (CDAI)	0–76	Remission: 0.0–2.8 Low activity: 2.9–10.0 Moderate activity: 10.1–22.0 High activity: 22.1–76.0	28 tender joint count 28 swollen joint count Pt Global VAS: 0–10 Ph Global VAS: 0–10
Simplified Disease Activity Index (SDAI)	0–86	Remission: 0.0–3.3 Low activity: 3.4–11 Moderate activity: 11.1–26.0 High activity: 26.1–86	28 tender joint count 28 swollen joint count Pt Global VAS: 0–10 CRP (mg/dl) 0–10
Routine Assessment of Patient Index Data 3 (RAPID3) (range 0–10)	0–10	Remission: 0–1.0 Low activity: 1.1–2.0 Moderate activity: 2.1–4.0 High activity: 4.1–10	Multidimensional HAQ (MDHAQ) Pain VAS: 0–10 Pt Global VAS: 0–10
Disease Activity Score (DAS) 28 erythrocyte sedimentation rate (ESR)	0–9.4	Remission: < 2.6 Low activity: ≥ 2.6–< 3.2 Moderate activity: ≥ 3.2–≤ 5.1 High activity: ≥ 5.1	28 Tender joint count 28 Swollen joint count ESR: 0–100

VAS, visual analog scale; *Pt Global VAS*, patient global assessment of disease activity; *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein

*Adapted from reference [2]. These measures were recommended by American college of Rheumatology for use in clinical practice

Management of RA in clinical practice

Case 1

Sixty-year-old female with medical history of hypertension presented to her rheumatologist's office for follow-up of RA, which was diagnosed 1 year ago. She had been taking methotrexate 25 mg oral weekly with 1 mg daily of folic acid. Two months ago, she began noticing increased pain and swelling in her hands, shoulders, and feet. She ran a local baking business and had noticed reduced productivity at work. Examination at the office visit revealed moderate disease activity as measured by CDAI of 16 and Routine Assessment of Patient Index Data 3 (RAPID3) score of 3.7.

Case 2

Fifty-year-old female with history of RA presented with complaint of painful discoloration in her toes for 1 week. Patient had history of RA diagnosed 2 years ago. She had begun treatment with adalimumab 4 weeks ago after failure of methotrexate. Patient had no prior history of Raynaud's phenomenon or another autoimmune disease. Her examination revealed erythematous, violaceous macules in multiple toes bilaterally.

Currently available drugs to treat RA include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), targeted synthetic DMARDs (tsDMARDs; currently approved tsDMARDs in the USA include the Janus kinase (JAK) inhibitors), and biologic DMARDs (bDMARDs). Biosimilars, products highly similar to already approved biologic drugs, are also being used for the treatment for RA, with a potential for cost-savings. The American College of Rheumatology (ACR) and The European League Against Rheumatism (EULAR) have developed treatment algorithms to guide clinicians in management of RA with these drugs [3•, 4••]. While both generally agree on most recommendations, key distinctions are outlined in Table 2. Aletaha et al. highlighted some of the similarities and differences in a recent review [6]. The 2020 ACR RA guideline was pending publication at the time of submission of this article.

Initial therapy

The 2015 ACR treatment guideline distinguishes between early (< 6 months) and established RA (≥ 6 months) based on duration of RA symptoms and offers an algorithm for each scenario, while the EULAR RA treatment guideline does not make this distinction. Nevertheless, the initial treatment recommendations for patients who have not been treated with a DMARD are essentially the same. There is no international consensus on definition of "early RA" based on symptom duration, and is likely to evolve with the discovery of early biomarkers of RA. It is known that joint damage may begin within weeks to months of symptom onset, and radiographic progression may occur in the first 2 years of the disease [7]. Prolonged symptom duration is associated with radiographic progression and a lower chance of sustained remission [8].

Table 2. Differences between ACR and EULAR guidelines for the treatment of rheumatoid arthritis

Item	ACR	EULAR
Location of expert panel	USA	International (UK, North America, Latin America, Asia, Australia)
Methods	GRADE (strong and conditional recommendations)	EULAR standardized operating procedures for the development of recommendations Standards of the Oxford Center for Evidence Based Medicine
Panel composition	Core leadership team (4 rheumatologists; 1 methodologist) Literature review team (3 rheumatologists; 3 methodologists; 1 librarian) Voting panel (9 rheumatologists with expertise and clinical experience in treating RA and 2 patient representatives) Content panel (4 rheumatologists with expertise and clinical experience in treating RA)	Steering committee (8 rheumatologists, 1 patient representative and 2 fellows) Task force (47 individuals including steering committee); Task force included 3 patients, 2 health professionals, and 2 delegates of the EULAR young rheumatologists' network Emerging NETwork
Financial conflict	All people involved declared financial conflicts before the start of the process, and throughout the development of the guideline. Only < 50% people on all panels combined could have a financial conflict; Only < 50% on each of the 4 teams could have a financial conflict.	All task force members disclosed their potential conflicts of interest to the EULAR executive committee before the start of the process. No requirement for panel composition based on the conflicts of interest
Intellectual conflict	Intellectual conflicts, such as a prior publication or presentation on an RA therapeutic, were recognized as important and were disclosed.	No requirement for declaration of these conflicts
Review Process	Guideline authors and all 4 teams ACR guideline subcommittee ACR Quality of Care committee ACR Board of Directors Arthritis & Rheumatism journal review process	Task force members EULAR executive committee Annals of Rheumatic Diseases journal review process
Key principles		
Patient distinction based on symptoms duration	Early RA (< 6 months of symptom duration) Established RA (≥ 6 months of symptom duration)	No such distinction
Failure of initial therapy (with csDMARD)	Combination of csDMARDs or TNFi or non-TNFi (tofacitinib not included for early RA)	No prognostic factors: add or switch csDMARDs Poor prognostic factors: add bDMARDs or Jak inhibitor
Stratification of patients based on prognostic factors	Disease activity (moderate/high)	Risk factors Persistently moderate to high disease activity High acute phase reactants High swollen joint count Presence of antibodies (RF and/or ACPA) at high levels Combination of above Presence of early erosions Failure of two or more csDMARDs

Table 2. (Continued)

Item	ACR	EULAR
Topics covered		
Comorbidities	Made recommendations for congestive heart failure Hepatitis B Hepatitis C Malignancy Serious infections TB screening	None
Vaccinations	Made recommendations	None (separate guideline published) [5]

Therefore, the treatment of RA should be started as soon as the diagnosis is made with dual goals of improving clinical outcomes and long-term disease prognosis [9].

The preferred initial therapy recommended by both the ACR and the EULAR RA treatment guideline is csDMARD monotherapy. Among csDMARDs, methotrexate (MTX) is the preferred drug of choice as first-line treatment. MTX has several advantages with proven clinical efficacy, safety, and low cost. MTX has shown efficacy in both RA of long duration and early-undifferentiated inflammatory arthritis making it a reasonable initial choice [10]. Although some studies demonstrate superior clinical and radiographic efficacy of using biologic DMARD monotherapy (etanercept) [11] or combination of biologic plus methotrexate (e.g., adalimumab + MTX in PREMIER study, etanercept + MTX in COMET study) or triple therapy [12] as initial treatment for RA compared with MTX alone [13, 14], other studies such as the TEAR study show that long-term outcomes are not impacted if patients start MTX as initial therapy and escalate treatment based on disease activity [15]. Methotrexate in combination with other csDMARDs is also not superior to methotrexate alone when used as initial therapy, with concomitant glucocorticoids [16].

Methotrexate when administered orally or subcutaneously should be escalated within 4–6 weeks to an optimal dose of 20–25 mg weekly. Folic acid should be used, if needed in doses up to 5 mg/day, to reduce the risk of several MTX-associated adverse events [17]. Higher doses of methotrexate may be associated with unwanted adverse effects that may lead to drug discontinuation. In those cases, other csDMARDs, leflunomide or sulfasalazine, should be considered as part of the first-line treatment strategy. Short-term glucocorticoids (< 3 months) as a "bridge therapy" are recommended until csDMARDs has reached its efficacy and should be tapered when feasible. Consideration of intra-articular joint injections is also available as an adjunctive strategy (EULAR). Long-term use of prednisone at dose above 10 mg should be avoided due to the risk of adverse events associated with long-term use. If glucocorticoids cannot be tapered, escalation of DMARD therapy should be strongly considered.

Monitoring should be frequent in active disease, occurring every 1–3 months. If the target disease activity state is not achieved within 3–6 months despite csDMARD monotherapy, treatment should be adjusted.

The ACR and EULAR treatment recommendations differ slightly at this stage. The ACR recommends using either combination of csDMARDs or adding or switching to tumor necrosis factor inhibitor (TNFi) or non-TNFi biologic for both early and established RA. Addition of a tsDMARD (tofacitinib) to methotrexate is a recommended option for established RA (≥ 6 months duration). These options were not in an order of preference due to lack of direct comparative evidence in clinical trials. With most patients with RA present with at least 1–3 months of symptoms and the initial csDMARD monotherapy trial is needed for 2–3 months, almost every patient with early RA meets the established RA definition by the time first escalation from the csDMARD monotherapy is made or within 1–2 months of such a change. After csDMARD monotherapy failure, combinations of csDMARDs (MTX + sulfasalazine (SSZ 3–4 g/day); MTX + leflunomide (20 mg/day); MTX+(hydroxychloroquine (HCQ)400 mg/day); SSZ + HCQ; or triple therapy with MTX + SSZ + HCQ can be used. Triple therapy was non-inferior to etanercept plus methotrexate in patients with RA who had active disease despite methotrexate therapy [18]. A systematic review and network meta-analysis (NMA) of 158 trials with over 37,000 patients with RA demonstrated that triple therapy was similar to methotrexate plus biologic DMARD or tofacitinib in controlling disease activity [12]. However, the discontinuation rates of treatment are higher in triple therapy than combination therapy of MTX plus bDMARDs and there is less persistence and adherence [19, 20]. In one study of 3724 patients on etanercept and methotrexate (ETN-MTX) and 818 patients on triple therapy, compared with triple therapy, ETN-MTX was significantly associated with greater adherence (odds ratio 1.79, 95% confidence interval (CI) 1.47 to 2.17) and persistence (odds ratio 1.45, 95% CI 1.20 to 1.72) [21]. The decision to pursue a csDMARD combination therapy versus biologic therapy needs to be balanced against the risk of adverse effects, drug toxicity, access to medications, patient preference, ease of administration, cost, and adherence.

EULAR, at the stage of DMARD monotherapy failure, recommends stratifying patients into those with poor prognostic factors (positive rheumatoid factor, anti-cyclic citrullinated peptide antibody, and failure of two or more csDMARDs, high disease activity, early erosions). In the presence of poor prognostic factors, addition of bDMARDs or a tsDMARDs is recommended rather than another csDMARDs. In the absence of poor prognostic factors, either combination of csDMARDs or switching to another csDMARDs (leflunomide, *sulfasalazine* alone) can be considered. All prognostic markers are not further specified with regard to their measurement thresholds. Furthermore, there is no universally accepted list of prognostic factors in RA and the relative importance of these factors varies among recommendations and clinical studies. The 2012 ACR RA treatment guideline stratified treatment recommendations by presence/absence of prognostic factors, while the current 2015 ACR RA guideline stresses on disease activity measurement and to treat to target, due to a frequent overlap and concordance between these prognostic factors and active RA. Nevertheless, these prognostic factors are often associated with worse disease outcomes as reported by a study from Corrona registry showing less occurrence of low disease activity or remission in patients with greater number of prognostic factors indicating that their presence may imply moderate/high disease activity in which aggressive management with biologics is equitable [22].

Combination therapy

Biologic DMARDs when initiated after csDMARD failure should be used in combination with a csDMARDs whenever possible. MTX is the most well-studied csDMARDs in the combination therapy and is associated with a lower risk of immunogenicity with monoclonal antibody biologic DMARDs [23]. Other csDMARDs can also be used though less robust data are available. Combination therapy offers advantages of superior efficacy than monotherapy with conventional or biologic DMARD alone. In TEMPO, a double-blind, randomized controlled trial (RCT), 686 patients with active RA who had inadequate response to a csDMARDs other than methotrexate were randomly allocated to treatment with etanercept 25 mg (subcutaneously twice a week), oral methotrexate (up to 20 mg every week), or the combination. The ACR response in 24 weeks and primary radiographic endpoint was significantly better in the combination of etanercept and methotrexate compared with methotrexate or etanercept alone [24]. Similarly, abatacept plus MTX showed more robust efficacy compared with MTX or abatacept alone [25]. In AVERT trial, higher proportion of RA patients with poor prognostic factors (positive rheumatoid factor and anti-cyclic citrullinated peptide antibody) achieved remission with abatacept plus MTX (60.9%) versus MTX alone (45.2%) or abatacept monotherapy (42.5%) [26]. Similar results have been seen with adalimumab [13] and certolizumab [27]. In a large double-blind RCT (FUNCTION) of MTX-naive patients with early RA, tocilizumab monotherapy achieved DAS 28 ESR remission in patients at week 24 similar to combination of tocilizumab with MTX (39 versus 45% of patients) though suppression of structural joint damage was numerically greater in combination with MTX compared with monotherapy at week 52 [28].

Combination therapy is strongly advocated by the guidelines. Real-world data show that one-third of RA patients are receiving biologic monotherapy [29]. A number of factors likely contribute to this scenario, including contraindications, adverse effects, lack of adherence, and persistence to a csDMARDs. Strategies to mitigate adverse effects from csDMARDs such as dose reduction, conversion of oral methotrexate to subcutaneous, and the use of folate with methotrexate may help improve adherence. If monotherapy is to be used, non-TNFi biologics or tsDMARDs can be considered. Tocilizumab monotherapy displayed greater efficacy to adalimumab [30] and may have equal efficacy in comparison with tocilizumab with MTX. A 2015 NMA of 28 RCT of biologics as monotherapy or combination therapy demonstrated that as monotherapy, tocilizumab displayed better clinical efficacy compared with TNFi or tofacitinib [31]. A Cochrane systematic review and NMA of 46 RCT of biologic or tofacitinib monotherapy in 2017 concluded no significant difference [32]. Combination therapy should be favored whenever possible; however, several patient-related factors including comorbidities will impact the final choice of biologic in clinical practice.

Treatment following failure of first biologic DMARDs

If patient's disease activity fails to respond to initial bDMARDs or tsDMARDs, treatment with another biologic is indicated [32]. Claims data from commercial and Medicaid healthcare plans in the USA show that TNFi are the most commonly used initial biologics after csDMARD failure [33]. However, TNFi is not effective in all RA patients, similar to any other DMARDs. In fact, only 25–42% of patients reach the treatment target of ACR50 response rate with TNFi [34]. Patients who do not respond to biologics can be classified in those who never showed an adequate response (primary non-responders) or those who initially had a response but lost it over the course of time (secondary non-responders) perhaps from development of anti-drug antibodies. Two options are available in these scenarios, switching to alternative TNFi or switching to a bDMARDs with another mode of action. Both guidelines recommend using a biologic with a different mechanism of action over a second TNFi.

The evidence of efficacy of TNFi cycling (sequential use of second TNFi) comes from both uncontrolled studies [35] and controlled RCT. The GO-AFTER trial included patients with RA who had previously received TNFi and showed significantly higher ACR 20 responses with golimumab compared with placebo group [36]. It strengthened the notion that a second TNFi with a different molecular structure may still be effective after initial TNFi failure. Similarly, REALISTIC study [37] and more recent EXXELERATE study proved the efficacy of certolizumab pegol in patients with RA with active disease who have had prior TNFi use [38]. The data supporting a strategy to switch biologics to another mechanism of action are limited. In RA patients from Corrona registry with prior exposure to ≥ 1 TNFi who initiated rituximab or another TNFi, rituximab was associated with an increased likelihood of achieving low disease activity or remission compared with TNFi with comparable adverse effects [39]. Similar results were found in another observational SWITCH RA study in which seropositive (rheumatoid factor) patients had significantly greater improvements in disease activity with rituximab than those with second TNFi [40]. A study from Swedish Rheumatology register compared patients initiating TNFi, rituximab, abatacept, or tocilizumab in 2010–2016 as first bDMARDs ($n = 9333$), or after switch from TNFi as first bDMARDs ($n = 3941$). Treatment effectiveness was assessed as the proportion of patients with EULAR Good Response/Health Assessment Questionnaire improvement. Patients receiving non-TNFi in particular tocilizumab and rituximab had better clinical response than TNFi both as first and second biologic [41]. A 52-week multicenter, open-label RCT evaluated a total of 300 patients with RA who had insufficient response to TNFi therapy [42]. These patients were randomized to receive another TNFi or a non-TNFi biologic and the choice of biologic was determined the treating clinician. A total of 69% patients in the non-TNFi group and 52% in the second TNFi group achieved a good or moderate EULAR response (OR, 2.06; 95% CI 1.27 to 3.37; $P = 0.004$) at week 24.

However, this study had limitations with regard to lack of blinding, not allowing certain biologics and lack of power to detect differences in adverse effects. Additionally, the use of wide variety of non-TNFi biologics limited the understanding as to which specific biologic should be used after failure of initial biologic. While both TNFi cycling and switching approaches are considered reasonable after initial TNFi failure, there is lack of direct head to head comparison between them [43]. In patients who are primary non-responders to TNFi, a biologic with a different mechanism of action should be preferred as it is likely that disease activity is dominantly driven by non-TNF pathway in these cases. If patient has persistent disease activity on TNFi monotherapy, addition of csDMARDs can be considered for attaining a better efficacy.

Tapering of RA treatment

Tapering is appealing considering treatment-related adverse effects and financial cost burden but must be weighed against potential harms of tapering such as risk of disease relapses [44–48]. Tapering implies reduction of dose or the frequency of dosing. A systematic review and meta-analysis of nine RCT of bDMARD discontinuation versus continuation showed that discontinuation of bDMARDs lead to an increased risk of losing remission or low disease activity and radiographic progression; however, tapering doses of bDMARDs did not increase the risk of relapse or radiographic progression, even though there was an increased risk of losing remission [49••]. EULAR recommends that if a patient is in "persistent remission," tapering of glucocorticoids should be done first followed by considering taper of bDMARDs or tsDMARDs. If patient remains in persistent remission, tapering of csDMARDs could be considered. No definition of persistent remission was provided, so we assume that authors might be referring to remission for at least a reasonable period of 6–12 months or longer. The ideal patient profile in which tapering should be considered is not clear. Presence of anti-cyclic citrullinated peptide antibodies has been linked to higher relapse risk [50]. Tapering should only be considered in patients who are in remission and not with low disease activity. The remission needs to be stable and sustained over time, ideally over a period of at least 6 months. Strict remission criteria such as ACR/EULAR Boolean or CDAI remission criteria should be used as patients may still have active disease with DAS28 criteria [51]. Tapering of treatment should also be a shared decision-making process and patient must be made aware of a possible relapse.

Case 1 continued

Escalation of RA treatment was recommended for active disease. When drug options were discussed, patient expressed hesitancy to do self-injections due to severe needle phobia. She lived 2.5 h away from the clinic location. As a solo owner of her business, she preferred not to take time off for making trips for infusions. Based on patient's preference to take oral medications, tofacitinib 5 mg twice a day was initiated along with a course of prednisone 15 mg daily,

which was tapered off over 4 weeks. At follow-up in 6 months, patient had achieved disease remission on her current regimen.

Case 2 continued

Laboratory evaluation showed positive ANA (1:320 homogenous pattern; previously negative) with negative SSA, SSB, anti-Smith, DsDNA, RNP antibodies, and normal urinalysis, complement, and immunoglobulin levels. Cryoglobulins, hepatitis C antibody, hepatitis B surface antigen, serum protein electrophoresis, and immunofixation tests were negative. Chest radiograph was also negative. Patient was referred to dermatology and they suspected a diagnosis of chilblain lupus. Patient reported that she had been gardening, out in cold without wearing warm footwear. Although cold-induced chilblains were in differential, based on her new positive ANA and temporal association of her symptoms with initiation of adalimumab, drug-induced lupus phenomenon was felt more likely. Patient was advised warming measures, cold avoidance, and adalimumab was stopped, following which her symptoms resolved. Patient was then started on tocilizumab 162 mg every 2 weeks subcutaneously which led disease remission in her case at follow-up.

Management of comorbidities in RA

Case 3

A 59-year-old Caucasian male with seropositive RA for 7 years presented to his rheumatologist for follow-up. The patient reported that he had been feeling well and denied joint swelling or pain. He was taking methotrexate 20 oral weekly, folic acid 1 mg daily, and tocilizumab 162 SQ once weekly. He occasionally used prednisone when he experienced a flare of RA. He smoked 10 cigarettes a day. His father had a history of ischemic heart disease. His blood pressure was 140/86. Examination showed subluxation at metacarpophalangeal joints in hands and mild tenderness in his right wrist. CDAI calculated in the office was 3 consistent with low disease activity. On laboratory evaluation, his total cholesterol level was 202 mg/dl, high-density lipoprotein cholesterol level was 42 mg/dl, and low-density lipoprotein (LDL) cholesterol level was 160 mg/dl.

Patients with RA have a high burden of comorbid conditions that are either usually related directly to disease activity or as a result of treatment complications. The risk of cardiovascular disease in markedly increased in RA and increases mortality by 50% compared with the general population [52]. The heightened risk is not fully explained by traditional cardiovascular disease risk factors and RA-related systemic inflammation is thought to be contributing to promotion of atherosclerosis. The commonly used cardiovascular disease risk prediction models often underestimate the risk of CVD in RA patients [53]. EULAR recommends a multiplication factor of 1.5 to predict the risk more accurately [54••]. Studies show that controlling RA inflammation reduces the risk of cardiovascular events [55]. Deploying a strategy of "treat to target" is therefore a very important step to mitigate cardiovascular disease risk in this patient population. Clinicians must also emphasize screening and management of traditional cardiovascular disease risk factors including treating hypertension, diabetes mellitus, obesity, dyslipidemia, encouraging smoking cessation, and

recommending lifestyle modifications [56]. Medications such as non-steroidal anti-inflammatory drugs and glucocorticoids that are known to cause deleterious adverse effects on cardiovascular health should be kept to a minimum.

The interpretation of lipid profile in RA can be complex due to interplay of lipids with inflammation. Therefore, lipid screening should be best done when the disease activity is in remission or at least stable. Systemic inflammation may decrease lipid levels and thus some patients may not receive adequate treatment as their lipid levels may be in "low category" yet they remain at a high risk of CVD [57]. Patients with low levels of low-density lipoprotein cholesterol are particularly at risk of cardiovascular disease, a concept referred to as "lipid paradox" [58]. A recent study explored the burden of subclinical atherosclerosis in RA patients with low levels of low-density lipoprotein cholesterol (LDL-C) and found that in RA patients not on lipid lowering therapy with LDL-C less than 70 mg/dl, the coronary artery calcium scores were fourfold higher compared with non-RA controls, including the calcium scores associated with CVD events (≥ 100 units) [59]. The authors concluded that in this subgroup of patients, more advanced investigations for CVD risk assessment and primary prevention measures may be needed.

RA treatments increase the lipid levels [60] that raises a question with regard to cardiovascular risk-benefit balance. However, the findings from the ENTRACTE trial suggest that risk of major adverse cardiovascular events with tocilizumab is comparable with that with etanercept and that perhaps these lipid changes are a result of improved inflammation and may not be detrimental to cardiovascular health [61]. In fact, several studies have shown CVD risk improvement with RA treatments. A recent systematic review and meta-analysis of 14 observational studies showed a lower risk of cardiovascular events in patients with TNFi compared with csDMARDs, possibly due to a reduction in systemic inflammation [62]. These findings stress on the importance of tight control over disease activity in addition to management of traditional cardiovascular risk factors to prevent poor cardiovascular outcomes in RA patients.

Case 3 continued

Cardiovascular risk assessment was performed using 10-year risk of atherosclerotic cardiovascular disease based on the risk calculator by American Heart Association (AHA) and the American College of Cardiology (ACC) guidelines from 2013 and was noted to be 17.1% which was an intermediate risk category [63]. When his RA was taken into account, the risk increased considerably to 25.6% (after multiplication × 1.5), which then put him in the high-risk category. Lifestyle modification, nutrition counseling, exercise, smoking cessation, treatment for hypertension, and statin therapy were recommended.

Conclusion

Newer advances in the treatment of RA have made remission or low disease activity achievable and have enabled patients to lead a good quality life. To provide optimal care to RA patients, it is important to diagnose it early, initiate DMARD therapy at the time of diagnosis, and achieve disease control with a treat to target strategy. Monitoring of drug related adverse effects should be done regularly, and steps to mitigate those risks should be taken. Patients with

RA are at an increased risk of infections including influenza, pneumococcal disease, and herpes zoster, which can be prevented with vaccinations [64]. EULAR recently updated recommendations for vaccination in adult patients with rheumatic diseases, which is available for use by clinicians in addition to recommendations from Centers for Disease Control and Prevention [5]. Emphasis must be placed on management of comorbid conditions, which can adversely affect patient's health. It is often debated whether the primary care physician or the rheumatologist should take the responsibility of managing the comorbid conditions. Given that rheumatologists are likely more familiar with RA disease process and have increased vigilance for comorbidities, they should take the ownership of these issues and actively collaborate with primary care providers. Establishing this partnership is prudent to provide multi-disciplinary care to RA patients while aiming for excellent clinical outcomes.

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Compliance with Ethical Standards

Conflict of Interest
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IRB Approval
Since this was not a research study, no IRB approval was needed.

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- • Of importance
- •• Of major importance

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