Table 4: Summary of Recommendations in Included Guidelines

Recommendations and supporting evidence	Quality of evidence, strength of recommendations, GRADE, or level of agreement
EULAR (2020)[9]	
Recommendation "Methotrexate (MTX) should be part of the first treatment strategy (p. 690)."[9] **Evidence informing this recommendation was not provided.**	**LoE**: 1a (SR of RCTs) **SoR**: A (consistent level 1 studies)[a]
Recommendation "In patients with contraindication to MTX (or early intolerance), leflunomide or sulfasalazine should be considered as part of the (first) treatment strategy (p. 690)."[9] **Evidence informing this recommendation was not provided.**	**LoE**: 1a (SR of RCTs) **SoR**: A (consistent level 1 studies)
Recommendation "Short-term GC should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered as rapidly as clinically feasible (p. 692)."[9] **Three clinical trials suggested that MTX + GC showed similar effectiveness when compared to MTX + biologic DMARDs.**	**LoE**: 1a (SR of RCTs) **SoR**: A (consistent level 1 studies)
Recommendation "If the treatment target is not achieved with the first csDMARDs strategy, in the absence of poor prognostic factors, other csDMARDs should be considered (p. 692)."[9] **Evidence informing this recommendation was not provided.**	**LoE:** 5 (expert opinion without explicit critical appraisal) **SoR**: D (level 5 evidence[b] or troublingly inconsistent or inconclusive studies of any level)

Recommendations and supporting evidence	Quality of evidence, strength of recommendations, GRADE, or level of agreement
APLAR (2019)[12]	
Recommendation "Starting treatment with csDMARD monotherapy, preferably MTX, is recommended as soon as the diagnosis of RA is made (p. 359)."[12] **Evidence for the use csDMARDs, particularly MTX, as first-line therapy for patients diagnosed with RA was presented in previous 2016 EULAR[20] and 2015 ACR[14] treatment guidelines. The efficacy of using MTX monotherapy as first-line treatment for patients with RA was outlined in a 2014 SR and moderate-quality evidence from individual studies. The previous recommendation found in the 2015 version of this guideline presented 2 strong recommendations on csDMARDs as first-line RA treatment and that MTX is the preferred csDMARD. Based on current and past moderate-quality evidence, the previous 2 statements were integrated into 1 recommendation.**	**Quality of Evidence:** Moderate (moderately confident in the effect estimate) **SoR:** NR
Recommendation "Patients who cannot tolerate MTX may receive other csDMARDs such as LEF or SSZ as first-line treatment. HCQ, iguratimod, bucillamine, cyclosporine, intramuscular gold or tacrolimus may also be considered depending on availability (p. 361)."[12] **This recommendation is consistent with the previous recommendation in the 2015 version and is consistent with the 2016 EULAR[20] treatment guideline. Three SRs and one RCT provided evidence for the efficacy of LEF compared to MTX. One SR and 2 RCTs support SSZ as an alternative to MTX. There were limited data on the efficacy of the other mentioned csDMARDs.**	**Quality of Evidence:** Moderate (moderately confident in the effect estimate) **SoR:** NR
Recommendation "In patients with high disease activity, combination csDMARD therapy should be considered, with close monitoring of therapy-related toxicities (p. 361)."[12] **This recommendation was based on RCTs in which patients with active RA were provided combination therapy. Four RCTs showed that triple therapy was more efficacious than monotherapy but was accompanied with higher hepatotoxicity. An additional 7 RCTs that looked at double or triple therapy versus monotherapy had similar findings. A previous Cochrane review from 2002 also showed higher efficacy in combination therapy compared to monotherapy.**	**Quality of Evidence:** Low (confidence in the effect estimate is limited) **SoR:** NR

Recommendations and supporting evidence	Quality of evidence, strength of recommendations, GRADE, or level of agreement
French Society for Rheumatology (2019)[11]	
Recommendation "Methotrexate is the first-line DMARD in patients with active RA, starting at a dosage of at least 10 mg/week then reaching the optimal dosage within no more than 4–8 weeks (p. 141)."[11] **Evidence informing this recommendation was not provided.**	**LoE:** 1a (SR of RCTs) **SoR:** A (consistent level 1 studies)
Recommendation "In DMARD-naive patients who have contraindications or early intolerance to methotrexate, leflunomide and sulfasalazine are good alternatives (p. 141)."[11] **Evidence informing this recommendation was not provided.**	**LoE:** 1a (SR of RCTs) **SoR:** A (consistent level 1 studies)
Recommendation "While awaiting the effects of csDMARD therapy, oral or parenteral glucocorticoid therapy can be considered, in a low cumulative dosage, if possible for no longer than 6 months. The glucocorticoid dose should be tapered to nothing as promptly as possible (p. 141)."[11] **Evidence informing this recommendation was not provided.**	**LoE:** 1a (SR of RCTs) **SoR:** B (consistent level 2[c] or 3 studies,[d] or extrapolations from level 1 studies)
Recommendation "In patients with an inadequate response or intolerance to methotrexate, the treatment must be optimized. In patients with adverse prognostic factors, add-on bDMARD or tsDMARD therapy can be considered, using a TNFα antagonist, abatacept, an IL-6 pathway antagonist, a JAK inhibitor, or, under specific circumstances, rituximab. In patients without adverse prognostic factors, a switch to another csDMARD (leflunomide, sulfasalazine) or the combination of several csDMARDs can be considered; if this strategy fails or is contraindicated, targeted therapy (with a bDMARD or tsDMARD) should be considered (p.141)."[11] **Evidence informing this recommendation was not provided.**	**LoE:** 1b (individual RCT) **SoR:** A (consistent level 1 studies)
Brazilian Society of Rheumatology (2018)[12]	
Recommendation "The first line of treatment should be a csDMARD started as soon as the diagnosis of RA is established (p. 4)."[12] **Evidence for this recommendation was described as low to moderate.**	**LoA:** 9.93 (mean score out of 10) Quality of evidence was described as low to moderate **Strength of Recommendation:** NR

Recommendations and supporting evidence	Quality of evidence, strength of recommendations, GRADE, or level of agreement
Recommendation "Methotrexate is the first-choice csDMARD (p. 6)."[12] **Moderate-quality evidence suggested that there was no significant difference in the efficacy of csDMARDs for most relevant outcomes including the number of painful and swollen joints, disease activity, pain, and functional capacity. High evidence suggested there were more adverse events with LEF compared to MTX; however, low to very low evidence suggested that MTX had the highest risk of hepatic pulmonary adverse events.**	**LoA:** 10 Quality of evidence was described as very low to high **Strength of Recommendation:** NR
Recommendation "Combination of two or more csDMARDs, including MTX, may be used as the first line of treatment (p. 6)."[12] **High to moderate evidence suggested that triple therapy with MTX + SSZ + HCQ and MTX + LEF compared with MTX monotherapy showed an improved response. Moderate to low evidence suggests that there was no clinically significant difference in MTX alone or in combination in other disease activities, radiographic progression, and therapeutic safety.**	**LoA:** 9.62 Quality of evidence was described as low to high **Strength of Recommendation:** NR
Recommendation "After failure of first-line therapy with MTX, therapeutic strategies include combining MTX with another csDMARD (leflunomide), with two csDMARDs (hydroxychloroquine and sulfasalazine), or switching MTX for another csDMARD (leflunomide or sulfasalazine) alone (p. 6)."[12] **Moderate to low evidence suggested combination therapies with MTX may provide a better response, with no significant difference in radiographic progression or adverse events from discontinuation.**	**LoA:** 9.12 Quality of evidence was described as low to moderate **Strength of Recommendation:** NR

Recommendations and supporting evidence	Quality of evidence, strength of recommendations, GRADE, or level of agreement
NICE (2018)[13]	
Recommendation "For adults with newly diagnosed active RA: • Offer first-line treatment with cDMARD monotherapy using oral methotrexate, leflunomide or sulfasalazine as soon as possible and ideally within 3 months of onset of persistent symptoms. • Consider hydroxychloroquine for first-line treatment as an alternative to oral methotrexate, leflunomide or sulfasalazine for mild or palindromic disease. • Escalate dose as tolerated (p. 8-9)."[13] "Consider short-term bridging treatment with glucocorticoids (oral, intramuscular or intra-articular) when starting new cDMARD (p. 9)."[13] **Overall evidence suggested that starting treatment with more than 1 csDMARD was no more effective than starting with a monotherapy csDMARD approach. Additionally, evidence from RCTs in DMARD-naive patients showed no difference in the effectiveness of MTX, LEF, and SSZ as monotherapies. The committee agreed that any of these csDMARDs may be used as first-line therapies.**	Quality of evidence and strength of recommendations were NR
Recommendation "Offer additional cDMARDs (oral methotrexate, leflunomide, sulfasalazine or hydroxychloroquine) in combination in a step-up strategy when the treatment target (remission or low disease activity) has not been achieved despite dose escalation (p. 9)."[13] **Evidence from RCTs was limited regarding the use of glucocorticoids for symptom relief in patients starting new DMARD therapy and no evidence was found regarding the effectiveness of glucocorticoids in terms of disease activity, QoL, or function. The committee agreed that the use of glucocorticoids may be considered on a case-by-case basis.**	Quality of evidence and strength of recommendations were NR

Recommendations and supporting evidence	Quality of evidence, strength of recommendations, GRADE, or level of agreement
ACR (2016)[14e]	
Recommendations for patients with symptomatic early RA: Recommendation "If the disease activity is moderate or high, in patients who have never taken DMARD: • Use DMARD monotherapy over double therapy • Use DMARD monotherapy over triple therapy (p. 8)."[14] **Overall, 7 RCTs informed this recommendation. The strength for this recommendation is conditional because of low-quality evidence. Additionally, the evidence for this recommendation was shown to be imprecise. It was suggested that there was little difference in the benefit of double therapy over monotherapy and triple therapy may be desired by some patients.**	**SoR:** Conditional (uncertainty of harms and benefits because of low-quality evidence) **LoE:** Moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate) **LoE:** High (further research is very unlikely to change our confidence in the estimate of effect)
Recommendation "If disease activity remains moderate or high despite DMARD monotherapy (with or without glucocorticoids), use combination DMARDs or a TNFi or a non-TNF biologic (all choices with or without MTX, in no particular order of preference), rather than continuing DMARD monotherapy alone (p. 8)."[14] **One RCT provided low-quality evidence that suggested that when DMARD monotherapy was failing, adding treatment options is supported and recommending no additional treatment is not an option.**	**SoR:** Strong (the benefits outweigh the harms) **LoE:** Low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate)
Recommendations for patients with established RA Recommendation "If disease activity is moderate or high, in patients who have never taken DMARD: • Use DMARD monotherapy (MTX preferred) over tofacitinib • Use DMARD monotherapy (MTX preferred) over combination DMARD therapy (p. 11)."[14] **Overall, 8 RCTs informed this recommendation. This recommendation is conditional because, despite positive evidence for tofacitinib, conflicting evidence suggested that benefit, risk, and cost favoured MTX monotherapy. The evidence for DMARD monotherapy over combination DMARD therapy was of low quality because evidence supporting the benefit of double therapy over monotherapy was indirect and imprecise.**	**SoR:** Conditional (uncertainty of harms and benefits because of low-quality evidence) **LoE:** High (further research is very unlikely to change our confidence in the estimate of effect) **LoE:** High (further research is very unlikely to change our confidence in the estimate of effect)

Recommendations and supporting evidence	Quality of evidence, strength of recommendations, GRADE, or level of agreement
Recommendation "If disease activity remains moderate or high despite DMARD monotherapy, use combination traditional DMARDs or add a TNFi or a non-TNF biologic or tofacitinib (all choices with or without MTX, in no particular order of preference), rather than continuing DMARD monotherapy alone (p. 11)."[14] **Overall, 14 RCTs informed this recommendation. This recommendation is strong because clinical experience supported adding treatment options when DMARD monotherapy is failing. Additionally, voting supported biologic DMARD therapy used in combination with MTX because of evidence of efficacy compared to biologic DMARD monotherapy.**	**SoR:** Strong (the benefits outweigh the harms) **LoE:** Moderate to very low (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; we are very uncertain about the estimate)
Todoerti et al. (2013)[15]	
Recommendation "MTX must be considered the DMARD of first choice in RA patients both alone and in combination (with low dosage glucocorticoid and/or other DMARDs) (p. 209)."[15] **One meta-analysis and one RCT suggested that MTX-based treatment with the addition of a low-dose steroid (such as a glucocorticoid) improved outcomes related to radiographic progression and lower disease activity.**	**LoE:** 2b (individual cohort study) **SoR:** B (consistent level 2 or 3 studies, or extrapolations from level 1 studies)
Recommendation "In patients that are non-responders to MTX at the maximum tolerated dosage, combination therapy can be started with DMARD or a biological agent (p. 209)."[15] **One Cochrane review suggested that combining MTX with other DMARDs compared to MTX alone had no significant advantage in DMARD-naive or non-respondent patients, except for the combination of MTX + HCQ + SSZ (known as the O'Dell protocol). Additional evidence compared the efficacy of triple therapy to adding a biologic DMARD to therapy and suggested that the addition of the biologic DMARD improved clinical and radiographical outcomes.**	**LoE:** 1b (individual RCT) **SoR:** B (consistent level 2 or 3 studies, or extrapolations from level 1 studies)

Recommendations and supporting evidence	Quality of evidence, strength of recommendations, GRADE, or level of agreement
CRA (2012)[16]	
Recommendation "Glucocorticoids (GC; oral, intramuscular, or intraarticular) can be added to DMARD therapy as part of the initial treatment strategy of patients with RA (I), and may be an option for managing flares, as bridge therapy while waiting for DMARD to take effect, or for symptom control if no other options exist (IV). GC should be used in the lowest possible dose and tapered as rapidly as clinically feasible (IV) (p. 1569)."[16] **One SR of RCTs that informed the EULAR 2010 guidelines suggested that short-term treatment with GC was beneficial for symptom control and inhibiting radiographic progression when added to DMARD monotherapy of combination therapy. Other evidence informing the NICE 2009 guidelines showed there was a discordance between strong evidence for the use of GC and the paucity of other research studies. Additional evidence from the EULAR 2007 guidelines suggested there was a risk of adverse events depending on the dosage of GC used.**	**LoE:** I (meta-analyses, SRs of RCTs, or individual RCTs), IV (expert opinion) **SoR:** A (strong recommendation)/D (consensus recommendation)
Recommendation "Methotrexate is the preferred DMARD with respect to efficacy and safety and should be the first DMARD used in patients with RA unless contraindicated (p.1569)."[16] **RCT and observational evidence from the EULAR 2010 guidelines suggested that MTX was effectives in DMARD-naive patients with early moderate to severe RA. Additionally, no other csDMARD or biologic DMARD monotherapies were shown to have better clinical efficacy compared to MTX. One SR supported the beneficial safety of long-term MTX.**	**LoE:** I (meta-analyses, SRs of RCTs, or individual RCTs) **SoR:** A (strong recommendation)
Recommendation "Initial combination therapy with traditional DMARD should be considered, particularly in patients with poor prognostic features, moderate-high disease activity, and in patients with recent-onset disease. Combination therapy should also be considered in patients who have an inadequate response to monotherapy (p. 1571)."[16] **RCT evidence informing the ACR 2008 guidelines suggested there was efficacy in DMARD combinations in different clinical situations. An SR of RCTs and observational studies informing the NICE 2009 guidelines suggested that several combinations (including GC) was superior to DMARD monotherapy. An SR of RCTs informing the EULAR 2010 guidelines found low-quality evidence in trials comparing combination therapy to monotherapy.**	**LoE:** I (meta-analyses, SRs of RCTs, or individual RCTs) **SoR:** B (moderate recommendation)

Recommendations and supporting evidence	Quality of evidence, strength of recommendations, GRADE, or level of agreement
Recommendation "When treating with combination therapy, methotrexate (MTX) should be used as the anchor drug unless contraindicated. Combinations not including MTX can be considered on a case-by-case basis (p. 1571)."[16] **Evidence informing the NICE 2009 guideline and ACR 2008 guideline provided details for combination therapy in RA. At least 1 RCT showed increased efficacy for a number of combination therapies over monotherapy.**	**LoE:** I (meta-analyses, SRs of RCTs, or individual RCTs) **SoR:** A (strong recommendation)
Recommendation "Combination therapy with leflunomide (LEF) and methotrexate (MTX) should be used with caution as it is associated with higher toxicity (GI and liver) (I) and has no added benefit relative to other DMARD combinations (IV) (p. 1572)."[16] **Evidence from 1 RCT suggested combination therapy with MTX + LEF had better efficacy compared to MTX + placebo in patients with high disease activity. It should be noted that LEF was associated with the risk of severe liver injury. Additionally, several Canadian provincial formularies require patients to fail LEF or MTX + LEF prior to accessing biologic DMARD therapy.**	**LoE:** I (meta-analyses, SRs of RCTs, or individual RCTs), IV (expert opinion) **SoR:** A (strong recommendation)
SIGN (2011)[17]	
Recommendation "Low-dose oral corticosteroids can be used in combination with DMARD therapy for short term relief of signs and symptoms, and in the medium to long term to minimize radiological damage (p. 9)."[17] **A Cochrane review of RCTs suggested that low-dose corticosteroids were effective in the short-term relief of symptoms compared to NSAIDs and minimized radiographical damage in the medium- to long-term. An additional Cochrane review found that corticosteroids in combination with DMARDs reduced the rate of progression for RA.**	**Quality of Evidence:** A (please refer to Table 2 for description of GRADE)
Recommendation "Methotrexate and sulfasalazine are the DMARDs of choice due to their more favourable efficacy and toxicity profiles (p. 10)."[17] "DMARD therapy should be sustained in patients with early RA to control the signs and symptoms of disease (p. 10)."[17] **Evidence from an SR suggested that the efficacy of MTX was similar to other common csDMARDs including LEF and SSZ, but HCQ was less effective. Additional evidence from 2 RCTs suggested sustained use of DMARD therapy was necessary because of relapse symptoms and signs occurring with therapy withdrawal.**	**Quality of Evidence:** A **Quality of Evidence:** B

Recommendations and supporting evidence	Quality of evidence, strength of recommendations, GRADE, or level of agreement
Recommendation "A combination DMARD strategy, rather than sequential monotherapy, should be considered in patients with an inadequate response to initial DMARD therapy (p. 11)."[17] **An SR of 3 RCTs suggested that combination therapy was more effective than sequential monotherapy in overall RA improvement and the reduction in progression. MTX was the most common DMARD in combination therapy.**	**Quality of Evidence:** A

ACR = American College of Rheumatology; bDMARD = biologic disease-modifying antirheumatic drug; CRA = Canadian Rheumatology Association; csDMARD = conventional synthetic disease-modifying antirheumatic drug; DMARD = disease-modifying antirheumatic drug; EULAR = European League Against Rheumatism; GC = glucocorticoids; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HCQ = hydroxychloroquine; IL-6 = interleukin 6; JAK = Janus kinase; LEF = leflunomide; LoA = level of agreement; LoE = level of evidence; MTX = methotrexate; NICE = National Institute for Health and Care Excellence; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; QoL = quality of life; RA = rheumatoid arthritis; RCT = randomized controlled trial; SIGN = Scottish Intercollegiate Guidelines Network; SoR = strength of recommendation; SR = systematic review; SSZ = sulfasalazine; TNF = tumour necrosis factor; TNFi = tumour necrosis factor inhibitor; tsDMARD = targeted synthetic disease-modifying antirheumatic drug.

[a]Level 1 studies refer to SRs of RCTs, individual RCTs, and "all or none" studies.

[b]Level 5 evidence refers to expert opinion without explicit critical appraisal.

[c]Level 2 studies refer to SRs of cohort studies, individual cohort studies, or "outcomes" research and ecological studies.

[d]Level 3 studies refer to SRs of case-control studies and individual case-control studies.

[e]The American College of Rheumatology uses the term "DMARD" to describe conventional synthetic DMARD therapy.