TABLE 2. DMARDs[18,19,23] *(Continued)*

bDMARDs: costimulation inhibitors		
Abatacept (SC, IV)	• Baseline TB testing and annually while on therapy • Hepatitis B, hepatitis C • CBC count, liver function tests, creatinine at baseline and every month for 3 months, then every 3 months thereafter • Monitor blood glucose with IV formulation	• Use in pregnancy: not recommended due to insufficient data • Risk of serious infections (TB, zoster, invasive fungal, and other opportunistic infections) • Malignancy • Hepatitis B reactivation • Anaphylaxis • In IV formulation, elevated blood glucose due to maltose in solution; not a problem with SC formulation • Use with caution in patients with COPD due to increased dyspnea and adverse reactions
bDMARDs: anti-B cell (CD20 inhibitors)		
Rituximab (IV)	• Baseline TB testing and annually while on therapy • HBV, HCV • CBC, liver function tests, creatinine at baseline and every month for 3 months, then every 3 months thereafter	• Use in pregnancy: Not recommended due to B-cell depletion in neonates • Boxed warning for risk of hepatitis B reactivation, mucocutaneous reactions such as SJS, infusion reactions, progressive multifocal leukoencephalopathy • Risk of increase in opportunistic infections • Risk of cardiac conduction disorders
bsDMARDS		
Adalimumab, etanercept, infliximab, and rituximab have biosimilar medications available	See drug details above	See drug details above

Methotrexate is a folate antagonist and is teratogenic (pregnancy category X).[6] Leflunomide (pregnancy category X) also is teratogenic, is a pyrimidine synthesis inhibitor, essentially inhibiting rapidly dividing cells, in particular lymphocytes.[6]

If the patient fails to improve, presents or remains with moderate to high disease activity, fails to achieve the target of remission or low disease activity, additional DMARDs should be added to the therapeutic regimen.[18,19] Under the ACR guidelines, the decision as to which category of medication to choose depends on moderate to high disease activity. EULAR guidelines are dependent on the presence or absence of poor prognostic factors, such as moderate to high disease activity as determined by the DAS28; high ESR or CRP; high swollen joint count; positive rheumatoid factor or ACPA; early erosions on radiography; and failure of two or more csDMARDs.[15,18,19] In patients with moderate to high disease activity and no response to DMARD monotherapy for early RA, the ACR recommends the following therapeutic options: combination csDMARDs; TNF inhibitor bDMARDs +/- methotrexate; or non-TNF inhibitor bDMARDs; all of the choices can add short-term glucocorticoids.[18] The ACR makes the same recommendation for patients with established RA, but adds the option of a Janus kinase inhibitor (JAKi).[18] The EULAR criteria offer slightly different recommendations. In the absence of poor prognostic factors, the recommendation is to change or add another csDMARD.[18] If poor prognostic factors are present, a switch to a bDMARD or JAKi is recommended.[19]

Failure to achieve remission on this new protocol requires a change to a new bDMARD or JAKi.[19] Both guidelines recommend that even if patients fail one medication in a class, clinicians should try prescribing different drugs in the same class, because response varies across patients. Although the preferred goal is remission, studies have shown only 10% to 50% of patients achieve sustained remission.[10] Remission is defined as greater than 6 months in which all the following criteria are met:

- one or no tender joints
- one or no swollen joints
- CRP of 1 mg/dL or less
- patient global assessment of 1 or less (range, 0-10).[18-20]

Some authors suggest that dose reduction may be attempted in patients with sustained remission; however, if the patient has a disease flare, clinicians must be ready to increase medications promptly.[11,19] The ACR strongly encourages against discontinuing all RA medications even in patients in sustained remission.[18] The goal of treatment for RA is to reduce disease activity and the rate of joint destruction. The mainstay of pharmacologic therapy is early intervention with use of nonbiologic and biologic DMARDs together with adjunctive medications such as NSAIDs, oral and intra-articular corticosteroids, and analgesic medications, including opioids.

TABLE 3. Comparing the ACR and EULAR guidelines[18,19]

Disease activity	ACR guideline		Poor prognostic factors	EULAR
	Early RA	Established RA		
Initial diagnosis: low disease activity	DMARD monotherapy (methotrexate preferred) +/- short-term glucocorticoids	DMARD monotherapy (methotrexate preferred) +/- short-term glucocorticoids	Initial diagnosis: No contraindications for methotrexate	Methotrexate +/- short-term glucocorticoids
Initial diagnosis: moderate to high disease activity	DMARD monotherapy (methotrexate preferred) +/- short-term glucocorticoids	DMARD monotherapy (methotrexate preferred) +/- short-term glucocorticoids	Initial diagnosis: Contraindications for methotrexate	Leflunomide or sulfasalazine +/- short-term glucocorticoids
Symptoms improved at 3 months and achieved target at 6 months: continue on regimen				
If symptoms NOT improved at 3 months or target NOT achieved at 6 months, see below				
Moderate to high disease activity	Choose from: • Combination csDMARDs OR • TNF inhibitor bDMARDs +/- methotrexate OR	Choose from: • Combination csDMARDs OR • TNF inhibitor bDMARDs +/- methotrexate OR	NO Poor prognostic factors	Change to or add: • Leflunomide or sulfasalazine alone OR • csDMARD combination*
	• non-TNF inhibitor bDMARDs +/- methotrexate	• non-TNF inhibitor bDMARDs** +/- methotrexate OR • JAKi +/- methotrexate	Poor Prognostic Factors Present	Add to current regimen:
	+/- short-term glucocorticoid with any regimen	+/- short-term glucocorticoid with any regimen		• bDMARD OR • JAKi
Symptoms improved at 3 months and achieved target at 6 months: continue on regimen				
If symptoms NOT improved at 3 months or target NOT achieved at 6 months, see below				
Moderate to high disease activity		• Switch to a different medication in the same class (TNF inhibitor bDMARD or non-TNF inhibitor bDMARD) +/- methotrexate OR • Switch to a medication in a different class (TNF inhibitor bDMARD or non-TNF inhibitor bDMARD first before JAKi) +/- methotrexate		• Change the bDMARD OR • Change the JAKi OR • Change to a different class of medication

*Most frequently used csDMARD combination is methotrexate, sulfasalazine, and hydroxychloroquine
**Non-TNF inhibitor drugs include IL-6R inhibitors, costimulation inhibitors, and anti-B cell (CD20 inhibitors)

NONPHARMACOLOGIC TREATMENT

Nonpharmacologic intervention also is important for patients with RA to improve or maintain mobility, strength, and endurance. A significant aspect of treatment is proper patient education about the disease, treatment, and health maintenance so patients can be better involved in the management of their disease. Consultations with physiatry and occupational and physical therapies are invaluable because they provide assistance with splints and orthotic devices, exercise programs, education on joint protection, adaptive equipment use and training, and methods to conserve energy.[21] Consultation with a nutritionist also can be beneficial, especially for patients with severe RA, who frequently suffer from malnutrition or anorexia. Patients with obesity would also benefit from consultation with a nutritionist to help modify their eating habits; excess weight puts stress on joints. Heat and cold therapies also may provide relief of joint pain. When joint deformity becomes severe, surgical intervention can provide pain relief and improve joint function.

Patients with RA should have regularly scheduled appointments with their primary care provider to monitor their general health, paying particular attention to their cardiovascular health. Patients with RA have an increased risk of coronary artery disease and should be counseled about cardiovascular risk factors and started on statins or other medications if they are at higher risk.[1,22] In addition, before starting therapy, the ACR recommends that patients have the pneumococcal, hepatitis B, influenza, human papillomavirus, and zoster virus vaccines.[18] If biologic DMARDs are initiated before appropriate vaccination, the patient cannot receive live vaccines. Patients may be given inactivated vaccines following special protocols.

CONCLUSION

The case patient was started on oral methotrexate therapy for her RA, but was switched to parenteral dosing due to gastrointestinal intolerance. She experienced remission on this regimen and after 1 year, attempted a dose reduction. The reduction led to a flare of her RA. She was returned to her original dose of subcutaneous methotrexate in addition to a short course of glucocorticoids with subsequent resolution of her flare. The patient was counseled that if she desires pregnancy in the future, she will need to be transitioned to sulfasalazine and to establish care with high-risk obstetrics. The patient expressed understanding and agreement with the plan.

RA is a chronic, systemic, autoimmune, inflammatory disease characterized by prolonged morning stiffness, symmetric swelling and pain typically of the wrists, MCP, PIP, and MTP joints. Early recognition and diagnosis of RA may allow intervention with appropriate DMARDs with a decrease in the destructive arthropathy that can occur with this disorder. The ultimate goal of therapy is prolonged remission or low-disease activity, a decrease in joint destruction, and improved quality of life. Pharmacologic and nonpharmacologic therapy require a multidisciplinary team approach with appropriate referrals to rheumatology, physiatry, OT, PT, nutrition, and, in women wishing to become pregnant, high-risk obstetrics. **JAAPA**

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