Clearing up potential misconceptions about the treatment of rheumatoid arthritis and the use of methotrexate in combination therapy

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RHEUMATOID ARTHRITIS (RA) IS A SYSTEMIC autoimmune disease that characteristically affects the small joints of the hands and feet, causing swelling, pain and stiffness. There may also be extra-articular, multisystem manifestations and increased risk of other comorbid complications. If left untreated, joint deterioration will be present in the majority of patients by 1 year. The most common complications of this destructive arthritis is joint deformity and premature disability. Treatment with disease-modifying antirheumatic drugs (DMARDs) is important because they help improve symptoms and prevent and halt the progression of this inflammatory disease.^{1,2}

The prognosis for patients with RA has dramatically improved over the past 2 decades due to multiple factors, primarily, earlier diagnosis, treatment targeted to remission or low disease activity, the use of conventional synthetic DMARD (csDMARD) in combination and the availability of biologic DMARD (bDMARD) and targeted synthetic DMARD (tsDMARD) therapies.¹⁻⁴

What is treat to target?

Achieving and maintaining remission or low disease activity using a “treat-to-target” approach is now recommended as the standard of care in RA. The overarching principle is that remission is the desired goal and that all therapies available should be used to achieve this outcome. This is endorsed by Canadian, American and European guidelines.⁴⁻⁶

This strategy incorporates an early and more aggressive treatment strategy using either an

initial combination of csDMARDs (e.g., methotrexate [MTX], hydroxychloroquine [HCQ], leflunomide, sulfasalazine) or frequent reassessment with dose escalation and/or addition of therapy (e.g., biologics or targeted synthetic therapies) until desired targeted outcomes are achieved. A treat-to-target approach has been shown to slow or even alter the course of the disease.⁷ There is also evidence of improved long-term outcomes, and the strategy is cost-effective compared with older, more gradual approaches to initiating DMARD therapy.⁸

Although some evidence supports the use of bDMARD and tsDMARD therapy as an effective strategy for patients with early RA (duration <6 months) who are naïve to csDMARD therapy, guideline recommendations are in line with current drug coverage requirements that patients try cheaper and effective csDMARDs. While there are treatment barriers for patients with RA due to the high price of bDMARD and tsDMARD therapy, evidence supports the use of csDMARD therapy as an effective strategy.⁹

If a patient cannot achieve an adequate response with csDMARD therapy, then a bDMARD (or tsDMARD) is considered. Depending on the current drug regimen, the new drug may be simply added to MTX and HCQ, or it may be substituted for another drug (e.g., MTX and HCQ continued, leflunomide [LEF] discontinued).⁴⁻⁶

Again, although some trial data supports the use of some bDMARDs (e.g., etanercept, tocilizumab) and tsDMARDs (e.g., tofacitinib) as monotherapy, most often they will be used in

conjunction with MTX (e.g., adalimumab),^{10,11} or alternatively, LEF if MTX is not well tolerated, with or without other csDMARDs.

In addition to generally improving the effectiveness of therapy, MTX also reduces the formation of antidrug antibodies. The antibodies reduce bDMARD efficacy, increase adverse effects and decrease drug survival.^{12,13}

Both placebo- and active-controlled trials in patients with active RA have demonstrated the efficacy of bDMARD and tsDMARD therapy,^{13,14} and long-term observational studies confirm their relative safety.^{15,16}

Why is MTX considered an anchor drug in RA?

MTX is considered the preferred csDMARD for RA. It has been proven to slow progression and prevent joint erosion and deformity^{4,5} as well as reduce cardiovascular morbidity and improve survival, and it is generally well tolerated.^{4,5,17} It should be the first DMARD used unless contraindicated.

It is the anchor, because if tolerated, alternate DMARD therapies will be added until the target of remission or low disease activity is achieved. It is also considered an anchor drug because it helps other csDMARDs work better and enhances or sustains the efficacy of bDMARDs and tsDMARDs.

Patients may need several medications in combination to achieve remission or low disease activity

MTX monotherapy achieves remission or low disease activity in about 30% of patients. Comparatively, a treat-to-target desired outcome is achieved more often, in about two-thirds of patients, when MTX is combined with other csDMARDs.^{2,4,18,19}

If your patient is prescribed 2 or more DMARDs (e.g., MTX, LEF, sulfasalazine, HCQ, biologics, or targeted synthetic therapies), we need to help them understand the benefits and importance of using these drugs concomitantly, as well as counsel on the potential risks.

Managing drug interactions and side effects

Pharmacists are alerted to potential drug interactions between MTX and some bDMARDs, nonsteroidal anti-inflammatory medications (NSAIDs), penicillins and proton pump inhibitors on dispensing software, often stemming

from the use of high-dose MTX for cancer treatment. There are several potential mechanisms for MTX drug interactions; however, inhibition of renal tubular secretion is most probable. A recent review of pharmacokinetic data and case reports demonstrated that although there may be an increased risk of low-dose MTX adverse effects in a small number of patients using an NSAID, penicillin, or proton pump inhibitor, the available evidence supports the use of these drugs in combination.²⁰

Pharmacists should continue to monitor for potential MTX adverse effects (symptoms and changes to laboratory parameters) as they normally would in practice. Factors that increase the risk of MTX adverse effects include renal dysfunction, hepatic impairment, hypoalbuminemia and age >70 years. The *Canadian Pharmacists Journal* recently published practice guidance for pharmacists on the therapeutic management of RA.²¹

Approach to embedding patient-centred care and promoting health literacy for better clinical outcomes

The therapeutic approach for RA continues to evolve. The Canadian Agency for Drugs and Technologies in Health is currently updating their previous 2010 review of the clinical evidence of benefits and harms for drugs used in the management of RA.²²

It is a complex therapeutic topic, made more challenging because of the small proportion of the population affected, reducing the frequency of patient interactions and so, perhaps, pharmacists' ease in counselling. We can easily review a product monograph and speak to DMARD side effects as part of our duty of care, recognizing potential harm as a valid concern of our patients. However, effectively communicating the benefits in addition to the risks is just as important, given the clear efficacy of DMARD therapy to reduce joint deformity and disability, decrease morbidity and mortality and improve function and thus quality of life. It's a balance.

Patients must also understand the risks of not receiving treatment. Sometimes less is more in starting the conversation—seeking to understand what they “heard” from their rheumatology care providers and giving patients a little information at a time to help clarify the risks of not treating the disease, along with the risks and benefits from the prescribed medications. This is especially

important with culturally and ethnically diverse populations.²³ Two models you could use are Kleinman's questionnaire²⁴ or Galanti's 4-C's of culture, which is a downloadable mnemonic provided at www.ggalanti.org/the-4cs-of-culture/ to help clinicians remember what questions to ask to obtain the patient's point of view.²⁵

It is a skill that needs practice and ultimately, we want to discover what motivates our patients to engage in self-care. Assisting our patients to make informed decisions about their health is our duty of care.

In addition, various subjective questionnaires to assess therapy adherence have been created, but there is no gold standard. The Compliance-Questionnaire-Rheumatology is a rheumatology-specific instrument.²⁶ Two other common adherence scales are the Morisky Adherence Questionnaire and the Medication Adherence

Report Scale.^{27,28} These scales perform well compared with semistandardized interviews, but some studies suggest they are unreliable when compared with electronically measured medication compliance.^{29,30}

What if your patient tells you they are taking all their pills, but the medication record shows late fills and the patient reports not doing well? Are they also missing their rheumatology care provider appointments and routine lab tests? Be aware of patients who show up infrequently.

Communicating about combination DMARD therapy can certainly be challenging in clinical practice because of time constraints, patient misinformation and our own lack of familiarity/comfort with the therapeutic area. Clear practitioner and patient information regarding the benefits and potential risks of DMARD therapy is provided at www.rheuminfo.com. ■

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