Drug-Induced Gastrointestinal and Hepatic Disease Associated with Biologics and Nonbiologic Disease-Modifying Antirheumatic Drugs

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KEYWORDS

• Drug-related ADRs and adverse reactions • Immunosuppressive agents
• Antirheumatic agents • Gastrointestinal diseases • Liver diseases • Mouth diseases
• Pancreatic diseases • Chemical and drug-induced liver injury

KEY POINTS

- Long-term methotrexate use is associated with hepatotoxicity and fibrosis.
- Azathioprine and other nonbiologic disease-modifying antirheumatic drug use is associated with a variety of unique hepatic, biliary, and pancreatic complications.
- Rituximab use is strongly associated with an increased risk of viral hepatitis B virus reactivation, although tumor necrosis factor-alpha inhibitors and other treatments also confer reactivation risk to lesser degrees.
- Tofacitinib and interleukin-6 inhibition use may increase the risk of gastrointestinal perforation events.
- Anti-interleukin-17 therapies have been associated with incident or worsening inflammatory bowel disease, although data are ambiguous.

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INTRODUCTION

The invention and discovery of various nonbiologic and biologic disease-modifying therapies have revolutionized the care of rheumatic and other autoimmune disease. Although the strides made in therapy are remarkable, the use of these agents, as with all therapies, confers risks in the form of adverse drug reactions (ADRs) (**Table 1**). These ADRs, defined by the World Health Organization as "a response to a drug which is noxious and unintended, and which occurs at doses normally used,"[1] include significant gastrointestinal ADRs, that is, "side effects." The authors briefly introduce and review the mechanism of action of disease-modifying therapies commonly used in the care of rheumatic disease. Frequently encountered and drug-specific gastrointestinal ADRs are discussed, including reviews of the primary literature describing these reactions. Guidelines and standard of care practices, where they exist, for screening, monitoring, and management of these reactions, are summarized.

CONVENTIONAL DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS

Methotrexate

High-dose intravenous formulations of methotrexate (MTX) were first used as a chemotherapeutic in cancer treatment in the 1940s. Lower dosing regimens via oral and subcutaneous routes were later pioneered and approved for use in psoriasis and rheumatoid arthritis (RA) in the 1960s and 1980s, respectively.[2] MTX is now one of the most widely used antirheumatic medications, used in a variety of inflammatory diseases. It is a folate antimetabolite, and mechanisms of action include inhibition of DNA synthesis, repair, and replication. Specifically, its antimetabolite effects are mediated via inhibition of dihydrofolate reductase and, therefore, purine synthesis. At lower doses typically used in the treatment of rheumatic diseases, this mechanism of action is less important; however, at these doses, MTX and its metabolite MTX-polyglutamate dephosphorylate extracellular adenine nucleotides. Through this effect, it is hypothesized that extracellular adenosine levels are increased, with downstream reductions in lymphocyte proliferation and production of cytokines, including tumor necrosis factor-alpha, interleukin-1 (IL-1), and IL-12.[3–5]

Hepatotoxicity

Hepatotoxicity associated with long-term oral MTX use in psoriasis was initially described in the 1960s. Early reports suggested rates of fibrosis of up to 14% to 50%, and 11% to 26% for clinical cirrhosis following several years of use.[6] At the time of early studies, cumulative MTX exposure was significantly higher than is typically used today, and daily dosing (rather than weekly) was common. In addition, folic acid supplementation (demonstrated to reduce hepatotoxicity[7]) was not commonly used at the time of early landmark studies. Concurrent alcohol use, viral hepatitis, and other uncontrolled factors may also have contributed to the very high rates of toxicity.

Pathologic changes to the liver seen with long-term MTX exposure include steatosis, stellate cell hypertrophy, and fibrosis. The mechanism of action of this toxicity is incompletely understood. Theories include prolonged accumulation of MTX polyglutamate and folate depletion.

Of note, later studies in the setting of RA suggest the incidence of advanced hepatocellular changes at much lower rates, approximately 5%.[8,9] In addition to the uncontrolled factors noted above in early studies, liver function monitoring protocols varied in this population when compared with the early psoriasis literature. It should also be