Miscellaneous Adverse Events with Biologic Agents (Excludes Infection and Malignancy)

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KEYWORDS

• Anti-tumor necrosis factor • Infliximab • Adalimumab • Golimumab
• Certolizumab pegol • Complications • Infusion reactions • Autoimmune disease

KEY POINTS

- The risks of nonmalignant, noninfectious complications secondary to anti-tumor necrosis factor (TNF) therapy are low.
- The most frequent complications are infusion reactions and injection site reactions.
- Autoantibodies are frequently found, but true drug-induced lupus erythematosus is rare.
- Paradoxic psoriasiform reactions to anti-TNF are being described more frequently and appear to be a class effect.
- Most complications do not require cessation of anti-TNF therapy.

INTRODUCTION

Anti-tumor necrosis factor-α (anti-TNF) agents are frequently used in the treatment of inflammatory bowel disease (IBD). Currently, there are 4 anti-TNF therapies that are Food and Drug Administration (FDA)-approved for moderate to severe IBD: infliximab and adalimumab for both Crohn disease and ulcerative colitis, golimumab for ulcerative colitis, and certolizumab pegol for Crohn disease. Although these agents are efficacious, they are associated with a low risk for adverse events, the most common of which are injection-site and infusion reactions. In most situations, the benefit of anti-TNF agents outweighs the rare risk of complications. For most noninfectious, nonmalignant adverse events, cessation of anti-TNF therapy typically leads to improvement or resolution of drug-induced complications.[1,2] In this article, the current knowledge

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Gastroenterol Clin N Am 43 (2014) 543–563
http://dx.doi.org/10.1016/j.gtc.2014.05.002 **gastro.theclinics.com**
0889-8553/14/$ – see front matter

regarding the noninfectious and nonmalignant toxicities associated with anti-TNF agents is summarized.

BODY

Infusion Reactions

Infusion reactions to infliximab can be categorized based on their timing, pathogenesis, and severity. Most reactions are acute, nonimmune, and mild-to-moderate. Infusion reactions are classified as acute or delayed based on the timing of onset in relation to the infusion. Acute infusion reactions develop within 24 hours of the infusion with most occurring during the infusion. Delayed infusion reactions develop more than 24 hours following the infusion, with most occurring 5 to 10 days after an infusion.[3] Several infusion reactions are likely related to the presence of antibodies against the anti-TNF compound. The main risk factor for the development of antibodies to infliximab (ATI) formation is the episodic dosing of infliximab. In contrast, concomitant therapy with immunosuppressive agents (eg, azathioprine, mercaptopurine, or methotrexate) decreases the risk of ATI formation, and similarly, lowers the risk of infusion reactions.[4,5]

Acute Infusion Reactions

Acute infusion reactions can be classified as allergic reactions, immunoglobulin E (IgE)-mediated type 1 anaphylactic reactions, or nonimmune, rate-related reactions. True anaphylactic reactions are very rare.[3] To determine the pathophysiology of infusion reactions to infliximab, Cheifetz and colleagues[3] studied a cohort of 11 patients who had a total of 14 acute infusion reactions. All patients had normal serum tryptase levels, and serum IgE levels were normal in the 7 cases in which they were measured, suggesting that these infusion reactions were not due to classical allergic type 1 IgE-mediated hypersensitivity.[6] Similarly, a Danish group found no anti-infliximab IgE in 20 cases following severe infusion reactions.[6]

Epidemiology

The prevalence of acute infusion reactions to infliximab varies widely in the literature, ranging from 3% to 20%.[3,7–11] In the Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) registry, 3% of infliximab infusions resulted in an acute infusion reaction, most of which were mild.[11] Similarly, Cheifetz and colleagues[3] and Colombel and colleagues[8] reported acute infusion reactions in 5% of patients at Mt Sinai Medical Center and 3.8% of patients treated at Mayo Clinic, respectively.

Classification and symptoms

Infusion reactions can also be classified based on their severity. Cheifetz and colleagues[3] developed a classification scheme based on symptoms (**Table 1**). In their cohort, most infusion reactions were classified as mild (51%), with 21% considered

Table 1
Classification of acute infusion reactions

Mild	Flushing, dizziness, diaphoresis, nausea, palpitations, hyperemia
Moderate	Chest pain, hypertension (>20 mm Hg increase in systolic blood pressure), hypotension, fever, urticaria, dyspnea, chills, rash
Severe	Hypertension (>40 mm Hg increase in systolic blood pressure), hypotension, significant dyspnea, bronchospasm, stridor, wheezing, rigors