Emerging Adverse Cutaneous Drug Reactions

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KEYWORDS

• Monoclonal antibody therapy • Cutaneous drug reaction • Infliximab • Etanercept • Adalimumab • Rituximab

KEY POINTS

- More than 2 decades have passed since the Food and Drug Administration approval of muromonab-CD3 (Orthoclone OKT3) ushered in the era of monoclonal antibody therapy for the treatment of human disease.[1]
- Despite having relatively favorable safety profiles overall, these drugs are not without potential side effects, some of which are occasionally severe enough to prompt discontinuation of the drug.[2]
- The market for tumor necrosis factor α (TNFα) inhibitors is currently occupied by 4 monoclonal antibodies (adalimumab, infliximab, certolizumab pegol, and golimumab) directed against the TNFα protein, and 1 TNF-receptor fusion protein (etanercept).

INTRODUCTION

The past several decades have seen the advent and rapidly expanding use of biological agents in the treatment of chronic disease states ranging from organ transplant rejection to rheumatoid arthritis and lymphoproliferative disorders. As increasingly large pools of patients have been enrolled in treatment protocols using these agents, physicians have become acquainted with both desired and adverse events associated with their use. Dermatologists frequently encounter patients affected by cutaneous drug reactions associated with the use of biological agents, and should therefore be familiar with the full range of side effects that have been reported in the literature. This review discusses these adverse cutaneous effects, their underlying mechanisms, and efforts to predict and minimize their occurrence.

ADVERSE REACTIONS TO MONOCLONAL ANTIBODIES

More than 2 decades have passed since Food and Drug Administration (FDA) approval of muromonab-CD3 (Orthoclone OKT3) ushered in the era of monoclonal antibody therapy for the treatment of human disease.[1] With the introduction of infliximab (Remicade), etanercept (Enbrel), and adalimumab (Humira) to inhibit activity of tumor necrosis factor α (TNFα), physicians augmented their armamentarium in the battle against autoimmune diseases such as rheumatoid arthritis (RA), Crohn disease, and psoriasis. Monoclonal antibodies directed against vascular endothelial cell growth factor (VEGF) (bevacizumab), ErbB2 (trastuzumab), and CD20 (rituximab) have joined the anti-TNFα agents as the most extensively prescribed drugs in this class, which together account for some of the

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Dermatol Clin 30 (2012) 695–730
http://dx.doi.org/10.1016/j.det.2012.06.016
0733-8635/12/$ – see front matter

top-selling biotechnology drugs. To date more than 20 monoclonal antibody therapies have been approved for use by the FDA.

Despite having relatively favorable safety profiles overall, these drugs are not without potential side effects, some of which are occasionally severe enough to prompt discontinuation of the drug.[2] Although adverse reactions affecting the skin are usually tolerated sufficiently to allow continued use, they can be distressing to the patients, who will often seek the attention of their physician(s). As a consequence it is important that rheumatologists and dermatologists who might encounter these adverse reactions in their clinical practice be familiar with the incidence and, when known, the pathogenesis of these reaction processes. In many cases, the adverse reactions fall under the rubric of a "class effect" and can therefore be expected from any of the agents using the same mechanism of action, whereas in other cases there appear to be reaction patterns that are specific to individual agents that are rare or unreported with remaining members of the class. This article reviews the reaction patterns observed across the broad range of biologics in use currently, while discussing possible underlying mechanisms and efforts to minimize their occurrence.

TNFα Inhibitors

The market for TNFα inhibitors is currently occupied by 4 monoclonal antibodies (adalimumab, infliximab, certolizumab pegol, golimumab) directed against the TNFα protein, and 1 TNF-receptor fusion protein (etanercept). These medications are used to treat a broad range of autoimmune conditions including psoriasis, RA, Crohn disease, ankylosing spondylitis, and various off-label conditions.

Injection-site and infusion reactions

The most common dermatologic complaint associated with the use of monoclonal antibodies is the injection-site reaction defined by edema, erythema, pruritus, and/or pain. The incidence of injection-site reactions ranges from 3% to 49%, and appears to be a function of both the specific anti-TNFα agent used and the underlying disease process.[3–10] These studies indicate that RA patients, especially those treated with etanercept, are at significantly increased risk of developing injection-site reactions in comparison to patients with psoriasis or Crohn disease. While patients typically experience a decrease in frequency and severity of injection site reactions over the course of treatment, worsening reactions with continued administration are reported.[3,6,11,12] Histologically, infiltrates of $CD8^+$ T cells characterize the primary and recurrent reactions, consistent with a type IV delayed hypersensitivity reaction.[11]

Infusion reactions include pruritus, urticaria, chills/fevers, anaphylaxis, and vital-sign alterations that occur, by definition, within 2 to 24 hours following infusion of the drug. Rates of infusion reactions with TNFα inhibitors range from 3% to 24%, depending on the trial and the disease under treatment.[13–16] Pretreatment with corticosteroids in an effort to reduce infusion reactions appears to have little value, and may even have the paradoxic effect of increasing rates of infusions reactions.[17–21] Instead, regular administration without prolonged interdose intervals seems to be the most effective means of preventing antibody formation leading to infusion reactions.[22,23]

Infections

Numerous case reports have surfaced that suggest an association between infections and the use of TNFα inhibitors.[15,24,25] Both systemic and cutaneous infections have been observed,[26] suggesting that immunosuppression related to anti-TNFα therapies renders patients more susceptible to infectious pathogens. However, RA patients, one of the major patient demographics receiving TNFα inhibitors, exhibit higher infection rates compared with the general population, which may account for some of the observed infectious complications.[27] That said, comparison between RA patients using anti-TNFα antibodies and those prescribed other disease-modifying antirheumatic drugs (DMARDs) revealed an adjusted relative risk of 4.28 (95% confidence interval, 1.06–17.17).[28] Lee and colleagues[24] reported 13 patients (of 150 in total) who developed cutaneous infections while on infliximab, adalimumab, or etanercept, which included pityriasis versicolor, tinea corporis, impetiginized eczema, herpes simplex, and *Staphylococcus aureus*.

Fungal, bacterial, and viral infections have all been reported at higher rates in patients using anti-TNFα agents, but none severe enough to require hospitalization.[25] A study of 500 patients using infliximab described 48 patients with infectious events including cases of abscesses, upper respiratory tract infections, pneumonia, cellulitis, shingles, chicken pox, genital herpes, and candidal onychomycosis.[15] As regards viral infections, a prospective cohort study comparing monoclonal anti-TNFα antibodies, etanercept, and DMARDs indicated a statistically significant increased risk for herpes zoster specific to the monoclonal agents, although the investigators considered that the risk fell below the level of clinical significance.[29] Psoriasis patients treated with etanercept also experienced an increased incidence of