Subcutaneous Injectable Drugs Hypersensitivity and Desensitization

Insulin and Monoclonal Antibodies

Sevim Bavbek, MD[a,*], Min Jung Lee, MD[b]

KEYWORDS

• Adalimumab • Etanercept • Omalizumab • Insulin • Injection site reactions
• Systemic hypersensitivity reactions • MoAbs • TNF-α inhibitors

KEY POINTS

- Etanercept and adalimumab are valid alternatives in the treatment of refractory inflammatory and autoimmune diseases, but local and systemic hypersensitivity reactions (HSRs) may prevent their use in sensitized patients.
- Rapid subcutaneous desensitization in patients with local and systemic HSRs to anti-tumor necrosis factor-α seems to be an effective treatment strategy.
- Rare incidences of systemic HSRs to insulin may be managed through desensitization.
- The mechanism of HSRs to omalizumab is not well-understood and desensitization has an unclear role for this agent.

TUMOR NECROSIS FACTOR-α INHIBITORS

Tumor necrosis factor-α (TNF-α) is one of the central mediators of inflammation, and TNF-α inhibitors are useful in certain "refractory" cases of inflammatory and autoimmune disorders in which TNF-α plays a major role in pathogenesis.[1] Today, 5 registered TNF-α antagonists—namely, infliximab, etanercept, adalimumab, certolizumab, and golimumab—are available on the market.[2] These agents are generally well-tolerated and safe, but they can induce a wide variety of adverse reactions. Among TNF-α inhibitor–induced adverse reactions, hypersensitivity reactions (HSRs), local

The authors do not have any commercial or financial conflict of interest and any funding sources relevant to this article.
[a] Division of Immunology and Allergy, Department of Chest Diseases, Ankara University, School of Medicine, Mamak Street, Ankara 06100, Turkey; [b] Division of Allergy and Immunology, UT Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390, USA
* Corresponding author.
E-mail address: bavbek@medicine.ankara.edu.tr

Immunol Allergy Clin N Am ■ (2017) ■–■
http://dx.doi.org/10.1016/j.iac.2017.06.001
0889-8561/17/

or systemic, are infrequent; although the true incidence is unknown.[3] We limit our discussion to 2 injectable TNF-α antagonists, etanercept and adalimumab.

Etanercept

Etanercept is a fusion protein that binds irreversibly and competitively to membrane and circulant TNF-α molecule, and prevents them from binding to their receptors on immune effector cells. Etanercept is used in the treatment of multiple rheumatologic conditions such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and juvenile idiopathic arthritis; however, it may cause local and less commonly systemic HSR, limiting its use in sensitized patients.[4,5]

Adalimumab

Adalimumab is a recombinant, fully human IgG1 monoclonal antibody against TNF-α and is also indicated for the treatment of several chronic inflammatory diseases.[6] Adalimumab, as a fully humanized anti–TNF-α inhibitor, has not been expected to cause immune-mediated reactions, but has been infrequently associated with HSR.[7,8]

Clinical Presentations of Hypersensitivity Reactions to Etanercept and Adalimumab

Although generally well-tolerated and safe, a variety of adverse effects including HSR are increasingly being recognized in the setting of TNF-α inhibitors. The most common reactions with etanercept and adalimumab are local infusion and injection reactions, which are induced by subcutaneous biologic agents, are called injection site reactions (ISR), and are characterized by erythema, swelling, itching, or infiltrated plaques[7,9,10] (**Fig. 1**A, B). In clinical trials, ISRs have been found in up to 37% of etanercept-treated patients compared with 10% of the placebo-treated patients.[11,12] Like etanercept, in placebo-controlled clinical trials, an ISR was reported in between 3.2% to 20% of the adalimumab-treated patients compared with 1.8% to 14% of the placebo-treated patients.[13] These reactions may occur within a few minutes (immediate reactions) or later (delayed reactions) and generally were mild to moderate in severity, lasted 1 to 5 days, and occurred during the first month of treatment.[14,15]

In contrast, both immediate and delayed types, local and systemic immune-mediated HSR have been described with etanercept and adalimumab.[7,9,16] Both etanercept and adalimumab-induced immediate systemic HSR such as pruritus, urticaria, angioedema, and anaphylaxis have been reported rarely in the medical literature.[10,17–20]

In addition, delayed-type HSRs, thromboembolic events, serum sickness–like reactions, and cutaneous reactions, including maculopapular rash, leukocytoclastic vasculitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have also described with the use of etanercept and adalimumab. In cases with severe skin reactions, the majority of the affected subjects were female and were being treated for rheumatoid arthritis.[12,21]

Underlying Mechanisms and Diagnostic Approach to Local and Systemic Hypersensitivity Reactions to Etanercept and Adalimumab

The mechanisms underlying HSR to etanercept and adalimumab have not been extensively studied. However, immediate HSRs to biologic agents have been closely related to the development of antidrug antibodies, both IgE and non-IgE isotypes.[6,22] Prick and intradermal skin tests with early readings have been used to detect the presence and biological activity of serum IgE to relevant biologic agents. In this regard, a few attempts have been done with skin testings to etanercept and adalimumab. Prick testing have been performed using commercially available etanercept and