Clinical, Histological, and Immunophenotypic Characteristics of Injection Site Reactions Associated With Etanercept

A Recombinant Tumor Necrosis Factor α Receptor: Fc Fusion Protein

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Objective: To study injection site reactions (ISRs) associated with etanercept therapy.

Design: Retrospective chart review, along with prospective analysis of selected patients experiencing ISRs associated with etanercept therapy.

Setting: Academic rheumatology/immunology unit and dermatology clinic.

Subjects: Patients with rheumatoid arthritis, juvenile rheumatoid arthritis, inflammatory seronegative arthritis, psoriatic arthritis, psoriasis, or inflammatory bowel disease.

Interventions: Skin biopsy specimens were taken from selected patients experiencing ISRs.

Main Outcome Measures: Incidence of ISRs and histological and immunophenotypic analysis of ISRs in 3 patients undergoing prospective study.

Results: Twenty-one (20%) of 103 of all patients receiving etanercept reported ISRs, all within the first 2 months of inception of therapy. The reactions occurred 1 to 2 days after the last injection and resolved within a few days. Moreover, eventual waning of reactions was observed, with none proving to be dose limiting. Histological examination of all biopsy specimens showed an inflammatory infiltrate composed of predominantly lymphoid cells and some eosinophils, in a perivascular cuffing pattern, without evidence of leukocytoclastic vasculitis. The infiltrating lymphoid cells were predominantly activated mature (HLA-DR+/CD3+/CD4−/CD8+) cytotoxic T lymphocytes, with a small number of CD4+ cells. A biopsy specimen from a recall ISR showed strong HLA-DR expression by epidermal keratinocytes.

Conclusions: Injection site reactions associated with etanercept therapy are common, and may be an example of a T-lymphocyte–mediated delayed-type hypersensitivity reaction, with waning over time due to eventual induction of tolerance.

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Novel biological therapeutics that target specific cytokines are emerging as agents that are capable of controlling inflammation in autoimmune disorders. These agents have potentially fewer long-term adverse effects than corticosteroids or nonsteroidal anti-inflammatory and disease-modifying antirheumatic drugs. In 1998, the US Food and Drug Administration approved one of the most current disease-modifying antirheumatic drug treatments, etanercept, for refractory rheumatoid arthritis (RA). In June 2000, the indication for etanercept was expanded to include first-line therapy for reducing signs and symptoms and delaying structural damage in patients with moderately to severely active RA. Moreover, a preliminary analysis of randomized clinical trials of etanercept for psoriatic arthritis and psoriasis demonstrated that patients treated with etanercept experienced improvement in the signs and symptoms of their disease and an increase in their functional ability compared with control subjects.1,2

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Etanercept is a recombinant tumor necrosis factor α (TNF-α) soluble receptor fused to the Fc fragment of IgG2. It acts as a potent competitive inhibitor of TNF-α. Although the etiology of RA has not been elucidated, TNF-α—a proinflammatory cytokine produced by macro-

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In controlled trials, injection site reactions (ISRs) developed in 42% of patients treated with etanercept. These reactions are the most common adverse effect of this treatment. The pathogenesis of these ISRs is unknown. All ISRs were initially described as mild to moderate (erythema and/or pruritus, pain, or edema) and generally did not necessitate discontinuation of therapy. The first 2 months of etanercept therapy. The median number of injections at the time of onset of the ISR was 4 (range, 3-8). The ISRs occurred approximately 1 to 2 days after the last injection and resolved within 2 to 3 days.

Patients who experienced ISRs generally occurred in the first month and subsequently decreased in frequency. Overall, etanercept therapy is well tolerated, but there have been reports of unusual complications. Brion et al. reported development of discoid lupus and necrotizing vasculitis in patients with RA who were receiving etanercept therapy. Smith and Skelton recently reported a rapid onset of 1 or more cutaneous squamous cell carcinomas in 5 patients with RA after starting etanercept therapy. Further evaluation is needed to determine whether a causative relation exists between TNF-α antagonism and these adverse events.

Considering the newly expanded indication for etanercept therapy for RA and its potential future uses for treatment of primary dermatologic and other inflammatory conditions, it is important to augment the body of knowledge about etanercept ISRs and to elucidate their dermatopathologic and immunologic features.

Herein, we describe the clinical, histologic, and immunophenotypic aspects of ISRs associated with etanercept therapy. These ISRs represent the most common adverse effect of etanercept; however, they do not appear to be dose limiting. Furthermore, our analyses suggest that etanercept ISRs may be an example of a T-lymphocyte-mediated delayed-type hypersensitivity (DTH) reaction, with eventual induction of tolerance.

MATERIALS AND METHODS

We performed a retrospective review of medical records of patients receiving etanercept injections since January 1, 1999, at Strong Memorial Hospital Rheumatology and Immunology Unit, Rochester, NY. We focused only on patients currently treated with etanercept. We collected the occurrence, description, and duration of ISRs and the patients’ age, sex, type of disease, and list of current medications.

Three patients with RA were chosen to be the subjects of a detailed analysis of their ISRs (histological and immunochemical analyses) (Table 1). These patients met the study specifications (ie, an active ISR) and gave informed consent. Skin biopsy specimens were taken from the ISRs.

SKIN BIOPSY SPECIMENS

Two 4-mm punch biopsy specimens were obtained from each patient using sterile, standard technique. One of the biopsy specimens was frozen in optimal cutting temperature compound at −70°C until the time of study; the other biopsy specimen was fixed in formaldehyde and then embedded in paraffin for preparation of 4-µm sections for hematoxylin-eosin or Giemsa staining.

IMMUNOTYPING FROZEN TISSUE

We performed 1- and 2-step immunofluorescent staining of frozen tissue using standard techniques. Isotype-matched, mouse antirat (MAR, clone 18.5) antibody with irrelevant specificity served as a negative control for nonspecific background tissue staining in all cases. Frozen sections of surgical tonsil specimens served as a positive control for tissue staining with monoclonal antibodies in all cases. The following monoclonal antibodies with specificity against defined antigens were used to stain skin biopsy specimens: anti-CD4 (helper T lymphocytes), CD8 (cytotoxic T lymphocytes [CTL]), CD1a (Langerhans cell marker), CD14 (endotoxin receptor on human monocytes) (Diace AS, Oslo, Norway); and anti-HLA-DR (BD Pharmingen, Mountain View, Calif). Photomicrographs were taken using a fluorescent microscope (Eclipse E800; Nikon, Tokyo, Japan) equipped with a digital camera.

phages and T lymphocytes—contributes to the mechanism of synovitis and joint destruction. Etanercept therapy, administered in twice weekly subcutaneous injections, relieves joint pain and swelling and morning stiffness.

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Patients who experienced ISRs generally responded well to treatment with etanercept. None of the reactions resulted in interruption or discontinuation of therapy. On average, marked resolution of symptoms of arthritis was attained. Only periodic symptoms of joint pain, inflammation, and stiffness were experienced af-
The skin biopsy specimen from the recall ISR exhibited strong staining of epidermal keratinocytes with anti–HLA-DR monoclonal antibody, indicating class II major histocompatibility complex expression by keratinocytes (Figure 2).

There also were rare CD1a+ cells in the epidermis and the dermis, presumably epidermal and migrating Langerhans cells. There were rare CD14+ cells, consistent with monocytes. No other pertinent findings were identified.

COMMENT

In clinical trials, ISRs were reported as the most common adverse effect of etanercept. Therapy with other immunomodulating injected proteins has been associated with clinically and histologically heterogeneous ISRs (Table 2). In this retrospective study of patient medical records, 21 (20%) of all 103 patients receiving etanercept injections, regardless of the underlying disease, reported ISRs. This number is lower than the 42% reported in the clinical trials.3,9 The reason for the lower incidence of ISRs in our cohort may be related to the retrospective nature of our study, in which most patients were not directly examined for ISR; medical records were reviewed for documentation of an ISR, and in some instances, patients were interviewed. Very mild ISRs may not have been noted by patients and therefore not documented in the medical records or during interviews.

In 8 (40%) of 20 patients with any ISR in our study, ISRs developed at previous injection sites after the last injection (recall ISR). Despite the common use of injected immunomodulators and their associated ISRs (Table 2), recall ISRs have not been associated with any of these therapies until etanercept came into use. Etanercept recall ISRs bear some similarity to fixed-drug eruptions (FDEs), a distinct form of a drug allergic reaction in which characteristic skin lesions recur at the same location each time an offending agent is ingested.10 Clinically, FDEs present as solitary or multiple erythematous macules that often evolve into edematous plaques and may become bullous in intermediate stages. Patients occasionally experience localized pruritus or burning. Any

Table 1. Summary of Immunohistochemical Analysis of Skin Biopsy Specimens From ISR*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Type of ISR (Time of Onset)</th>
<th>CD3</th>
<th>CD4</th>
<th>CD8</th>
<th>CD14</th>
<th>CD1a</th>
<th>HLA-DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1†</td>
<td>Primary (fifth injection)</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>Rare</td>
<td>Rare</td>
<td>epidermis +; dermis +</td>
</tr>
<tr>
<td>2‡</td>
<td>Primary (third injection)</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>Rare</td>
<td>Rare</td>
<td>epidermis +; dermis +</td>
</tr>
<tr>
<td>3§</td>
<td>Recall (third injection)</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>Rare</td>
<td>Rare</td>
<td>epidermis +; dermis +</td>
</tr>
</tbody>
</table>

*ISR indicates injection site reaction; 1 plus sign, few cells, strong staining intensity; 2 plus signs, intermediate number of cells, strong staining intensity; and 3 plus signs, many cells, strong staining intensity.
†A 69-year-old white woman with a 32-year history of deforming erosive rheumatoid arthritis (RA) refractory to treatment with minocycline hydrochloride, azathioprine sodium, gold sodium thiosulfate, methotrexate, sulfasalazine, and hydroxychloroquine sulfate before starting etanercept therapy. The ISR was not dose limiting. Etanercept controls this patient’s symptoms very well.
‡A 64-year-old white woman with a 30-year history of deforming RA. She was glucocorticosteroid dependent, with other failed immunosuppressive therapies (methotrexate, penicillamine, azathioprine, gold, and cyclosporine) before starting etanercept therapy. The ISR was not dose limiting. Etanercept controls this patient’s symptoms very well.
§A 47-year-old white woman with a 15-year history of RA, refractory to treatment with methotrexate, hydroxychloroquine, and nonsteroidal anti-inflammatory drugs. The primary and recall ISRs were not dose limiting. Etanercept controls this patient’s symptoms very well.

**Histopathologic Findings**

Skin biopsy specimens were taken at the peak of ISR eruption, approximately 24 hours after an etanercept injection. The character and severity of the pathologic changes noted in the biopsy specimens from all 3 patients (2 patients with primary and 1 patient with recall ISR) were remarkably similar (Figure 2). Histological changes were noted primarily in the dermis.

There was a mild edema and vasodilation in the reticular dermis, along with a mild to moderate mononuclear cell infiltrate in a perivascular cuffing pattern. Giemsa staining demonstrated that the inflammatory infiltrate also contained a moderate number of eosinophils, some of which were degranulating. There were also small numbers of neutrophils and macrophages admixed in the infiltrate.

**Immunohistochemical Analysis of Skin Biopsy Specimens**

We determined the immunophenotypes of the inflammatory infiltrate in skin biopsy specimens from the 3 patients experiencing primary or recall ISRs. Enhanced cellular HLA-DR expression was noted in the dermis, specifically in cells infiltrating in a perivascular pattern. This suggested an increase in HLA-DR expression by endothelial cells and the perivascular infiltrate. To further investigate this phenomenon, the biopsy specimens were stained with anti-CD3 or anti-CD4 or anti-CD8 phycoerythrin-conjugated monoclonal antibodies. Most of the cellular infiltrate was composed of cells with an HLA-DR+/CD3+/CD4+/CD8− phenotype, indicating an activated mature CTL lineage. However, some of the infiltrate expressed CD4 (an HLA-DR+/CD3+/CD4+/CD8− phenotype), consistent with a mature helper T-lymphocyte lineage.

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part of the skin or mucous membranes may be involved, and healing of the lesions occurs in 10 to 14 days.

The precise mechanism by which therapeutic agents generate FDEs is unknown. A current hypothesis suggests that the drugs act as haptons, binding some unknown extracellular or intracellular epidermal protein components or receptors. The CD8\(^+\) CTLs seemed to play a major role in initiating the flare-up reaction and pre-

Figure 1. Clinical features of etanercept injection site reactions (ISRs). A, Patient 1 with mild primary ISR. After the third subcutaneous injection of etanercept, an approximately 3-cm erythematous reticulated patch with some mild purpura appeared at the site of the most recent injection on the left anterior thigh. B, Patient 2 with moderately severe primary ISR (described in Table 1). After the third subcutaneous injection of etanercept, an approximately 7-cm erythematous, indurated annular plaque appeared at the site of the most recent injection on the left lateral arm. C, Patient 2 with moderately severe recall ISR. After the third subcutaneous injection of etanercept, 2 approximately 7.5-cm erythematous, indurated annular plaques appeared at 2 previous injection sites on the abdomen.
serving the cutaneous memory function of the FDE.\textsuperscript{18} The CD8\textsuperscript{+} T lymphocytes were the predominant cell type in both primary and recall ISRs (Table 2). Although our immunohistochemical analysis of primary and recall ISRs showed predominately CD8\textsuperscript{+} T cells, the inflammatory cell composition may evolve over time. At earlier time points (before 24 hours), other effector cells such as CD4\textsuperscript{+} T lymphocytes may be more prominent.

On activation with interferon $\gamma$ (INF-$\gamma$), human keratinocytes can express the genes for all the known molecules necessary for the production of major histocompatibility complex class II peptide complexes, and display peptide-loaded HLA-DR on the cell surface.\textsuperscript{20} In this context, it is not surprising that the skin biopsy specimen from the recall ISR exhibited strong HLA-DR expressivity of epidermal keratinocytes. Recall ISRs are likely to represent a more vigorous, generalized hypersensitivity reaction in an allergic host, and primary ISRs may represent a localized, primary hypersensitivity reaction. This may explain why keratinocytes in the recall, but not the
primary, ISRs expressed HLA-DR, since secondary immune reactions tend to be more vigorous than primary reactions. Comparative studies of a larger number of recall and primary ISRs will clarify this.

A variety of human skin disorders with lymphoid infiltrates are associated with keratinocyte HLA-DR expression, eg, graft-vs-host disease, allergic contact dermatitis, tuberculosis reactions, and lichen planus. Since IFN-γ has been reported to produce some of the manifestations of type IV DTH, to be a potent stimulator of lymphocyte migration into the skin, and to be a major mediator of lymphocyte recruitment into DTH, keratinocyte HLA-DR expression in a recall ISR suggests a cutaneous DTH response.

Since we demonstrated that the perivascular infiltrate of etanercept ISRs consisted primarily of mature activated CTLs, in some cases, type IV hypersensitivity reactions can also involve CD8+ T lymphocytes. The CD8+ T lymphocytes are now recognized as mediators of DTH reactions in allergic contact dermatitis, drug eruptions, asthma, and autoimmune diseases. In the past, this inflammatory effector capability of CD8+ CTLs was rarely recognized; however, substantial data now exist to indicate that these diseases may be mediated by CD8+ DTH.

The ensuing CD8+ T-lymphocyte response illustrates the role of CD8+ T-lymphocyte DTH mechanisms in allergic contact dermatitis, asthma, drug eruptions, and autoimmune diseases. Similar to the DTH reactions mediated by CD4+ T lymphocytes, each of the response phases in CD8+ T-cell–mediated DTH reactions takes several hours; therefore, the mature response also appears only 24 to 48 hours after challenge. This is in contrast to an IgE-mediated (type I) allergic response, which would be expected to have an immediate phase that occurs within several minutes after injection and is associated with a wheal-and-flare skin reaction and, potentially, systemic anaphylaxis. The ISRs seen after injection of etanercept usually take several hours to develop, and no patients have experienced anaphylactoid symptoms.

Although the exact data on the number of ISRs experienced by each patient were not recorded for this study, all but 1 of the 21 patients with ISRs stopped experiencing ISRs with continuing etanercept therapy. Waning of ISRs has been described with other subcutaneously injected protein drugs, such as interferon alpha. Most patients (79%) receiving subcutaneous interferon beta injections experience ISRs during the first 3 months, whereas this number decreases to 47% in the second 6 months of therapy. If, as we suggest, the ISRs to etanercept are immune mediated, then the decrease in ISRs over time may be due to desensitization or acquired tolerance. Subcutaneous administration of protein pollens (eg, grass pollen) is known to induce tolerance and decrease the size of the early and late cutaneous responses. Thus, in a double-blind, placebo-controlled trial of immunotherapy with subcutaneous injections of a standardized pollen extract in 40 adults, clinical improvement was accompanied by a decrease in the severity of the late-phase skin responses. This immunotherapy was associated with suppression of allergen-induced T-lymphocyte infiltration, suggesting that it may work through induction of T-cell tolerance. Recruitment of CD8+ T cells, however, was not influenced by treatment in that study.

Irritant contact dermatitis (ICD) may be a cause of etanercept ISRs. Skin irritation could result from the high concentration of etanercept (25 mg injected in a 1-mL volume), or the agent could be one of the components of the delivery vehicle (eg, mannitol, sucrose, and tromethamine). Irritant contact dermatitis may be defined as a nonimmunologic inflammatory reaction of the skin to an external agent. The clinical and histological expression of ICD is quite variable and may be indistinguishable from the allergic type. Various mediators, including interleukin 1 (IL-1), IFN-γ, histamine, prostaglandins, leukotrienes, and others have been implicated in ICD. Among these, leukotriene B4 is chemotactic and stimulates CD8+ T lymphocytes, and also can augment interleukin 1, IFN-γ, and prostaglandin release from monocytes. Irritant contact dermatitis reactions may exhibit a waning phenomenon called hardening or tachyphylaxis. Hardening has not been studied extensively, despite its widespread occurrence in many cases of ICD induced by various chemical and physical agents. The skin becomes slightly erythematous and hyperkeratotic from frequent contact with an irritant, and, eventually, a high irritant concentration can be tolerated. If the hardening stimulus is withdrawn, the skin reactivity returns to its previous level. Hardening appears to be an irritant-specific phenomenon, because the reactivity to other irritants is not decreased and may even be increased. Thus, hardening to ICD due to etanercept may be an alternate explanation for waning of etanercept ISRs with time.

CONCLUSIONS

We have described the clinical, histological, and immunophenotypic aspects of ISRs associated with etanercept therapy. These ISRs represent the most common ad-

**Table 2. Clinical Trial Incidence and Characteristics of ISRs Associated With Other Selected Immunomodulating Injected Proteins**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Reaction</th>
<th>Incidence, No. (%)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α</td>
<td>Local erythema and induration</td>
<td>16/16 (100)</td>
<td>Varney et al²</td>
</tr>
<tr>
<td>IFN-α</td>
<td>Local erythematous ISRs</td>
<td>59/203 (29)</td>
<td>Rycroft et al¹³</td>
</tr>
<tr>
<td>IFN-β</td>
<td>Injection site erythema, swelling, pruritus, or bruising</td>
<td>27/30 (90)</td>
<td>Yang et al¹⁴</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Injection site necrosis with histological evidence of LCV in some biopsy specimens of lesions</td>
<td>6/124 (5)</td>
<td>Hoffman-LaRoche Inc¹⁵</td>
</tr>
<tr>
<td></td>
<td>Injection site erythema or tenderness</td>
<td>9/63 (14)</td>
<td>Logun-Clubb and Stacy¹⁷</td>
</tr>
</tbody>
</table>

*ISR indicates injection site reaction; TNF-α, tumor necrosis factor α; IFN-α, interferon α; and LCV, leukocytoclastic vasculitis.*
verse effect of etanercept; however, they do not appear to be dose limiting. Furthermore, we presented evidence suggesting that etanercept ISRs may be an example of a T-lymphocyte–mediated DTH reaction, with eventual induction of tolerance. Physicians should be familiar with this complication of etanercept therapy, as the indications for this medication are likely to expand to include psoriatic arthritis, psoriasis vulgaris, and other autoimmune diseases. Clinical trials for etanercept use in psoriatic arthritis and psoriasis are already under way at multiple centers across the United States.

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