Leukocytoclastic Vasculitis Associated with Tumor Necrosis Factor-α Blocking Agents

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ABSTRACT. ***Objective.*** To describe the clinical features of leukocytoclastic vasculitis (LCV) associated with the use of tumor necrosis factor-α (TNF-α) blockers.

Methods. The Adverse Events Reporting System (AERS) of the US Food and Drug Administration (FDA) was queried for reports of patients who developed LCV during or after starting etanercept or infliximab from date of approval of each agent through September 6, 2002.

Results. Thirty-five cases of LCV were identified, 20 following etanercept administration and 15 following infliximab administration. Seventeen of the 35 (48.5%) were biopsy-proven cases and the others had skin lesions that were clinically typical for LCV. Twenty-two of 35 (62.8%) patients had complete or marked improvement of skin lesions upon stopping the TNF-α blocker. Three patients who had received etanercept had continuing lesions despite discontinuation of the drug; one of these patients improved when switched to infliximab. One patient who received infliximab was reported to have continuing lesions despite discontinuation of the drug and treatment with prednisone and antihistamines. Six patients experienced a positive rechallenge (recurrence of LCV on restarting therapy with a TNF-α blocker) and 3 patients a negative rechallenge phenomenon. LCV lesions improved in patients despite continuing use of concomitant medications reportedly associated with LCV.

Conclusion. Therapy with TNF-α blocking agents may be associated with the development of LCV. Skin lesions improved on discontinuation of anti-TNF-α therapy in most patients. Other causes of LCV should be excluded, and evaluation for systemic involvement with appropriate investigations is recommended. (J Rheumatol 2004;31:1955–8)

Key Indexing Terms:
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INFLIXIMAB

Tumor necrosis factor-α (TNF-α) is an important mediator of inflammation and has been reported to have potent disease-modifying effects in several immune-mediated diseases including rheumatoid arthritis (RA)[1-3], other connective tissue disorders[4-6], and Crohn's disease[7,8]. Etanercept (Enbrel, Immunex, USA), a p75 tumor necrosis factor receptor (TNFR) fusion protein conjugated to the Fc region of human IgG immunoglobulin, is administered as a subcutaneous injection twice weekly. Infliximab (Remicade, Centocor, USA), a chimeric monoclonal antibody against TNF-α, is administered as an intravenous infusion. Both agents have been reported to be safe and effective in the treatment of RA[2,3]. Etanercept has been approved by the US Food and Drug Administration (FDA) for the treatment of juvenile RA and psoriatic arthritis (PsA). Infliximab is also approved by the FDA for the treatment of refractory Crohn's disease[7]. There have been several reports of various adverse events associated with these drugs including leukocytoclastic vasculitis (LCV)[9-11]. LCV is a small-vessel vasculitis involving dermal postcapillary venules. The disorder may be associated with numerous etiologies such as infection, cryoglobulinemia, drugs, malignancy, and a variety of autoimmune diseases. Drugs cause roughly 10% of the cases of LCV[12]. Patients usually present with palpable purpura, typically on the lower extremities, accompanied sometimes by abdominal pain, arthralgia, and renal involvement. The skin lesions can evolve into vesicles, nodules, ulcerations, hemorrhagic bullae, and necrosis[13]. Other manifestations include urticaria, bronchospasm, asthma, eosinophilia, and drug fever[12]. Possible pathogenetic mechanisms include antigen-antibody interactions, direct drug toxicity on vessel walls, autoantibodies reacting with endothelial cells, or cytokine-mediated reaction to the vascular endothelium associated with interferon-γ and interleukin 6 or induction of

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autoantibodies such as antineutrophil cytoplasmic antibody (ANCA)[13].

We describe a series of patients who developed new onset LCV or worsening of preexisting LCV while undergoing therapy with the TNF-α blocking agents etanercept and infliximab.

MATERIALS AND METHODS

The FDA's Adverse Events Reporting System (AERS) is a database consisting of reports of adverse events related to approved drugs and biologic products. AERS encodes descriptions of adverse events using the *Medical Dictionary for Regulatory Activities* (MedDRA 4.0), an international classification system of adverse events, diagnoses, and signs/symptoms. Using several search terms (Table 1), all reports received by the FDA from date of approval for each drug (for etanercept, November 2, 1998; for infliximab, August 24, 1998) through September 6, 2002, were queried for possible cases of LCV. The individual adverse event reports were evaluated to determine whether they were consistent with LCV. In this case series cutaneous necrotizing vasculitis was considered to be synonymous with LCV. In cases where a biopsy was not performed or was not diagnostic of LCV, we assessed the description of the clinical presentation of lesions for the presence of palpable purpura with or without accompanying systemic symptoms.

RESULTS

Thirty-five patients were identified as having developed clinical features of LCV, 20 patients following etanercept administration and 15 following infliximab administration (Table 2).

The vast majority of patients were female (29/35), with an age range of 13 to 75 years. Duration of disease reported in 5 RA patients taking etanercept ranged from 18 to 27 years. The disease duration was reported in only one patient with Crohn's disease taking infliximab and was 2 years. The median time from the start of etanercept to the onset or worsening of vasculitic skin lesions was 28 weeks (range 2 to 103 wks). We were unable to determine this for infliximab because of the different dosing schedules used for different diseases and lack of exact dates in the reports. In 15 of 35 patients, lesions initially appeared on the lower extremities and then became diffuse; the location of the initial lesion was not noted in the other patients. In 3 etanercept-treated patients, lesions were reported to start at the injection site and spread; 2 patients were reported to have a positive antinuclear antibody (ANA) titer. Other skin lesions that were described included urticaria, bullae, petechiae, and nodules. Systemic symptoms (number of patients in parentheses) reported along with LCV included arthralgias (3), altered mental state (1), fatigue (1), myalgias (1), malaise (1), pedal edema (1), fever (2), peripheral neuropathy of sensory-motor type (1), cerebrovascular accident (1), abdominal pain (1), pleuritic pain (2), pericardial effusion (1) and hematuria (1). Two patients with RA taking etanercept and one Crohn's disease patient taking infliximab were noted to have evidence of systemic involvement. Seventeen of the 35 diagnoses (48.5%) were biopsy-proven, of which all except one (ankylosing spondylitis patient taking infliximab) were diagnoses of RA. In the remaining patients the diagnosis was based on the reported physical examination findings of skin lesions that were clinically typical for LCV. Twenty-two of 35 patients had complete or marked improvement of skin lesions upon stopping treatment with TNF-α blocking agents; 13 of these were biopsy-proven. Skin lesions in 3 patients who received etanercept remained unchanged despite discontinuation of the drug. Of these 3 patients, one improved upon being switched to infliximab. One patient who had received infliximab had ongoing lesions despite discontinuation of drug. Six patients (5 taking etanercept and one infliximab) experienced recur-

Table 1. Search terms used in the Adverse Events Reporting System search.

Application site bruising
Ecchymosis
Gangrene NOS
Hemorrhagic subcutaneous
Hemorrhagic subepidermal
Henoch-Schonlein purpura
Idiopathic capillaritis
Idiopathic thrombocytopenic purpura
Increased tendency to bruise
Leukocytoclastic vasculitis
Nodular vasculitis
Petechiae
Purpura NOS
Skin vasculitis NOS
Vascular purpura
Vascular skin condition NOS
Vasculitis rash

NOS: nitric oxide synthase.

Table 2. Clinical features of patients who developed leukocytoclastic vasculitis (LCV) associated with anti-TNF-α therapy.

	Etanercept	Infliximab
Age range, yrs	13–64	24–75
Male	4	2
Female	16	13
Diagnosis		
Rheumatoid arthritis	18	8
Juvenile rheumatoid arthritis	2	
Ankylosing spondylitis		1
Psoriatic arthritis		1
Crohn's disease		5
No. of patients with biopsy-proven LCV	13	4
Resolution of lesions		
Improvement	13	9
Ongoing rash	3	1
Unknown	4	5
Rechallenge phenomenon*		
Positive	5	1
Negative	2	2

* Defined as the reappearance or worsening of symptoms on reexposure to the agent.

rence of LCV after restarting therapy with TNF-α blockers (i.e., positive rechallenge phenomenon). One of these patients had resolution of lesions when etanercept was decreased to once a week dosing and worsening when the dosing was increased to twice a week. Another patient's LCV improved with discontinuation of infliximab, but flared when the patient began treatment with etanercept. However, 3 patients (2 of whom had biopsy-proven LCV) did not have recurrence of their skin lesions following rechallenge with the same agents. LCV lesions improved in more than half the patients despite continuing concomitant medications reportedly associated with LCV, such as methotrexate[14,15], sulfasalazine[16], azathioprine[17], quinine[18], lisinopril[19], losartan[20], furosemide[21], and naproxen[22]. In addition to discontinuation of their TNF-α blocker, 16 patients were reportedly treated with glucocorticoids. Comparison of characteristics of patients in whom LCV was proven by biopsy to those in whom a biopsy was not reported revealed no material differences between the 2 groups. However, there were more patients who did not have a biopsy reported in those exposed to infliximab (11 of 15) compared to etanercept (7 of 20).

DISCUSSION

The AERS database is a valuable tool for postmarketing surveillance and delineation of adverse events that are clinically relevant to the practicing physician. However, its limitations include: (1) adverse event reports to AERS do not necessarily represent causal relationships between the reported adverse event and the suspect drug; (2) underreporting of adverse events occurs commonly; (3) lack of detailed and sometimes erroneous/incomplete clinical information; and (4) lack of extended followup. LCV is a well known complication of RA and other autoimmune disorders. The cumulative incidence of LCV secondary to RA over 30 years has been reported to be about 5.1%[23]. According to data obtained from the drug manufacturers, between the periods that we looked for reports of LCV in the AERS database, the number of patients treated with these drugs (cumulative patient exposure) had been roughly 116,000 patients and 259,000 patient-years for etanercept (Enbrel, Immunex, USA) and 344,000 patients for infliximab (Remicade, Centocor, USA) worldwide. The comparatively small number of patients that had been reported to have developed LCV following exposure to anti-TNF-α agents and the fact that 3 patients (2 of these 3 were biopsy-proven) in the series did well on reintroduction of the drug (negative rechallenge) argue against a strong causal link between LCV and TNF-α blocking agents. However, factors that support an association of LCV and anti-TNF-α include the following:

1. The occurrence of LCV was temporally associated with initiation of TNF-α blockers. In 3 patients treated with etanercept, the skin lesions started at the injection site and spread to involve other areas of the body, supporting a role for a direct antigen-mediated hypersensitivity vasculitis.
2. Even though patients were reported to be on concomitant medications that have been associated with LCV, more than 50% responded with complete or partial resolution of their skin lesions upon discontinuation of the anti-TNF-α agents.
3. Positive rechallenge phenomena (reappearance or worsening of symptoms on reexposure to the agent) were seen in 6 patients. A positive rechallenge phenomenon has also been described previously, where a patient who had improved after discontinuing etanercept developed LCV with rechallenge with etanercept, and also demonstrated this phenomenon when switched to infliximab, suggesting the possibility that the relationship, at least in some cases, is not drug-specific[24]. In our case series, there was a patient in whom the reverse was noted (i.e., exposed to infliximab first, with development of LCV that recurred when the patient was switched to etanercept). Interestingly, there was also a patient who developed LCV with etanercept that resolved while receiving treatment with infliximab.
4. Recent reports of autoantibody formation during administration of TNF-α blocking agents raise the question whether these autoantibodies could be a drug-induced phenomenon, with clinico-pathogenetic significance in certain adverse events such as LCV, discoid lupus, and lupus-like symptoms along with ANA and anti-dsDNA antibodies[9-11,25]. It is possible that anti-drug antibodies, which have been described with both etanercept[26] and infliximab[3], may cause a hypersensitivity vasculitis in some cases[27]. Other unidentified pathophysiologic mechanisms may also play a role.

When an adverse drug reaction occurs infrequently, it is unlikely to be detected in premarketing clinical trials[28]. It is therefore important for the physician to recognize and report clinically significant adverse events to the FDA, other local regulatory authorities, or the drug manufacturer. Certain clinical inferences can be made from our study of the largest case series of LCV associated with anti-TNF-α agents. A thorough history and physical examination to determine the extent, if any, of systemic involvement of LCV is important. After other causes of LCV are eliminated, it is important to consider the role of TNF-α blocking agents in the causation of skin lesions suspicious for LCV. It is essential to confirm the diagnosis by skin biopsy with immunofluorescence and special stains and/or culture to exclude infectious agents. If confirmatory, discontinuation of the anti-TNF therapy should be considered. Since a few patients did not worsen on reintroduction of the agents, a cautious rechallenge may be warranted in those with few therapeutic options who require these agents to control their underlying disease.

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