

# Serum Sickness–Like Reaction Associated with Efalizumab

Sadia Ashraf-Benson, Geoffrey C Wall, and Lisa A Veach

Efalizumab is an immunosuppressive recombinant humanized immunoglobulin G1  $\kappa$  isotype monoclonal antibody that binds to human CD11a and is approved for treatment of moderate-to-severe plaque psoriasis.<sup>1</sup> Like other biologic therapies in use for various immunologic disorders, efalizumab is very effective in improving the symptoms and quality of life of patients with plaque psoriasis, but also has a unique adverse effect profile.<sup>2</sup> The most common adverse effects reported with efalizumab (with an overall incidence >20%) are upper respiratory infections, flu-like symptoms, and gastrointestinal symptoms.<sup>3</sup> Rare accounts of hypersensitivity or immune-mediated reactions with the drug are reported in the product information.<sup>4</sup> We report a case of a patient who developed serum sickness–like reaction (SSLR) after treatment with efalizumab.

## Case Report

A 37-year-old white female presented to an area hospital with a chief complaint of fever, rash, arthralgias, myalgias, fatigue, nausea, and vomiting that had been present for 10 days. She initially noted a rash involving the proximal extremities. The following day, the rash progressed and was accompanied by severe arthralgias, myalgias, and fever. Her reported temperatures reached as high as 39 °C. She was first evaluated for these findings by her primary

**OBJECTIVE:** To report a case of serum sickness–like reaction (SSLR) possibly induced by efalizumab, a recombinant humanized immunoglobulin G1  $\kappa$  isotype monoclonal antibody approved for treatment of moderate-to-severe plaque psoriasis.

**CASE SUMMARY:** A 37-year-old woman with plaque psoriasis who had been treated with efalizumab for 2 months developed a fever, erythematous rash, and progressive joint swelling and pain that required hospitalization. An exhaustive workup for infectious and rheumatologic causes of the patient's symptoms was negative. Given the relative temporal relationship between efalizumab therapy and the patient's signs and symptoms, a diagnosis of serum sickness was made. Systemic corticosteroids were initiated, which resulted in rapid resolution of the patient's signs and symptoms. Use of an objective causality assessment suggests that the patient's SSLR was possibly related to efalizumab.

**DISCUSSION:** Like many therapeutic monoclonal antibodies, efalizumab is associated with several adverse events, including allergic reactions. SSLR, a nonimmediate hypersensitivity syndrome, can occur with a variety of drugs including monoclonal antibodies. However, a MEDLINE search (1964–July 2008) identified only one other possible case of SSLR related to efalizumab.

**CONCLUSIONS:** Clinicians using efalizumab should be aware of this possible adverse reaction.

**KEY WORDS:** efalizumab, serum sickness.

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care physician. Amoxicillin was prescribed (well after the onset of rash and arthralgias) because of a history of streptococcal infection in the patient's spouse. Her past medical history was significant for plaque psoriasis, which she has had for more than 10 years. Initially, this was treated with topical corticosteroids and laser therapy for an unknown period, but these modalities were no longer effective. Oral medications were not used; the reasons for this were not known due to lack of patient information. Treatment with efalizumab was begun approximately 2 months prior to the onset of symptoms. The patient's social histo-

ry was unremarkable. She was not taking any other prescription or herbal medications. Her allergy history was significant for a past reaction to latex, which caused a mild pruritic rash.

On admission, a complete blood cell count revealed: white blood cells 20,480/ $\mu$ L, hemoglobin 13.9 g/dL, hematocrit 40.2%, platelet count  $260 \times 10^3$ / $\mu$ L, neutrophils 71%, bands 1%, lymphocytes 19%, monocytes 8.0%, and eosinophils 0%. The basic metabolic panel on admission showed: sodium 137 mEq/L, potassium 3.5 mEq/L, chloride 102 mEq/L, bicarbonate 27 mEq/L, blood urea nitrogen 4 mg/dL, creatinine 0.7 mg/dL, calcium 9.2 mg/dL, and glucose 125 mg/dL.

The woman's vital signs were: temperature 39 °C, heart rate 106 beats/min, and blood pressure 130/79 mm Hg. She appeared to be in mild distress and a diffuse maculopapular rash with areas of confluence was noted on her trunk, arms, and thighs. The rash was blanchable and had a hyperemic appearance. She also had large plaques of psoriasis on her abdomen. She had no oral lesions. The rest of the physical examination was unremarkable.

Cultures of urine and blood were obtained and ceftriaxone 1 g was administered intravenously on evaluation in the emergency department. Results of infectious mononucleosis screen and streptococcal A antigen tests were negative. She was admitted to the internal medicine service and ceftriaxone and vancomycin (1 g intravenously every 12 hours) were prescribed. On hospital day 2, the Infectious Disease service was consulted to determine the cause of the patient's signs and symptoms. Multiple viral and fungal serologies were performed. Mild elevation of her liver function test parameters were noted on hospital day 2: total bilirubin 1.4 mg/dL, direct bilirubin 0.7 mg/dL, alkaline phosphatase 214 U/L, aspartate aminotransferase 45 U/L, and alanine aminotransferase 45 U/L. Due to this finding and a report of mild abdominal pain, a right upper quadrant ultrasound was performed, which showed gall bladder wall thickening. Surgery evaluation resulted in a putative diagnosis of biliary dyskinesia possibly due to a viral syndrome; no operative intervention was indicated.

The patient's fevers continued and the symptoms progressed. Multiple joints were noted to be increasingly swollen, warm, erythematous, and tender to palpation. She also had transient erythematous streaks across her palms. The rash persisted and she continued to experience nausea, vomiting, fatigue, and shortness of breath. Results of multiple sets of blood cultures were negative, as were cultures from other sterile sites. Results of multiple viral and fungal serologies were also negative, including: cytomegalovirus, parvovirus, rubella, rubeola, coxsackie, histoplasma, enterovirus, HIV, and treponema screen. To aid in assessing possible collagen-vascular disease, various other laboratory tests were performed. These values included: C4 13.8

g/dL, C3 120 mg/dL, CH50 81 mg/dL, C-reactive protein 28.5 mg/dL, and erythrocyte sedimentation rate 99 mm/h. Result of an antinuclear antibody screen was negative, rheumatoid factor quantitative was less than 20 IU/mL, neutrophil cytoplasmic antibody was less than 1:20, and cyclic citrullated peptide antibodies was 4 EU.

The diagnosis of SSLR due to efalizumab therapy was thought to be most likely and on hospital day 7 antibiotics were discontinued and a rheumatology consultation was obtained. Intravenous methylprednisolone 40 mg twice a day was initiated that day for a total of 4 doses. Within 24 hours of the initiation of corticosteroid therapy, the woman experienced notable improvement. Fever resolved, joint swelling decreased, and the rash began to improve. The abdominal pain, leukocytosis, and mild elevation of the liver function test parameters also resolved; on hospital day 9, she was discharged. On follow-up, although the fever and systemic symptoms remained resolved, the patient's psoriatic lesions began to progress over the next several months. In addition, she developed arthritis in her hands and feet (synovitis of fingers and toes of asymmetric distribution) and was eventually diagnosed with psoriatic arthritis.

## Discussion

The patient was diagnosed as developing SSLR due to efalizumab. Use of the Naranjo probability scale showed that the association between the drug and the reaction was possible.<sup>5</sup> Although amoxicillin has been described as a cause of SSLR, this medication could not be the causal agent in our patient, as the onset and progression of signs and symptoms clearly predated the administration of amoxicillin.<sup>6</sup>

The patient's signs and symptoms, as well as her laboratory evaluation, presented a strong correlation to the constellation of symptoms in serum sickness. This syndrome is characterized by fever, rash, and arthralgias, which usually appear 2–4 weeks after the initiation of drug therapy.<sup>7</sup> This pattern of symptoms mirrored our patient's findings, although she had received approximately 8 weeks of efalizumab therapy. Her extensive laboratory evaluation eliminated a number of infectious etiologies.

Serum sickness is a type III immune complex antigen–antibody complement reaction. It is hypothesized that serum sickness results when a drug (hapten) binds to plasma protein and antibodies are generated in response to the drug–protein complex. Complement activation occurs when large quantities of soluble antigen–antibody (immune) complex fix to vascular endothelial receptors. Complement fragments attract and activate neutrophils, which release proteases that induce tissue injury.<sup>8</sup> After initial exposure to the drug, there is a latent period before the onset of a hypersensitivity reaction. During this period, the

drug–protein complex stimulates production of a number of activated immune effector cells and antibodies, which causes allergic sensitization.<sup>7</sup>

True serum sickness manifests as fever, lymphadenopathy, arthralgias, cutaneous eruptions, gastrointestinal disturbances, and malaise. It is also often accompanied by proteinuria without evidence of glomerulonephritis.<sup>9</sup>

SSLR is so named because of its clinical resemblance to true serum sickness, although the symptoms of SSLR are typically less severe. The pathogenesis is not well understood, but it is postulated that SSLR is not associated with circulating immune complexes. The reaction is often acute, but self limited. With more severe symptoms, as in our patient, management includes not only discontinuing the offending drug but also administering a short course of either intravenous or oral steroids. Further use of the drug that caused the reaction should be avoided.<sup>10</sup>

SSLR has been reported with several biologic drugs, including infliximab and rituximab.<sup>11,12</sup> A collection of cases involving infliximab demonstrated that, in patients with Crohn's disease and rheumatoid arthritis, such a reaction is typically delayed and can occur weeks after exposure to the drug.<sup>13</sup> Infliximab has also been reported to cause SSLR in a patient with psoriasis.<sup>14</sup> These authors attributed the development of SSLR symptoms to the possible development of human anticlonal antibodies, which may elicit the reaction. Our MEDLINE literature search revealed only one other occurrence of a patient hospitalized for SSLR in relation to efalizumab.<sup>15</sup> The possibility of the development of antibodies to the monoclonal antibody was also discussed as a putative mechanism in this case.

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## Reacción Parecida a la Enfermedad del Suero Asociada a Efalizumab

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## EXTRACTO

**OBJETIVO:** Describir una reacción parecida a la enfermedad del suero (RPES) inducida probablemente por efalizumab, un anticuerpo monoclonal recombinante humanizado isotipo IgG1 kappa, aprobado para el tratamiento de la psoriasis en placa de moderada a grave.

**RESUMEN DEL CASO:** Una mujer de 37 con psoriasis en placa que había sido tratada con efalizumab durante 2 meses, desarrolló fiebre, exantema eritematoso e inflamación articular progresiva, y dolor que precisaron hospitalización. No se encontraron causas reumatológicas ni infecciosas para los síntomas de la paciente. Dada la relación temporal entre el tratamiento con efalizumab y los síntomas de la paciente, se diagnosticó la enfermedad del suero. Se instauró un tratamiento con corticoides sistémicos que condujo a la rápida resolución de los síntomas de la paciente. Una valoración de causalidad objetiva sugiere que la RPES de la paciente estaba probablemente asociada a efalizumab.

**DISCUSIÓN:** Al igual que muchos anticuerpos monoclonales terapéuticos, efalizumab se asocia a varias reacciones adversas, entre ellas las reacciones alérgicas. Las reacciones parecidas a la enfermedad del suero, un síndrome de hipersensibilidad no inmediato, pueden aparecer con varios fármacos, entre los que se encuentran los anticuerpos monoclonales. No obstante, la búsqueda llevada a cabo en MEDLINE solo identificó un posible caso de RPES relacionado con efalizumab.

**CONCLUSIONES:** Efalizumab constituye un tratamiento relativamente nuevo para la psoriasis. Describimos un posible caso de RPES asociado a este fármaco. Los médicos que usen efalizumab deberían ser conscientes de esta posible reacción adversa.

Traducido por Violeta Lopez Sanchez

Une Réaction de Type Maladie Sérique Associée à l'Éfalizumab.

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RÉSUMÉ

**OBJECTIF:** Signaler une réaction de type maladie sérique probablement induite par l'éfalizumab, un anticorps monoclonal humanisé recombinant (IgG1) approuvé pour le traitement du psoriasis en plaques modéré à grave.

**PRÉSENTATION SOMMAIRE DU CAS:** Une femme âgée de 37 ans souffrant de psoriasis en plaques et traitée depuis 2 mois par de l'éfalizumab a dû être hospitalisée parce qu'elle a développé une fièvre, un érythème et un gonflement progressif des jointures associé à de la douleur. Une recherche exhaustive afin de trouver des causes infectieuses ou rhumatologiques pouvant expliquer les symptômes de la patiente s'est avérée négative. Étant donné les symptômes de la patiente et la relation temporelle avec la thérapie par l'éfalizumab, un diagnostic de maladie sérique a été posé. Des corticostéroïdes systémiques ont été instaurés ce qui a résulté en une

résolution rapide des symptômes de la patiente. Une évaluation objective du lien de causalité suggère qu'il existe un lien possible entre la réaction de type maladie sérique présentée par la patiente et l'éfalizumab.

**DISCUSSION:** Comme plusieurs des anticorps monoclonaux utilisés en thérapeutique, l'éfalizumab est associé à plusieurs effets indésirables, incluant les réactions allergiques. Les réactions de type maladie sérique, un syndrome d'hypersensibilité non immédiate, peuvent se produire avec plusieurs médicaments incluant les anticorps monoclonaux. Cependant, une recherche MEDLINE a permis d'identifier seulement un autre cas possible de réaction de type maladie sérique associée avec l'éfalizumab.

**CONCLUSIONS:** L'éfalizumab est un traitement relativement nouveau du psoriasis. Les auteurs signalent un cas de réaction de type maladie sérique ayant un lien possible avec l'éfalizumab. Les cliniciens qui utilisent l'éfalizumab doivent être au conscients de la possibilité de cet effet indésirable.

Traduit par Marie Larouche