

Cutaneous Vasculitis Induced by Etanercept and Tocilizumab

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Abstract

Biological disease modifying anti-rheumatic drugs (bDMARDs) have improved outcome of rheumatoid arthritis (RA). Tocilizumab (TCZ) is a monoclonal humanized anti-interleukin-6 receptor (IL6-R) which is indicated in case of inadequate response to one or more DMARDs or other biological treatment. Vasculitis has been reported with anti-TNF (Tumor Necrosis Factor) agents among more than 140 cases according to the BIOGEAS study group (a Study Group on Autoimmune Diseases of the Spanish Society of Internal Medicine) but only in two cases with TCZ. We report the first case of cutaneous vasculitis occurring under both anti-TNF therapy and TCZ.

Keywords: Cutaneous vasculitis; Anti-rheumatic drugs; Autoimmune diseases

Case Report

A 60-year-old woman was followed-up for seropositive and erosive RA fulfilling ACR 1987 criteria's. She was initially treated by methotrexate then associated to sulfasalazine without any significant benefits. Leflunomide was introduced for a period of 4 months with a prompt response. However, a generalized cutaneous rash appeared two weeks after initiating this treatment and disappeared at interruption. The patient was treated by infliximab (3 mg/kg/8weeks) with a good initial response because of active disease; methotrexate was maintained (10 mg/week). Then a secondary failure was observed although rising dose treatment and shortening time between perfusions (5 mg/kg/6weeks). After 7 months, we switched to etanercept (ETN) 50 mg/week. At the third week of treatment, the patient noticed a cutaneous ecchymotic rash of her legs, appearing few hours after the injection and disappearing spontaneously. She was hospitalized after 8 weeks of treatment, no skin lesions were found and the disease remains active. Ninth ETN injection was administrated under close monitoring. So she developed the same lesions described and respiratory distress. Steroids were administrated with a good outcome. Since a major adverse effect occurred under anti-TNF therapy we decided to switch the biological agent to TCZ (8 mg/kg/4weeks). After the second perfusion, identical skin lesion she acquired under ETN occurred, appeared few hours after infusion and cleared one week later (Figure1). A skin biopsy was performed showing leucocytoclastic vasculitis with a perivascular inflammatory infiltration. Laboratory tests showed normal peripheral eosinophil and lymphocyte counts. Test for antinuclear antibodies, Antineutrophil cytoplasmic antibody (ANCA) and cryoglobulinemia were negative. Complement levels were normal. TCZ was associated with a good response for RA activity. Considering cutaneous vasculitis as a minor side effect and after discussion with the patient and pharmacovigilance expert, we decided to continue this therapy with tight control. Every infusion was preceded with antihistamine drugs and steroid pulse. Till this day, the patient has received 7 perfusions. Skin lesions still appear at the same time and in the same places and disappear soon without others cutaneous or respiratory outcomes.



Figure 1: Ecchymosis on the front side of both leg appeared after the second tocilizumab infusion.

Discussion

Cutaneous vasculitis can occur as a complication of rheumatoid arthritis, although, the chronological link between ETN then TCZ administration and development of the skin lesions suggests drug-induced vasculitis in our patient. Persistence of skin lesions in spite of a good disease response was another proof of drug-induced vasculitis in case of TCZ.

RA can have cardio-vascular manifestations since it has been reported that rheumatic diseases could be associated to increased carotid intima-media thickness when explored by a two-dimensional echo-colour Doppler of the carotid arteries [1,2]. The other extra-articular cardio-vascular manifestation reported in RA is vasculitis.

Anti-TNF therapy has been increasingly associated with drug-induced auto-immune diseases and vasculitis is the most reported manifestation. Among anti-TNF agents, ETN was the most incriminated in this adverse effect. According to the BIOGEAS, vasculitis occurred under ETN in 51% of cases, under infliximab in 43% of cases and under adalimumab in 4% of cases. Vasculitis occurred as cutaneous lesions in 86% of cases [3]. The mechanism of induction of this side effect is not fully understood. It has been suggested that immune complexes of anti-TNF α /TNF α deposited in

small capillaries activated the complement and induced a type III hypersensitivity reaction [4]. Time between development of the cutaneous vasculitis and the drug administration is variable. A retrospective study reported a mean duration of TNF α antagonist therapy at vasculitis onset of 6.6 ± 13.4 months (range 0.5–80 months) [5]. In our case, cutaneous adverse effect appeared 3 weeks after initiation of etanercept. Withdrawal of the drug-induced vasculitis and administration of steroid and anti-histamines is usually associated with good outcomes. In literature, six of nine patients experienced rechallenge of the vasculitis after anti-TNF readministration [6]. Since our patient developed respiratory distress in addition to cutaneous induced side effect we opted for changing the type of the biological treatment.

Cutaneous vasculitis occurring under TCZ is less documented than under anti-TNF therapy. After a review of literature, only two cases were reported [7,8]. Histopathological findings concluded to leucocytoclastic vasculitis in one case such in our patient. The suggested mechanism that may contribute to the development of this type of vasculitis is similar to anti-TNF. As TCZ is an antibody against IL6-R, it binds to cell-surface IL6-R and after saturation to the soluble form of IL6-R. This immuno-complex of anti-IL6-R/soluble IL6-R may be accumulated in small vessels and induce a hypersensitivity reaction [9]. TCZ was administrated 2 months in one case and 30 months in the other case upon the drug-induced vasculitis appeared. In the two cases reported, cutaneous-induced effect was associated with a disease relapse. In our patient, unlike under ETN, disease activity has remarkably improved by TCZ even after skin lesions appearance. Considering this as a minor side-effect, we decided to reintroduce gradually TCZ with antihistamine and steroid cover. This may lead to “tolerization” as noticed by other authors [10]. Although TCZ was recommended to the treatment of auto-immune vasculitis, we should be aware of this potential paradoxical side effect.

Conclusion

Our report adds to the limited repertoire of case reports of anti-TNF and TCZ induced vasculitis, and serves as a useful reminder of this potentially serious complication.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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