# Paradoxical Reactions to Targeted Biological Treatments: A Way to Treat and Trigger?

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*Sir,*

New targeted therapies offer the possibility of blocking a specific biological activity underlying the primary pathological condition (1). However, the target may be involved in multiple complex immunological pathways, resulting in an unexpected response and/or onset of severe adverse events that may be at odds with the therapeutic goal (1).

We describe here four patients who developed contradictory reactions during treatment with biologicals. Their reactions lead us to ask: is it possible to treat and trigger at the same time?

## CASE REPORTS

*Case 1*. A 43-year-old man with rheumatoid arthritis (RA) had been treated with methotrexate for one year with little response. He had no personal or family history of psoriasis. Etanercept was introduced, but 17 weeks later, numerous pustules, scaly erythematous lesions and keratotic areas appeared initially on the soles and, a few weeks later, on the palms. Histology confirmed the diagnosis of pustular palmo-plantar psoriasis. Etanercept and methotrexate were discontinued and the patient was started on topical steroids and calcitriol, with improvement in 4 weeks. The joint disease flared and he was unresponsive to leflunomide. Methotrexate was reintroduced, improving the whole condition with no cutaneous side-effects.

*Case 2*. A 34-year-old man was followed for a severe recalcitrant plaque palmo-plantar psoriasis and no history of psoriatic lesions elsewhere. Various courses of phototherapy, acitretin and cyclosporine were all unsatisfactory. In March 2007, efalizumab therapy was initiated with a single subcutaneous conditioning dose of 0.7 mg/kg, followed by weekly doses of 1 mg/kg. After the fourth dose, the patient reported the emergence of well-demarcated, erythematous scaly papules and small plaques on the abdominal region. Topical corticosteroid therapy was initiated with complete regression of the lesions within 6 weeks. The patient continued on efalizumab therapy and achieved an excellent response after 12 weeks.

*Case 3*. A 52-year-old woman with RA (previous treatment: salazopyrin, hydroxychloroquine, methotrexate, leflunomide, adalimumab, infliximab, etanercept, anakinra) manifested fatigue, fever, arthralgias and polyserositis 8 weeks after initiating a cycle of 1000 mg rituximab infusions/2 weeks and methotrexate 20 mg/week. Investigations revealed proteinuria, positive anti-nuclear antibodies, positive anti-ds-DNA-antibodies, leucopaenia and anaemia. Systemic lupus erythematosus (SLE) was diagnosed and treated with prednisone 10 mg/day and mycophenolate-mofetil 2 g/day, with complete remission in 2 months. RA was refractory and she started weight-adapted infusions of abatacept 750 mg at weeks 0, 2, 4 and 8. At week 12 histologically confirmed psoriatic lesions were visible on her entire integument; abatacept was discontinued with complete remission with topical steroids and calcipotriol.

*Case 4*. A 40-year-old woman with ulcerative colitis since 2005 was seen in February 2008 with painful nodules on the lower extremities. Treatment history included various regimens with corticosteroids, mesalazine, methotrexate, azathioprine and cyclosporine. In October 2007, due to a progressive worsening of the disease, infliximab was introduced at 5 mg/kg scheduled at week 0, 2, 4 and every 8 weeks, but a scarce response after 3 infusions forced a total colectomy. Rectal bleeding and weight loss persisted, and a new course of infliximab was initiated. After the first infusion the patient complained of intense burning and pain on the ankles. Following the second infusion at week 2, two violaceous, painful nodules appeared, and a skin biopsy confirmed pyoderma gangrenosum (PG). By week 4 the nodules had become large, ulcerated plaques on both ankles (Fig. 1). At the patient's request, infliximab was discontinued. Cyclosporine was initiated at 5 mg/kg/day. After 3 weeks rectal bleeding and abdominal pain were under control, and the skin lesions had improved notably. The patient continues to receive cyclosporine 1 mg/kg/day, and PG is in remission.

## DISCUSSION

New biological therapies (tumour necrosis factor (TNF)-α blocking agents (infliximab, etanercept and adalimumab), anti-CD-11a monoclonal antibody (efalizumab), interleukin-1 receptor antagonist (anakinra), and anti-CTLA-4 fusion protein (abatacept)) have been developed to treat chronic inflammatory diseases, such as RA, ankylosing spondylitis (AS), inflammatory bowel disease (IBD), psoriatic arthritis, and psoriasis (1). Their increasing use can be confirmed by different national registries, such as the British Society of Rheumatology Biologics Registry (9536 patients from 2002 to 2004) (2) or the Italian PsoCare National Registry (6864 patients in 2008) (3).

Induction or worsening of psoriasis has been noted in patients with IBD, RA and AS treated with each of the three currently available TNF-α inhibitors, with a 5% prevalence that clearly exceeds the 1–2% prevalence expected by chance (4). In most cases, psoriasis appearing during anti-TNF-α therapy shows a pustular palmo-plantar pattern (as described in case 1) that is considered a class effect of TNF-α blocking agents rather than a drug-specific adverse event (4). This paradoxical psoriasis onset is in conflict with the well-documented therapeutic effect of anti-TNF-α agents in plaque psoriasis and also in palmo-plantar pustular psoriasis (4). The mechanism underlying this paradoxical phenomenon remains elusive, but the increased production of interferon (IFN)-γ after TNF-α blockage might play a role, as IFN-γ is a key element in the induction of psoriasis (4).

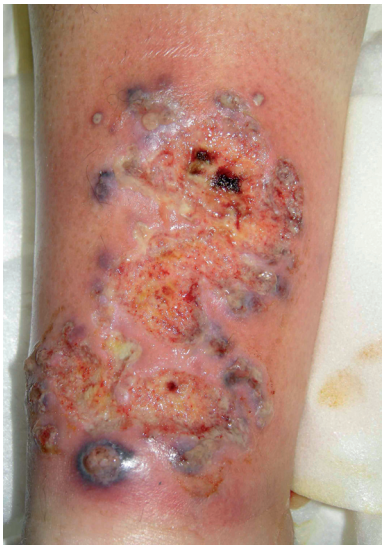

*Fig. 1. Case 4:* irregular ulcer with violaceous borders on the right ankle. "Satellite" lesions are present (pustules at the top of the ulcer; ulcerated nodule at its bottom). The patient was receiving infliximab infusions.

Several reports have described a switch of psoriasis morphology to palmo-plantar pustular psoriasis or "papular transient eruption" (a pustular psoriasis reaction located outside the palmo-plantar region) in patients receiving anti-TNF-α therapies or efalizumab for treatment of plaque psoriasis (5). Pathogenesis of this phenomenon is unexplained. Under conventional systemic therapies, such as cyclosporine, methotrexate and acitretin, a morphological switch of psoriasis is unusual (6). Case 2 illustrates the paradoxical switch phenomenon occurring under efalizumab therapy: the excellent response of the palmo-plantar psoriasis was accompanied by the appearance on the abdomen of a "papular transient eruption" (5) that resolved with topical steroids.

In considering cases 1 and 2, different questions arise: how can a single agent treat psoriasis or RA and, at the same time, induce psoriasis or a new psoriatic variant? Can paradoxical reactions be considered adverse events specifically associated with the target therapy? Does biological therapy induce a kind of Koebner phenomenon?

Case 3 presented two unforeseen phenomena: the rare onset of SLE after rituximab therapy and the emergence of psoriasis under abatacept therapy. In the absence of triggering factors or family history of SLE and psoriasis, the close temporal associations between disease onset and use of rituximab or abatacept, together with prompt recovery after drug withdrawal, provides level II evidence (probable) that these adverse events were drug-related (7). Rituximab has been used successfully to treat SLE (8) and abatacept is an effective treatment for psoriasis (9), underscoring once more the paradox of drug reaction.

In case 4, the onset of PG under infliximab therapy for ulcerative colitis was completely unexpected. Many reports regarding the successful use of infliximab for PG (10) are in contrast with two reported cases (including ours) of PG onset during anti-TNF-α therapy (11). Although PG has been widely reported with IBD (10), its onset during infliximab therapy is again a paradox.

A similarly paradoxical reaction was seen in another case (12), in which a patient with chronic plaque psoriasis developed thrombocytopaenia during etanercept treatment. In that case, the platelet count recovery after etanercept suspension and the relapse of thrombocytopaenia after re-exposure to etanercept suggested a causal relationship. While thrombocytopaenia is a recognized adverse event in association with efalizumab therapy (13), it is infrequently seen in patients receiving anti-TNF-α therapy. Etanercept and infliximab have been used successfully for the treatment of refractory immune thrombocytopaenic purpura (14), once again raising the question: how can the same drug treat thrombocytopaenia in some patients and have the opposite effect in other patients?

The advent of targeted molecular therapies provides the opportunity to improve our understanding of many neoplastic and chronic inflammatory conditions with a strong genetic component. The onset of unexpected and antagonistic reactions associated with these targeted therapies reveals the complexity of the immunogenetic pathways involved in human disease. A paradox provokes fresh thought about a contradictory event. Concerning the perennial paradox of progress, Somers & Somers wrote: "All creative achievement is disruptive and every partial solution promptly explodes and opens a new set of problems" (15).

*The authors declare no conflict of interest.*

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