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*The Journal of Rheumatology* is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.
Editorial

Tumor Necrosis Factor-α Inhibition and Palmoplantar Pustulosis: Janus-Faced Therapy?

Janus was the Roman god of beginnings and endings; he was thus represented as a double-faced head, the 2 faces gazing in opposing directions. Consequently, the term Janus-faced denotes a person or object that has 2 contrasting aspects.

Tumor necrosis factor-α (TNF-α) is a cytokine that may have such contrasting roles. It is well known that TNF-α is an early coordinator of the cytokine response to injury and is elevated in inflammatory diseases such as rheumatoid arthritis (RA)1. However, chronic TNF-α stimulation has the paradoxical consequences of both acting as an anti-inflammatory and downregulating T cell responses2. Ablation of TNF-α signaling by genetic TNF-α receptor deletion accelerates autoimmunity in lupus-prone NZB mice3. This dichotomy is also reflected in the clinical response to TNF-α inhibition.

TNF-α inhibitors are effective in the therapy of RA4, psoriasis and psoriatic arthritis5, ankylosing spondylitis6, inflammatory bowel disease7, and various inflammatory conditions. TNF-α inhibitors have, however, not been effective for the treatment of other inflammatory conditions such as Wegener’s granulomatosis8. New onset of multiple sclerosis-like disease has been noted in patients receiving TNF-α inhibitor therapy9. Potential proinflammatory side effects of TNF-α inhibitor therapy include lupus-like eruptions, dermatomyositis, and vasculitis10.

A number of recent publications call attention to another potentially paradoxical reaction to TNF-α inhibitor therapy, worsening or new-onset palmoplantar pustulosis or psoriasis11-13. How can TNF-α inhibition both treat and induce psoriasiform eruptions? Several articles appearing in this month’s Journal may shed light on this dichotomy and the clinical significance of this phenomenon: Cohen, et al14 present a new case series of patients developing new-onset psoriasis during TNF-α inhibitor therapy. Among 400 patients treated with either infliximab or etanercept, 6 patients with psoriasiform eruptions were identified. All their cases occurred in patients with no antecedent history of psoriasis. Interestingly, half of these eruptions were either pustular or follicular in appearance. Although the majority of cases resolved with topical therapy, in 2 cases the eruptions recurred when patients were receiving a different TNF-α inhibitor, arguing for a drug class effect. Richette, et al15 describe another patient with RA and no antecedent history of psoriasis who developed a papulopustular eruption on the soles following therapy with both infliximab and etanercept. Withdrawal of each of the TNF-α inhibitors resulted in improvement. Finally, Roux, et al16 describe 2 out of 442 patients treated with TNF-α inhibitors who developed new-onset palmo-plantar pustulosis while taking infliximab therapy.

These 3 reports add to the over 40 cases of psoriasiform eruptions developing in patients treated with TNF-α inhibitors. Certain themes emerge: The development of new eruptions is often delayed for months following therapy initiation, arguing against a common drug eruption mechanism. In favor of this, patch testing has been repeatedly negative. The reaction is uncommon and often does not mandate discontinuation of therapy. The reaction has been reported to occur with every TNF-α inhibitor in clinical use. Over half the reported cases have developed palmo-plantar pustulosis or pustular eruptions. Palmoplantar pustulosis is usually most common in the fifth or sixth decade, is slightly more common in women, and has a different HLA association than does psoriasis vulgaris17. Smoking may be a trigger, as cessation is associated with improvement18.

Unlike the cases described following TNF-α inhibitor therapy, palmoplantar pustulosis tends to be chronic. A rare variant, known as acute palmoplantar pustular psoriasis of Andrews, has been termed a “bacterid,” implying an eruption provoked by a remote bacterial infection19. This entity may be more akin to the eruptions noted following TNF-α inhibition.

See: Psoriasis induced by anti-TNF therapy, page 380 and 438; and New-onset palmoplantaris pustulosis following infliximab, page 434
Recent work on the pathogenesis of psoriasis and on the relationship between type 1 interferons and TNF-α may inform these observations. The type 1 interferon, interferon-α (IFN-α), has been implicated in the induction of psoriatic skin lesions\(^\text{20}\). The natural IFN-α-producing cells, termed plasmacytoid dendritic cells, have been identified in early lesions of psoriasis, and inhibition of IFN-α production can prevent the development of psoriatic lesions in mice grafted with human skin\(^\text{21}\). TNF-α inhibits both plasmacytoid dendritic cell maturation and IFN-α release\(^\text{22}\). It is conceivable therefore that inhibition of TNF-α could affect IFN-α levels. Indeed, TNF-α inhibitor treatment of children with idiopathic juvenile arthritis leads to the expression of an IFN-α-dependent “gene signature” by peripheral blood mononuclear cells, similar to the gene signature identified in patients with systemic lupus erythematosus\(^\text{23}\).

To determine if cutaneous IFN-α overexpression might underlie the development of pustular and psoriasiform eruptions in patients on TNF-α inhibitor therapy, we stained histologic sections of lesional skin for the expression of myxovirus-resistance protein A (MxA), an indicator of local IFN-α release\(^\text{24}\). Psoriasiform lesions from patients on TNF-α inhibitor therapy demonstrated enhanced perivascular and epidermal MxA staining when compared to patients with psoriasis vulgaris. This suggests that, in these patients, TNF-α inhibitor therapy may induce cutaneous IFN-α overexpression, predisposing to a psoriasiform eruption. It is possible that these elevated levels of IFN-α might allow more efficient triggering of skin lesions by trauma or infectious agents — as postulated in palmoplantar pustular psoriasis of Andrews\(^\text{19}\). Whether these patients truly have TNF-α blockade-induced IFN-α overexpression in the skin, and why this subset subsequently develops pustular eruptions, remains to be fully determined. In favor of this concept, both cutaneous lupus erythematosus\(^\text{24}\) and dermatomyositis\(^\text{25}\) have similarly been associated with elevated tissue levels of IFN-α and have been described to occur following TNF-α blockade.

Thus, while TNF-α blockade efficiently smothers inflammation, it may, like Janus, look the other way and light the fire of type 1 interferon-mediated immunity. Janus is also the god of the New Year. As we enter the New Year, we should be reminded that the art of medicine is not often black and white. These cases certainly highlight an area for fruitful collaboration between dermatologists and rheumatologists in which we may learn much about inflammation in general.

**REFERENCES**


