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Targeted therapy seems untargeted: TNF-α antagonists in psoriasis as an example

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Abstract

Biologic therapies have emerged as targeted treatments in psoriasis, offering personalized options for patients. However, when examining the cytokine network in psoriasis, this raises the question of whether biologics should be viewed as targeted therapies. This article reviews the literature focusing on the impact of tumor necrosis factor (TNF)-α antagonists on the cytokine profile and immunocytes in psoriasis. The literature suggests that the effects of TNF-α antagonists extend beyond TNF-α. These agents have a significant influence on various cytokines of the innate and adaptive immune system, including interferon-γ, interleukin (IL)-1, IL-4, IL-6, IL-8, IL-12, IL-17, IL-22, IL-23, and IL-24 in blood and skin. In addition, TNF-α antagonists also affect immunocyte counts, such as neutrophil elastase-positive cells. This demonstrates that, even though biologic treatments were initially designed to target specific molecules structurally, their function should not be narrowly considered targeted. This concept has important implications in clinical practice, including for the understanding and knowledgeable prediction of drug-related side effects, such as colitis, inflammatory bowel disease, myocarditis, and infections, as well as for taking necessary precautions before prescribing medications.

Keywords: adalimumab, biologics, infliximab, psoriasis, TNF-α antagonists

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Introduction

Topical treatments and conventional systemic therapies have been used for decades to treat psoriasis; however, treating severe cases of psoriasis can be challenging. The emergence of biologic therapies, such as tumor necrosis factor (TNF)-α and interleukin (IL)-12/IL-23, IL-17, IL-23, and IL-36 antagonists, has transformed the management of moderate-to-severe psoriasis. These treatments target specific molecules involved in the inflammatory process, providing effective and personalized options. Among the available biologic agents, TNF-α antagonists were the first to be approved and have become a cornerstone in psoriasis treatment (1).

TNF-α is a pro-inflammatory cytokine elevated in psoriasis skin and blood. Monocytes, macrophages, dermal dendrocytes, mastocytes, and peripheral blood mononuclear cells are all capable of producing and releasing TNF-α. By examining the cytokine network in psoriasis, one can note that TNF-α production is potentiated by IL-1, IL-2, and interferon (IFN)-γ. Reciprocally, TNF-α augments IL-1, IL-6, IL-8, and transforming growth factor (TGF)-α. Each of these cytokines interacts with other molecules, forming a broader and more complex network (1).

It could be speculated that interfering with this regulated system (e.g., by neutralizing TNF-α) would disrupt the entire cytokine network. Vasculitis, lupus, inflammatory myopathies, neurological inflammatory events, and paradoxical diseases (e.g., psoriasis, hidradenitis suppurativa, pyoderma gangrenosum, ocular inflammatory diseases, and inflammatory bowel diseases) have been reported in association with TNF-α treatment (2, 3), suggesting that "targeted treatments may not be truly targeted."

This article reviews the literature and examines the effect of TNF-α antagonists on the cytokine profile in psoriasis, focusing on the four Food and Drug Administration (FDA)-approved agents: etanercept, infliximab, adalimumab, and certolizumab.

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The effect of TNF-α antagonists on the cytokine profile in psoriasis

Etanercept

Etanercept is a TNF-α antagonist that received FDA approval for the treatment of psoriasis in April 2004. It is a TNF receptor-2 (p75) protein fused with the fragment crystallizable region of immunoglobulin G1, thus binding to soluble and membrane-bound TNF-α and TNF-β (4). Compared to other TNF-α antagonists such as adalimumab and infliximab, etanercept has similar affinity and 10-to-20-fold greater avidity to TNF-α (5).

Despite being a TNF-α antagonist, the effect of etanercept on the TNF-α profile is controversial. For example, in psoriasis, etanercept may either promote (6) or inhibit (7) the systemic release of TNF-α. It also downregulates cutaneous gene expression (8, 9) and release, as shown by immunohistochemistry (10).

The immunomodulatory effect of etanercept extends beyond TNF-α modulation. Evidence suggests it also downregulates the systemic gene expression of IL-1β (11), IL-6 (11), IL-8 (11), IL-12p35 (12), IL-12/IL-23p40 (11), IL-17 (13), IL-23p19 (11-13), and IL-33 (13). It also suppresses the systemic release of IL-1α (14), IL-1β (7), IL-6 (7, 14-16), IL-8 (15), IL-12 (7), IL-17 (7, 17), IL-22 (7, 17), IL-23 (7), IL-32 (7), and IFN-γ (14). On the other hand, etanercept promotes the systemic release of Th-2 cytokines, including IL-4 (12) and IL-10 (7, 15).

Locally, etanercept downregulates the cutaneous gene expression of IL-1β (8, 18), IL-8 (8, 12), IL-12/IL-23p40 (18), IL-17 (8, 18, 19), IL-19 (18), IL-20 (18), IL-22 (18), IL-23p19 (18), IL-24 (18), IFN-γ (8, 11), CXC chemokine ligand (CXCL)1 (18), CXCL10 (18), and CC chemokine ligand (CCL)20 (18). Concurrently, etanercept suppresses the cutaneous infiltration of inflammatory cells, including cluster of differentiation (CD)3+ cells, CD68+ cells, CD161+ cells, and elastase-positive cells (9).

Infliximab

Infliximab is a chimeric immunoglobulin G1κ monoclonal antibody that binds to and neutralizes soluble and transmembrane TNF-α. It was approved for the treatment of psoriasis in September 2006 (4).

Infliximab modulates cytokine release and T-cell expansion, exerting contradictory pro- and anti-inflammatory effects. For instance, even though it transiently augments systemic TNF-α, this is followed by a gradual and sustained inhibition of protein release (20, 21). In addition, infliximab was reported to induce generalized pustular psoriasis in a patient with Crohn's disease, accompanied by the expansion of circulating IL-17+ and IL-22+ CD4+ and CD8+ cells during psoriasis flare (22). However, infliximab also exhibits an anti-inflammatory effect. It expands regulatory T-cells (23) and transiently promotes IL-10 release (21).

At the level of skin, infliximab attenuates the infiltration of CD4+ cells (24, 25), CD8+ cells, CD11c+ cells, CD1a+ cells, CD3+ cells, and neutrophil elastase-positive cells (25). It also inhibits the local release of TNF-α, IL-8, IL-12, and IL-23 (25).

Adalimumab

Adalimumab is a recombinant human immunoglobulin G1 monoclonal antibody that binds to and neutralizes TNF-α. It obtained FDA approval for the treatment of psoriasis in January 2008 (4). However, although both are TNF-α antagonists, Bhutani et al. reported four cases with a paradoxical flare of psoriasis upon switching from etanercept to adalimumab (26), indicating potential differences in their cytokine profile.

The effect of adalimumab extends beyond TNF-α modulation. For instance, it inhibits the systemic release of IL-10 (27) and IL-22 (28) in psoriasis.

At the level of skin, adalimumab significantly inhibits elastase-positive cell infiltration (29, 30) and restores Langerhans cell count in lesional skin (31). However, it fails to alter CD4+, CD8+, CD25+, CD45RO+, CD45RA+, CD68+, and CD94+ cell count (29, 32). The effect of adalimumab on CD3+ and CD161+ cell count is still inconclusive (29, 30, 32). Adalimumab tends to reduce cutaneous infiltration of IL-17+ cells (30). It also downregulates the gene expression of Th-17 polarizing cytokines (IL-23A, transforming growth factor-β1, and IL-1β), Th-17 cytokines (IL-17 and IL-22), Th-1 polarizing cytokines (IFN-α), Th-1 cytokines (IFN-γ), and various chemokines (IL-8, CXCL10, and CCL20) (30, 33, 34). However, its effect on TNF-α is controversial (30, 33).

Certolizumab

Certolizumab is a humanized recombinant antibody fragment antigen-binding region specific for TNF-α, conjugated to polyethylene glycol. It obtained FDA approval for the treatment of psoriasis in May 2018 (4). Unfortunately, the cytokine profile of certolizumab in psoriasis is poorly characterized.

Clinical implications

Figure 1 summarizes the effect of TNF-α antagonists on cytokines in psoriasis. Understanding the actual impact of TNF-α antagonists on the cytokine network is crucial due to its clinical implications.

First, it helps explain many of the treatment-related side effects. For instance, etanercept inhibits IL-6 and IL-22 on the one hand, whereas the deficiency of IL-6 (35) and IL-22 (36) on the other hand is linked to the development and worsening of colitis. Studies have shown that more than 400 cases of inflammatory bowel disease may have been triggered by etanercept (37). Similarly, etanercept reduces IL-33 levels. IL-33 plays a protective role in the eye by preventing retinal detachment; consistently, IL-33 deficiency can lead to retinal degeneration and gliosis (38). This

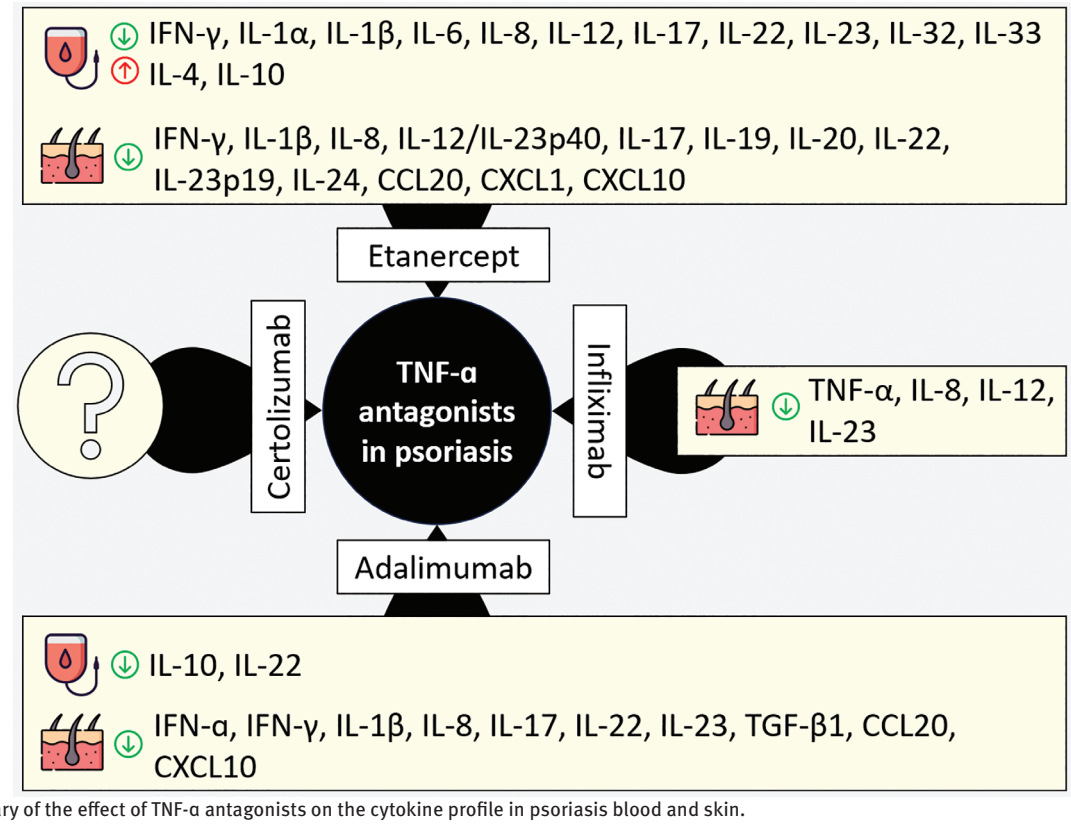

Figure 1 | Summary of the effect of TNF-α antagonists on the cytokine profile in psoriasis blood and skin.
CCL = chemokine ligand, CXCL = chemokine ligand, IFN = interferon, IL = interleukin, TNF = tumor necrosis factor, TGF = transforming growth factor.

is supported by reports of etanercept-associated toxic retinopathy in the literature (39).

Second, it helps scientifically predict side effects. For instance, IL-23 deficiency is associated with myocardial inflammation (40); therefore, one would expect that treatment with TNF-α antagonists may induce myocarditis, and this is true (Table 1).

Third, understanding the impact of TNF-α on various cytokines should prompt physicians to take necessary precautions before prescribing drugs. Precautions include opting for other treatment agents, dose adjustment, initiation of prophylaxis treatment concurrently, or close follow-up for the expected side effect for early intervention. For example, IL-17 deficiency makes patients more susceptible to chronic mucocutaneous candidiasis. Because IL-17 antagonists are not recommended for these patients, physicians may feel more at ease prescribing TNF-α antagonists. It is important to recognize that TNF-α antagonism inhibits IL-17, and there have been numerous cases of systemic and localized candida infections in patients receiving TNF-α antagonists (41).

Table 1 | **Summary of cytokine deficiency-reported associations and relevant side effects in TNF-α antagonists.**

Deficiency	Reported association	Relevant side effect
IFN-γ	Mycobacterial infection (42)	Mycobacterial infection (43, 44)
IL-6	Myocardial dysfunction (45)	Cardiomyopathy (46), reduced cardiac output (47)
	Colitis (36)	Inflammatory bowel disease (37)
IL-8	Pyelonephritis (48)	Urinary tract infections (49)
IL-12	Recurrent infections (50)	Serious infections (51)
IL-17	Chronic mucocutaneous candidiasis (52)	Systemic and localized candidiasis (41)
IL-22	Colitis (36)	Inflammatory bowel disease (37)
IL-23	Myocardial inflammation (40)	Myocarditis (53)
IL-33	Retinal degeneration and gliosis (38)	Toxic retinopathy (39)

IFN = interferon, IL = interleukin, TNF = tumor necrosis factor.

Conclusions

Even though targeted therapies have been designed to target a particular molecule structurally, this article has demonstrated that the impact of TNF-α antagonists extends beyond the targeted molecule to include disrupting immune cell count and cytokine level. This raises the question of whether TNF-α antagonists (and potentially other biologic treatments neutralizing molecules involved in inflammation) should truly be considered targeted treatments. This is particularly important in clinical practice in terms of understanding and predicting treatment-related side effects, as well as taking precautions before prescribing medications. The findings suggest that the biologics should be viewed as *structurally* targeted therapies, but *functionally* untargeted therapies.

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