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Commentary

Successful treatment of psoriasis with ustekinumab in patients with multiple sclerosis

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Abstract

Psoriasis is a chronic inflammatory disease, evolving from a complex interplay of genetic and environmental factors. In the recent years, we have seen much progress in understanding the immunopathogenesis of psoriasis, paving the way for new therapies with biologics. Currently, the most commonly used biologics in psoriasis are TNF inhibitors etanercept, infliximab and adalimumab, and the IL-12/23 inhibitor ustekinumab. As TNF inhibitors are contraindicated in patients with multiple sclerosis, ustekinumab remained the only biologic available for these patient before the recent approval of Secukinumab, an IL-17A inhibitor. Herein we report two patients with multiple sclerosis and comorbid psoriasis successfully treated with ustekinumab without progression of their multiple sclerosis. Our cases demonstrate that ustekinumab is a reasonably safe choice in this patient population. We also briefly reviewed new therapies currently under investigation, which will undoubtedly further expand our armamentarium for the treatment of psoriasis in patients with neuromuscular diseases.

Keywords: ustekinumab, psoriasis, multiple sclerosis, IL-23, IL-17

Case synopsis

Case 1: A 48 year old man presents with a long history of severe plaque type psoriasis, psoriatic arthritis, and multiple sclerosis. Past treatments for his psoriasis and psoriatic arthritis included methotrexate (cumulative dose 3 grams), and efalizumab. Efalizumab (initiated in 2007) cleared his skin disease, but was discontinued in March 2009, when it was no longer available. The patient's psoriasis was then treated with acitretin 25mg daily and topical medications for 2 years. However, his cutaneous lesions continued to worsen. The patient was subsequently started on ustekinumab in May 2011 and achieved 90% clearance of his cutaneous lesions 6 months after the initiation of therapy. In the three and half years since initiation of ustekinumab, the patient's multiple sclerosis has remained stable, without progression or improvement of disease. He is currently not on any immunotherapy for multiple sclerosis and is being monitored closely by his neurologist.

Case 2: A 66 year old female presents with a history of multiple sclerosis, moderate to severe plaque type psoriasis, and psoriatic arthritis. The patient's psoriasis and psoriatic arthritis had been successfully controlled with methotrexate for 4 years. However, treatment was terminated secondary to liver toxicity. She was then placed on IVIG (33 g/week every 4th week), but developed aseptic meningitis. The patient also had difficulty tolerating phototherapy owing to adverse syncope-like reactions to the heat. In July 2010, she was started on ustekinumab with >80% improvement in her skin disease 4 months after initiation of therapy. She continues to do well with occasional flare-ups of her scalp lesions, which have been well-controlled with topical medications. In the following 4 years since starting ustekinumab, her multiple sclerosis has remained stable without clinical evidence of progression.

Discussion

Despite recent progress in psoriasis therapies, options for patients with multiple sclerosis remain limited. Since their FDA approval, biologics have gained wide acceptance and increasing preference over the traditional immunosuppressants primarily owing to better defined targets, more convenient dosing, and improved side effect profiles. Among the biologics, the TNF inhibitors, etanercept and adalimumab, are most commonly used. However, TNF inhibitors are contraindicated in patients with neuromuscular diseases, including multiple sclerosis and Guillain Barré syndrome. Since its FDA approval, ustekinumab has proven to be a great addition to the armamentarium with comparable efficacy to TNF inhibitors [1-3]. Importantly, ustekinumab additionally underwent a phase II clinical trial for treatment of relapsing and remitting multiple sclerosis and demonstrated no benefits or harms [4].

Ustekinumab inhibits the common p40 subunit of IL-23 (subunits p19, p40) and IL-12 (subunits p35, p40). Since its discovery, IL-23 has been linked to autoimmune diseases and the p19 subunit has been shown to be over-expressed in Crohn disease, rheumatoid arthritis, and multiple sclerosis. Mice lacking the IL-23p19 and IL-12p40 subunits, but not those lacking the IL-12p35 subunit, are resistant to development of autoimmune disease, including experimental autoimmune encephalomyelitis (EAE, an animal model of multiple sclerosis) and collagen-induced arthritis (CIA, an animal model of rheumatoid arthritis). These data demonstrated that IL-23, rather than IL-12, is critical for development of autoimmunity. It has also been shown that IL-23-deficient mice have IFN-gamma-producing cells, indicating that IL-23-driven immune responses are IFN-gamma pathway independent [5].

Human genetics have further confirmed the important role of IL-23 in autoimmunity. Variants of the IL23R (IL-23 receptor) gene have been associated with a variety of autoimmune diseases, including psoriasis, Crohn disease, ulcerative colitis, ankylosing spondylitis, graft-versus-host disease, and less significantly, with celiac disease and multiple sclerosis. In addition, variants of the IL12B gene (coding for the p40 subunit) have been shown to be associated with psoriasis. Studies have also demonstrated that IL-23p19 and IL-12p40 mRNA levels are elevated in psoriatic skin lesions, and modulation of IL-23 activity attenuates disease severity [5]. Together, these data highlight IL-23 as a potential target for the treatment of a number of autoimmune diseases. Currently, two other IL-23 inhibitors, guselkumab and tildrakizumab, are undergoing early investigation for treatment of psoriasis [6]. Both antibodies are targeting the p19 subunits of IL-23.

Despite these promising findings, relatively little is known regarding the downstream effectors of IL-23 in psoriasis. Recent studies demonstrate IL-23 induces proliferation of Th17 cells, which are characterized by the production of IL-17A, IL-17F, and other related pro-inflammatory cytokines. IL-17 family cytokines are important for cell-mediated immunity against extracellular bacteria, fungi, parasitic infections, and epithelial immunity. Furthermore, IL-17R-deficient mice are highly susceptible to infections by yeast, fungi, and gram-negative bacteria [5]. On the other hand, Th17 cytokines are also overexpressed in a variety of autoimmune disorders and modulation of IL-17 pathway has shown great promise in the treatment of psoriasis and other inflammatory diseases. An IL-17A blocking antibody, secukinumab, was shown to effectively treat plaque psoriasis and psoriatic arthritis in phase 3 studies [6,7] and was recently approved by the FDA for treatment of moderate to severe plaque psoriasis. Other IL-17 pathway modulators, including an IL-17R antagonist (brodalumab) and another IL-17A inhibitor (ixekizumab), have been shown to improve psoriasis in phase 2 studies [8,9]. These are currently in the final stage of phase 3 trials for plaque psoriasis (clinicaltrials.gov identifiers: NCT01708629 and NCT01777191). In addition, secukinumab is undergoing trials for other psoriasis types, e.g. nail psoriasis and palmoplantar psoriasis, and active ankylosing spondylitis. These agents hold great promise as the newer generation of biologics for a variety of autoimmune diseases.

Ustekinumab has undergone rigorous clinical trials for multiple sclerosis and psoriasis [2-4]. In contrast to its high efficacy in the treatment of psoriasis, it does not provide a benefit in patients with multiple sclerosis, despite the fact that ustekinumab delayed white matter demyelination, prevented T2 lesion accumulation, and suppressed inflammation of pre-existing brain lesions in marmosets with established EAE [4]. This lack of clinical efficacy in multiple sclerosis has been postulated to be related to blood-brain barrier and inclusion of advanced patients in the clinical trial [4,10].

The two cases presented here demonstrate the effective treatment of psoriasis in the context of stable multiple sclerosis over a period of 3-4 years. Although further studies will be necessary to more completely elucidate both the therapeutic utility and safety profile of ustekinumab in multiple sclerosis, the data presented in these two cases of patients with co-morbid psoriasis is encouraging.

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