

CASE REPORT

Concurrent treatment of chronic psoriasis and asthma with ustekinumab

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A 56-year-old woman with a 40-year history of guttate flares of psoriasis associated with stress and infection as well as chronic asthma was treated with subcutaneous injections of ustekinumab, repeated after 1 month and then every 3 months. Her psoriasis completely resolved, and her capacity for exercise was markedly increased and asthma maintenance medications were no longer needed. Ustekinumab is a human monoclonal antibody that binds the p40 subunit of IL-12 and IL-23 to limit the progression of the Th1 and Th17 inflammatory immune responses that maintain many autoimmune and inflammatory diseases. Th17-related responses drive inflammation during late stages of chronic asthma and can also be blocked by ustekinumab. Blocking the underlying cytokine-mediated inflammatory responses for psoriasis with ustekinumab can also treat other chronic inflammatory diseases.

Key words: ustekinumab, psoriasis, asthma, chronic inflammation, IL-12p40

Introduction

Most treatments of chronic inflammatory diseases address the symptoms but not the mechanism or response that is promoting and maintaining the inflammation. Although triggered or initiated by trauma, infection or other means, the chronic inflammatory disease processes are maintained and reinforced by T-cell responses. For diseases such as rheumatoid arthritis, Crohn disease, and psoriasis, the pathogenic inflammatory response is maintained by T helper 17 (Th17) and T helper 1 (Th1) responses (1,2). Interleukin 17 (IL-17A,F), IL-22, and tumor necrosis factor alpha (TNF α) generated by Th17 cells promote and maintain the activation of epithelial cells and neutrophils to promote inflammatory conditions (2,3). Inflammatory processes of monocytes, macrophages and dendritic cells are initiated by interferon gamma (IFN γ) produced by natural killer (NK) cells, natural killer T cells and Th1 cells and then are maintained by TNF α .

Chronic asthma is initiated by IgE-related allergic reactions mediated by IL-4, IL-5 and directed by Th2 responses. Although the mechanisms for maintaining its chronicity are less well characterized, a Th17 component has been indicated for some forms and especially for steroid-resistant forms of chronic asthma (4,5).

Th17 responses can be initiated in two ways. Naïve T cells can be activated by IL-1, IL-6 and TGF β . Alternatively, memory T cells, as would be present during chronic disease, are stimulated and their action maintained by IL-23 (2). Th1 responses require

IL-12 for activation (6). IL-12 and IL-23 are related heterodimeric cytokines. The IL-12p40 subunit is present in both cytokines with IL-12 made up of p40 and p35 subunits, and IL-23 of p40 and p19 subunits. The receptor for these two cytokines shares a common subunit but differs in their specificity (7).

Ustekinumab is a human monoclonal antibody that was developed to bind the p40 subunit of IL-12 and IL-23 thus preventing interaction of the cytokine with the IL-12R β 1 receptor on the surface of natural killer and T cells and subsequent receptor-mediated signaling (8,9). As such, ustekinumab can be used to modulate the activation of pathogenic Th17 and Th1 responses. This case illustrates how ustekinumab treatment of psoriasis, by blocking IL-23 and IL-12 action, also limits the inflammatory processes exacerbating a patient's chronic asthma.

Case presentation

A 56-year-old woman presented with a 40-year history of intermittent guttate flares of psoriasis associated with stress and infection. Previous treatments included natural sun exposure, artificial UVB light, topical steroids, keratolytics, calcipotriene cream, medicated shampoos, and several courses of oral acitretin. A recent flare covered over 50% of her cutaneous surface and was unresponsive to all of these modalities. Treatment with a subcutaneous injection of ustekinumab 90 mg (98 kg weight) was initiated and repeated at 1 month and then every 3 months. Her psoriasis completely resolved in 4 months and remained clear for a year with injections every 3 months.

The patient, a nonsmoker, also had severe asthma since early childhood. She required chronic maintenance therapy with inhaled corticosteroids (fluticasone propionate HFA 110 mcg inhaler 2 puffs BID), a short-acting beta agonist (albuterol inhaler two puffs q4hour PRN), and a leukotriene receptor antagonist (montelukast 10 mg QHS). Systemic corticosteroid therapy (methylprednisolone) was used four to six times per year to treat exacerbations of her underlying asthma. After receiving treatment with ustekinumab, the patient's capacity for exercise was markedly increased. For instance, for the first time in over a decade she could shovel her driveway for 45 min without need of her inhaler or a rest. Over the next 6 weeks she was able to taper off all of her asthma maintenance medications completely. The patient reserved an albuterol inhaler for exacerbations of asthma, but required its use on only a few occasions over 6 months during this period. No methylprednisolone has been required since starting on her ustekinumab.

Table I. Pulmonary function tests prior to and after ustekinumab treatment.

	Prior to ustekinumab treatment ^a				Post-ustekinumab treatment ^b			
	Pre-bronchodilator		Post-bronchodilator		Pre-bronchodilator		Post-bronchodilator	
	Actual	% Predicted	Actual	% Predicted	Actual	% Predicted	Actual	% Predicted
FVC (L)	3.2	97	3.4	103	3.2	94	3.4	99
FEV-1 (L)	1.8	72	2.2	89	1.7	67	2.1	83
FEF25–75% (L/s)	0.9	31	1.3	48	0.7	26	1.2	42
FEV-1/FVC (%)	56	75	65	88	54	72	63	85

FVC = forced vital capacity; FEV-1 = forced expiratory volume in 1 s; FEF25–75% = forced mid-expiratory flow rate.

^aMaintenance therapy consisting of fluticasone, albuterol, and montelukast.

^bFluticasone, albuterol, and montelukast no longer used for maintenance therapy.

Post-ustekinumab pulmonary function tests (PFTs) were performed after two injections of ustekinumab and elimination of her maintenance medications and compared to PFTs performed a year earlier. Results are summarized in Table I. No significant decrease of her PFTs occurred despite elimination of maintenance inhaler drugs. Variable airflow obstruction continued in the patient, as indicated by decreased forced expiratory volume in 1 s (FEV1) and by the improvement conferred by bronchodilator treatment (72% of predicted to 89% of predicted) and the change in forced mid-expiratory flow rate (FEF 25–75%). These are specific indicators of small airway obstruction that respond to bronchodilators.

Reduction in scores in a Sydney Asthma Quality of Life Questionnaire indicated dramatic improvement in quality of life after treatment with ustekinumab as compared to earlier traditional maintenance therapy with fluticasone, albuterol, and montelukast (Figure 1) (10). An Asthma Control Test (ACT; QualityMetric Corporation, Lincoln, RI) was also performed which demonstrated improvement despite the lack of maintenance of asthma medications. The ACT is another validated tool for assessing asthmatic control that converts the response to a

five-question survey into a numerical value out of 25, with a higher score indicative of better control of asthma (11,12). The patient demonstrated improvement with a score of 25 after treatment with ustekinumab as compared to 21 while on traditional maintenance therapy.

Discussion

The concomitant amelioration of the patient's psoriasis and chronic asthma after ustekinumab therapy suggests therapeutic action on a focal element of inflammation for both diseases. For chronic asthma, the early phase is induced by IgE-related type I hypersensitivity reactions, which develop into a persistent inflammation caused by other mediators leading to progressive lung damage. It is unlikely that ustekinumab has an effect on the IgE-mediated early phase responses that are mediated by IL-4 and generated by Th2 responses. More likely, ustekinumab neutralization of IL-12p40 inhibits Th17 and/or Th1 responses involved in the later chronic stage of the disease.

Psoriasis, a chronic inflammatory skin disease, was historically considered to be a primary disorder of keratinocyte proliferation. More recent findings demonstrate that it is a consequence of cytokine-mediated autoimmune dysregulation (1). Chronic asthma also results from a cytokine-associated inflammatory process exacted on the respiratory airways (13). It is associated with smooth muscle constriction and swelling of air passages that limit air movement (13). This results in wheezing, shortness of breath, chest tightness, and coughing. By neutralization of IL-12p40, ustekinumab appears to block the maintenance cycle of inflammation common to both psoriasis and chronic asthma and treat both diseases (8,9).

Therapeutic use of ustekinumab for psoriasis was suggested by the presence of increased levels of IL-12p40 expression in psoriatic skin (3,14,15). Both IL-23 and Th17-related cytokines are elevated in cutaneous lesions and in the serum of psoriatic patients, and IL-23R gene variants have been associated with psoriasis (16). Blocking the IL-23/Th17 pathway with ustekinumab blocks a major mediator of psoriasis (Figure 2) (1,2,17). Ustekinumab has become a standard treatment for psoriasis as well as Crohn disease and rheumatoid arthritis (9) but there is no clinical indication, yet, for treatment of chronic asthma.

Airway obstruction in asthma is caused by a combination of airway smooth-muscle constriction and inflammation of the bronchi. Airway inflammation contains cellular infiltrates of eosinophils, neutrophils and activated helper T lymphocytes as well as mast cells (13). There are different modalities of chronic asthma, some of which become refractory to the usual corticosteroid based therapies. Treatments which address other modes of inflammation are required for these patients (18). For the patient in this case, the ustekinumab treatment appears to alleviate the

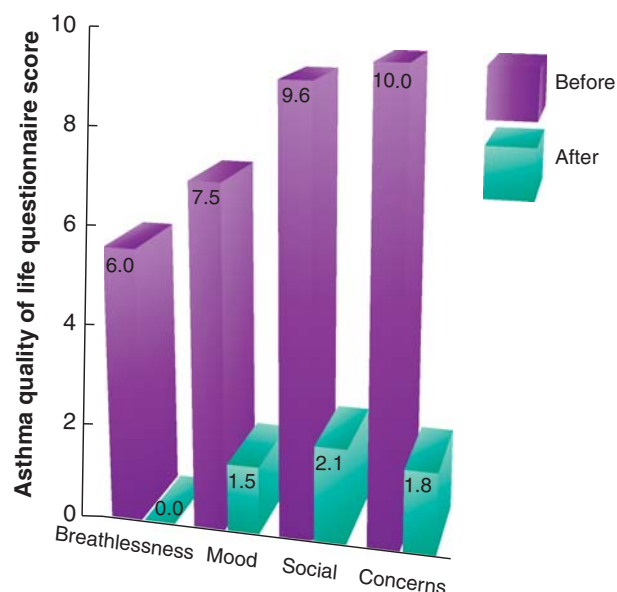


Figure 1. A comparison of Sydney-Asthma Quality of Life Questionnaire scaled scores pre- and post-ustekinumab treatment. Pre-ustekinumab asthma maintenance treatment consisted of fluticasone, albuterol, and montelukast. Post-ustekinumab maintenance treatment consisted of ustekinumab alone. Dramatic improvement in quality of life is seen in all categories after ustekinumab therapy.

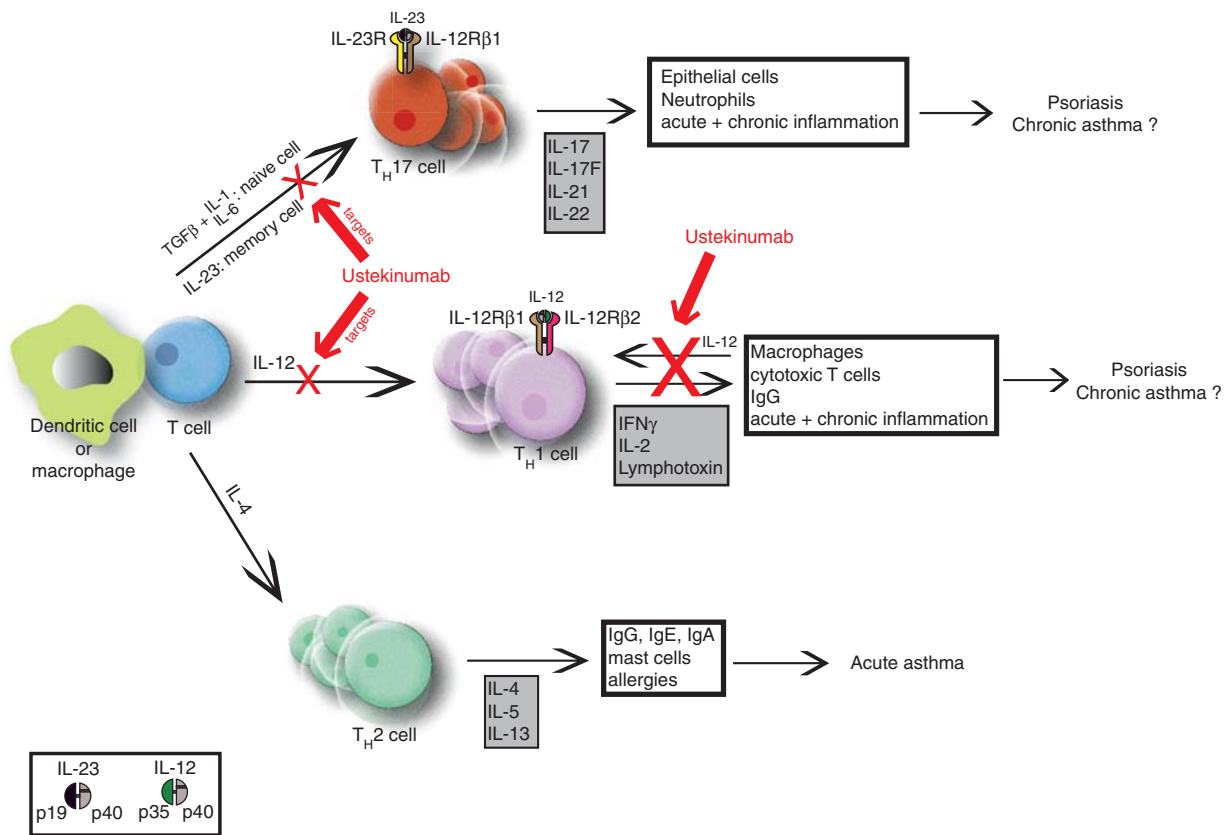


Figure 2. Ustekinumab binds the shared IL-12p40 subunit of IL-12 and IL-23 to block induction and maintenance of Th1 and Th17 inflammatory responses. Psoriasis and chronic asthma are mediated by T-cell-reinforced chronic inflammation. Psoriasis is a chronic inflammation mediated by Th1 and Th17 responses. IgE promotes acute asthma, which can progress to chronic asthma involving Th1 and Th17 responses.

inflammatory aspects of her disease but lung damage has already occurred and may not be repairable.

The role of IL-12p40 in asthma has been implicated by genetic studies in humans and also mouse models of asthma. Specific mutations in the IL-12B gene, which codes for IL-12p40, are associated with asthma severity in Caucasian and Chinese populations (19,20). Sputum samples from patients with severe asthma have elevated levels of IL17A (21), and IL-17-producing cells in lung tissues increase in patients with severe asthma (5). The importance of IL-17 was indicated when strains of mice that develop severe airway hyper-responsiveness were shown to produce elevated levels of both IL-17A and Th2 cytokines, whereas strains manifesting less severe airway hyper-responsiveness produced only Th2 cytokines and little to no IL-17A (22). The IL-17 responses induced by chronic allergen administration promote neutrophil action and also disrupt regulatory T-cell function (23). Also, neutrophilic airway inflammation followed transfer of antigen-specific Th17 cells in an antigen-triggered mouse model of asthma (24).

The surprisingly dramatic effects of ustekinumab on asthmatic signs and symptoms in our patient support the connection between IL-12p40 cytokines and chronic asthma. Oftentimes, patients suffer from multiple inflammatory syndromes supported by the underlying Th17 or Th1 immune responses. Modulation of the Th17 response, as demonstrated by immunization with CEL-2000 in a mouse model for rheumatoid arthritis (25), or as with ustekinumab in this case, can address the factor promoting the inflammatory disease. Based on this case and the mounting evidence of the role of Th17 in chronic asthma, we suggest that there is a subset of patients with psoriasis and chronic asthma in

which treatment with ustekinumab will block the progression of the IL-12p40-mediated comorbid Th17/Th1-promoted diseases. The same may be true for psoriatic patients with other comorbid IL-12p40-mediated Th17/Th1 diseases, such as rheumatoid arthritis, multiple sclerosis, and Crohn's disease (2). This case illustrates the need to pay attention to the potential beneficial effects of ustekinumab on comorbid Th17/Th1 inflammatory diseases when treating patients with dermatitis and subsequent change in therapy.

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