Ustekinumab in the treatment of severe rupioid psoriasis: A case report

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This paper describes a case of a patient with widespread rupioid psoriasis in whom ustekinumab was introduced because of a relative contraindication to conventional systemic treatment and insufficient effect of phototherapy. Improvement of his psoriasis was very rapid, with a decrease in the PASI of 63.4% (from 30.9 to 11.3) during the first 4 weeks of treatment and an additional 31.4% (from 11.3 to 1.6) within another 12 weeks. However, the patient’s psoriatic arthritis has not shown much improvement so far. Treatment with ustekinumab was tolerated well by the patient without any adverse events and also significantly improved his quality of life. Ustekinumab is a welcome extension of biologicals for the treatment of psoriasis because it represents an alternative to anti-TNFα preparations.

Introduction

Psoriasis is a chronic relapsing inflammatory skin disorder affecting about 1 to 3% of the population worldwide, and is often associated with significant morbidity and impaired quality of life (1–3).

It is presumed to be a multifactorial disease which is provoked in genetically predisposed individuals by various triggering factors (4, 5). Psoriasis appears to be mediated by abnormal immune system functioning, including T lymphocyte and macrophage activation and release of various cytokines (2, 6, 7). These include interleukin 12 (IL-12) and IL-23. IL-12 induces differentiation of CD4+ T cells into Th1 cells that produce type 1 cytokines such as interferon γ and tumor necrosis factor α (8, 9). IL-23 induces the development of Th17 cells producing proinflammatory cytokine IL-17 (9–11), which has been recently identified as mediating the tissue damage in psoriasis (12, 13).

In the treatment of psoriasis, topical therapy is sufficient in the majority of patients. However, 20 to 30% of people with psoriasis experience severe symptoms and may require systemic treatment such as methotrexate, cyclosporine, oral retinoids, or phototherapy (2, 3). This conventional treatment is unfortunately associated with multiple potential adverse events especially during long-term use (1, 2). These circumstances have led to the development of biologic agents that alter the specific immunological pathways involved in the development of psoriasis (2, 3).

In the Czech Republic there are currently three biologic agents of the anti-TNFα group on the mar-
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Case report

In June 2009 a 46-year-old man was referred to our clinic with widespread psoriasis of many years’ duration. The disease manifested in the predilection sites when he was 25 years old and then progressively spread to cover almost all of his body. Initially he was treated with various topical preparations and in 2007 he had phototherapy for about 4 months, but with only temporary effect. Systemic treatment was not introduced because of his hypertension and hyperlipidemia.

Since 1997 he has been suffering from pain in the small joints of the hands, and less often of the feet. A rheumatologist diagnosed him with psoriatic spondylarthropathy (HLA-B27 negative) with bilateral sacroiliitis and mild arthritis of the small joints of the hands and feet and treated him with prednisolone in 1997. In 2008 he was treated with leflunomide without much effect.

This patient has a family history of psoriasis; his grandmother had mild psoriasis. The patient himself is also being treated for hypertension and depression with losartan and citalopram, respectively. He also takes ibuprofen from time to time for joint pain. He is a heavy smoker at about 15 cigarettes a day, and he occasionally drinks alcoholic beverages. He works as an IT specialist. He is 180 cm tall and weighs 100 kg.

The patient was admitted to our clinic because of the extent of the disease and the failure of previous treatment. His PASI score at the time of hospitalization was 30.9 and BSA was 63% (see Figs. 1–3). In the laboratory there was slight leukocytosis (11.0 × 10E9/l), hyperuricemia (537 umol/l), hypercholesterolemia (6.38 mmol/l), hypertriglyceridemia (3.93 mmol/l), and elevated glycosylated hemoglobin (4.6%). Metabolic syndrome was diagnosed by an internist and hypolipidemic treatment with fluvastatin was introduced. Because of the relative contraindications to conventional systemic treatment (hypertension, hyperlipidemia, etc.), we decided to treat the patient with ustekinumab. A chest X-ray, Mantoux test (PPD), and Quantiferon test were all negative and therefore the pulmonologist had no contraindications to biological therapy. Because autoantibodies and serology of hepatitis viruses and Epstein-Barr virus were negative, we started treatment with ustekinumab on 30 July 2009 with an initial dose of 45 mg subcutaneously, without any adverse events after the application. The patient was then sent home; he returned for the second injection after 4 weeks (28 July 2009). His psoriasis had significantly improved even after just one injection of ustekinumab (with a PASI of 11.3 and BSA of 42%).

The third injection was administered on 20 October 2009, 16 weeks after the initiation of treatment. The patient tolerated the therapy very well and his psoriasis improved further (with a PASI of 1.6 and BSA of 5%); see Figures 4 and 5. However, the patient’s psoriatic arthritis has not shown much improvement so far. Laboratory results revealed no significant changes.
Discussion

Ustekinumab (STELARA) is a fully human IgG1κ monoclonal antibody produced in a murine myeloma cell line using recombinant DNA technology (11, 14, 15, 17). It binds with high specificity and affinity to the p40 subunit of cytokines IL-12 and IL-23, thereby preventing binding to the IL-12β 1 receptor on the surface of T cells and natural killer cells and subsequent IL-12 and IL-23 receptor mediated signaling (10, 15, 17). Thus ustekinumab inhibits IL-12 induced activation of Th1 cells and subsequently the release of proinflammatory cytokines including IL-2, and TNFα. Ustekinumab also reduces IL-23-induced activation of Th17 cells and the secretion of proinflammatory cytokine IL-17α (10, 17).

Ustekinumab is indicated for the treatment of moderate to severe plaque psoriasis in adults that fail to respond to, have a contraindication to, or are intolerant to other systemic therapies including cyclosporine, methotrexate, and PUVA (17). Our patient was fully indicated for biological treatment because of the severity of his psoriasis (initially PASI 30.9) and relative contraindications to conventional systemic treatment.

Contraindications to treatment with ustekinumab include hypersensitivity to the active substance or to any of the excipients and clinically significant active infection (17).

The recommended treatment scheme of STELARA is an initial dose of 45 mg administered subcutaneously at week 0, followed by a 45 mg dose at week 4, then every 12 weeks thereafter (17). Consideration should be given to discontinuing treatment in patients that have shown no response up to 28 weeks of treatment (17). For patients with a body weight > 100 kg the dose is 90 mg administered subcutaneously at week 0, followed by a 90 mg dose at week 4, then every 12 weeks thereafter. In our patient with borderline weight of 100 kg we hesitated regarding the dose, but in the end we chose the lower dose of 45 mg.

The therapeutic efficacy of ustekinumab was evaluated in a series of phase III trials in patients with moderate-to-severe plaque psoriasis.

In the large Psoriasis Followed by Long-Term Extension (PHOENIX-2 trial), 67% of patients treated with ustekinumab experienced at least a 75% PASI reduction at week 12 (14). In our patient the PASI reduction at week 12 was 71.5%.

Ustekinumab may increase the risk of infections and reactivate latent infections (11, 14–16). The most common infections (> 10%) are nasopharyngitis and upper respiratory tract infection (11, 13). Most are mild and do not necessitate discontinuation of the treatment. In controlled studies of psoriasis patients, the rates of infection or serious infection (cellulitis, diverticulitis, osteomyelitis, erysipelas, herpes zoster, gastroenteritis, pneumonia, and urinary tract infections) were similar between ustekinumab-treated patients and those treated with placebo (11, 14). Our patient has had no infectious complication of the treatment so far.

Prior to initiating treatment with ustekinumab, patients should be evaluated for tuberculosis infection. Ustekinumab must not be given to patients with active tuberculosis (15, 17). Treatment of latent tuberculosis infection should be initiated prior to administering ustekinumab (15, 17). Anti-tuberculosis therapy should also be considered prior to initiation of ustekinumab in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving ustekinumab should be monitored closely for signs and symptoms of active tuberculosis during and after treatment (15, 17). Our patient was thoroughly investigated before initiating the treatment with ustekinumab for latent TB and it was excluded, but we will do regularly checkups for TB during the treatment. Like other biologicals, ustekinumab has the potential to increase the risk of malignancy (11, 13, 15–17). Some patients that received ustekinumab in clinical studies developed cutaneous malignancies (spinoceullular carcinoma, basocellular carcinoma, and lentigo maligna melanoma) and non-cutaneous malignancies (prostatic carcinoma, large intestine carcinoma, thyroid gland carcinoma, hepatic carcinoma, and breast carcinoma), but the incidence of these malignancies was similar between ustekinumab-treated patients and those treated with placebo (9, 12). No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients that develop malignancy while receiving ustekinumab (15, 17). Thus, caution should be exercised when considering the use of ustekinumab in these patients (15, 17).
In clinical studies of ustekinumab, rash and urticaria have each been observed in < 2% of patients (11, 14). If an anaphylactic or other serious allergic reaction occurs, administration of ustekinumab should be discontinued immediately and appropriate therapy initiated (11, 14).

Approximately 5% of ustekinumab-treated patients develop low-titer antibodies to ustekinumab. No apparent correlation of antibody development to injection site reactions was seen. Efficacy tended to be lower in patients positive for antibodies to ustekinumab; however, antibody positivity does not predict a clinical response (11, 13, 17). Other adverse reactions included injection-site erythema, depression, dizziness, headache, diarrhea, pruritus, back pain, myalgia, and fatigue (11, 13, 17).

It is recommended that live viral or live bacterial vaccines such as Bacillus Calmette-Guérin (BCG) should not be given concurrently with ustekinumab. Specific studies have not been conducted in patients that had recently received live viral or live bacterial vaccines. Before live viral or live bacterial vaccination, treatment with ustekinumab should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Patients receiving ustekinumab may receive concurrent inactivated or non-live vaccinations (17).

**Conclusion**

Treatment with ustekinumab was fully indicated in our patient, resulting in very good and rapid therapeutic effect without any adverse events. Ustekinumab is a welcome extension of biologicals for the treatment of psoriasis because it represents an alternative to anti-TNFα preparations, which have their own limitations (demyelination, cardiac failure, etc.) However, the long-term efficacy and safety of ustekinumab must be evaluated by extensive long-term studies.

**References**

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