The body of evidence concerning the immunological basis of psoriasis has expanded greatly in recent years (1). The introduction of biologic agents targeting key steps in the pathogenesis of psoriasis has not only increased this knowledge, but has also augmented the treatment options for the disease with highly effective drugs (1). These agents include monoclonal antibodies that block key cytokines, such as tumour necrosis factor (TNF-α) and interleukin-12 or -23 (IL-12/23), which play crucial roles in the pathogenesis of psoriasis. We report here the case of a patient whose psoriasis exhibited a differential response to biologic therapy with the IL-12/23 antagonists briakinumab and ustekinumab.

CASE REPORT

A 43-year-old man presented at our department with a 26-year history of severe chronic plaque psoriasis. Clinical examination revealed large psoriatic plaques on the patient’s trunk, extremities, and scalp. He had a Psoriasis Area and Severity Index (PASI) score of 24.4. The patient was invited to participate in a phase 3, multicentre, randomized, double-blind study comparing the safety and efficacy of briakinumab vs. methotrexate in subjects with moderate to severe chronic plaque psoriasis (NCT00679731). He agreed to participate and was enrolled after providing written informed consent. In the study, the patient received briakinumab at a loading dose of 200 mg at week 0 and 4 and then at a dose of 100 mg subcutaneously (s.c.) every 4 weeks until week 24. The patient’s PASI decreased to 6.3 at week 12 and 4.8 at week 24 (i.e. a 75% reduction in PASI (PASI75)) (Fig. S1; available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1243). At week 24, the patient decided to discontinue his study participation for personal reasons. Eleven weeks after the protocol withdrawal of treatment at week 40, the median PASI score was 15.8 at week 0 to 0 at week 12. Since then the patient has been treated continuously with adalimumab for more than 12 months, has maintained a complete response to treatment, and has shown no new psoriatic plaques.

DISCUSSION

Safe, effective therapies for chronic plaque psoriasis are badly needed. Two IL-12/23 antagonists (ustekinumab and briakinumab) have been investigated for the treatment of psoriasis. Whereas ustekinumab has been approved for the treatment of chronic plaque psoriasis, briakinumab has recently been withdrawn from registration procedures. Mechanistically, both antibodies are similar (i.e. both bind to the p40 subunit of IL-12/23); immunologically, however, briakinumab is a recombinant exclusively human-sequence IgG1, 1 monoclonal antibody isolated from human phage display library, whereas ustekinumab is a fully human IgG1, k antibody generated in human immunoglobulin transgenic mice (2). In a 12-week multicentre, randomized, placebo-controlled phase 2 trial to evaluate the safety and efficacy of briakinumab (ABT-874) in the treatment of moderate to severe chronic plaque psoriasis, approximately 90% of the patients in the ABT-874 multiple-dose groups achieved a PASI75 or greater response by week 12 (2). A similarly good response was also noted in our patient.

In large randomized trials of ustekinumab (PHOENIX 1 and 2), 66–67% of patients receiving ustekinumab 45 mg achieved PASI75 at week 12 (3, 4). However, after protocol withdrawal of treatment at week 40, the median percentage improvement in PASI began to decrease gradually by week 44 and then deteriorated after week 52 (2). Among patients withdrawn from ustekinumab treatment, response was generally restored within 12 weeks of reinitiating such treatment (3). This is consistent with results from a retrospective data analysis report of a registry, in which 12 of 18 (67%) of patients treated under daily life conditions with ustekinumab at our department exhibited a PASI75 reduction (5). Based on this data, one would have expected an efficient PASI response after initiating ustekinumab in our patient reported herein. However, he did not respond to treatment with ustekinumab, even after having achieved PASI75 in response to treatment with briakinumab. What remains unclear is the mechanism underlying the differential response to briakinumab vs. ustekinumab treatment in the present case. Since most clinical trials of IL-12/23 antagonists to date have excluded patients previously exposed to any systemic
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anti-IL-12/23 therapy, little can be inferred about the potential interactions between previous and subsequent treatments with anti-IL-12/23 agents. Nevertheless, there are several possible explanations for the discrepancy in the efficacy of briakinumab vs. ustekinumab in the present case. First, briakinumab and ustekinumab may have different binding capacity to the p40 subunit of IL-12/23, potentially accounting for different efficacy of antibody treatment. Second, in the present case our patient’s first anti-IL-12/23 treatment with briakinumab may have led to the formation of cross-reactive antibodies to ustekinumab that effectively thwarted ustekinumab’s anti-psoriatic activity. Third, ustekinumab treatment may have produced anti-drug antibodies against itself, which thwarted its own response. However, antibody formation as a cause of therapeutic failure is rather unlikely because autoantibodies to ustekinumab were reported in only 5% of treated patients (4). Also, our patient had received methotrexate (which is known to suppress antibody formation) between treatment with briakinumab and ustekinumab. Lastly, briakinumab appeared to be highly dosed in its investigational studies. This was probably responsible for its superior efficacy in our patient, who was enrolled in such a study and received 200 mg for the first two treatments.

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REFERENCES