

CONCISE COMMUNICATION

Exacerbation of atopic dermatitis symptoms by ustekinumab in psoriatic patients with elevated serum immunoglobulin E levels: Report of two cases

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ABSTRACT

Psoriasis is a chronic inflammatory skin disease mainly mediated by a T-helper cell subset, Th17 cells. Recently, increased levels of total serum immunoglobulin (Ig)E have been reported in a subset of psoriatic patients. Ustekinumab (UST) is one of the most commonly used biologic agents for the treatment of moderate to severe plaque psoriasis, and a previous report also documented effectiveness of UST for psoriatic patients with high serum IgE levels. We experienced two psoriatic patients with high serum IgE levels, in whom UST completely improved psoriasis but paradoxically provoked or exacerbated atopic dermatitis (AD)-like symptoms. This reciprocal phenomenon suggests the shift of Th balance toward Th2, along with altered profiles of inflammatory cytokines. It appears prudent to consider the possibility of such adverse effects when treating psoriatic patients with UST with concomitant AD symptoms, a history of AD or high serum IgE levels.

Key words: adverse effect, atopic dermatitis, immunoglobulin E, psoriasis, ustekinumab.

INTRODUCTION

Psoriasis and atopic dermatitis (AD) are the most common chronic inflammatory skin diseases. Their clinical and pathophysiological features differ substantially.¹ Although a few patients may have psoriasis and AD concomitantly,² the simultaneous occurrence of both diseases appears to be rare.

Ustekinumab (UST) is a fully human monoclonal antibody against the common p40 subunit of interleukin (IL)-12 and IL-23, and its efficacy has been established for the treatment of psoriasis.¹ Here, we present two cases with paradoxical induction or exacerbation of AD-like symptoms during UST treatment for psoriasis.

CASE REPORTS

Case 1

A 59-year-old Japanese man presented with a 19-year history of psoriasis and his Psoriasis Area and Severity Index (PASI) score was 18 (Fig. 1a). He had no symptom or a previous history of AD. Laboratory examination showed elevated levels of total serum immunoglobulin (Ig)E (12790 IU/L; normal, <250) and thymus and activation-regulated chemokine (TARC) (1879 pg/mL; normal, <449). He initially received treatment with cyclosporin but it was then switched to UST because his psoriatic skin lesions became refractory. UST was administered

s.c. (45 mg) at week 0, 4 and every 12 weeks thereafter, which led to complete remission of psoriasis (Fig. 1b). However, the symptoms of AD such as pruritus and chronic eczematous dermatitis affecting flexural surfaces emerged after the initiation of UST (Fig. 1c). The diagnosis of AD was made using the criteria of Hanifin and Rajka,³ and it worsened gradually during UST treatment. After 172 weeks of the treatment with UST, his Scoring Atopic Dermatitis (SCORAD) rose up to 10 (Fig. 1d,e). Consequently, we terminated UST treatment and the symptoms of AD improved rapidly. Laboratory examination after the termination of UST showed decreased levels of total serum IgE (8186 IU/L) and TARC (441 pg/mL).

Case 2

A 39-year-old Japanese woman presented with a 21-year history of psoriasis and AD with a high serum IgE level. PASI score and SCORAD were 18 and 9, respectively. Laboratory examination showed elevated levels of total serum IgE (2619 IU/L) and TARC (1059 pg/mL). She initially started cyclosporin for the treatment of psoriasis but it was then switched to UST because of insufficient responses. Administration of UST 45 mg s.c. twice at week 0 and 4 resulted in complete remission of psoriatic skin lesions. However, the symptoms of AD worsened gradually after the initiation of UST treatment (Fig. 2a). Following 4 weeks of UST treatment, SCORAD rose up to 15 with a serum TARC level of 5338

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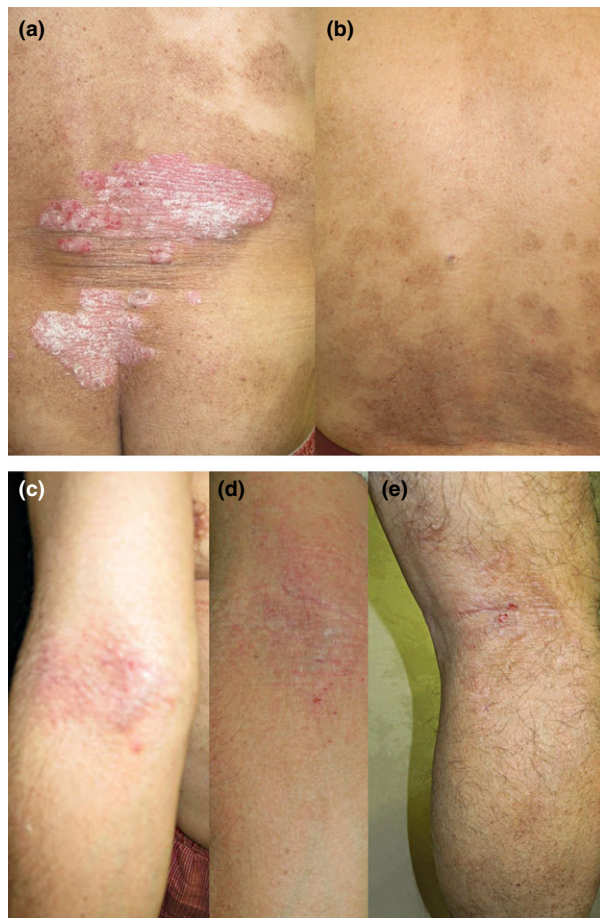


Figure 1. Clinical picture of patient 1. (a) Well-delineated erythematous scaling plaques on the back before ustekinumab (UST) treatment. (b) Postinflammatory hyperpigmentation after UST treatment. (c) Lichenified erythematous plaque on the flexor aspect of the right elbow emerging after the initiation of UST. (d) Exacerbation of the eruption on the right elbow during UST treatment. (e) New onset of pruritic lichenified lesion on the flexor aspect of the right knee during UST treatment.

pg/mL. We terminated UST treatment and the TARC level decreased to 316 pg/mL in parallel with rapid improvement of the symptoms of AD (Fig. 2b).

DISCUSSION

Recent studies indicate that the pathogenesis of psoriasis is mainly mediated by Th17 cells, preferentially producing IL-17, while AD is driven by Th2 and Th22 cells.¹ This substantial difference may account for distinct clinical symptoms between psoriasis and AD. Indeed, an inverse association of both diseases has been reported,¹ and their simultaneous occurrence appears to be rare, with only a few exceptions.²

Immunoglobulin E is a typical mediator of allergic diseases, such as atopic dermatitis and asthma, and increased serum IgE levels are the result of exaggerated Th2 cell responses.⁴



Figure 2. Clinical picture of patient 2. (a) Pruritic papules and erythematous plaques on the face during ustekinumab (UST) treatment. (b) Improvement of eczematous lesions after discontinuation of UST treatment.

Recently, however, increased levels of total serum IgE have been reported in 39–46% of patients with psoriasis.¹ The elevation of serum IgE levels in psoriasis may be caused partly through a Th2-independent mechanism. IgE production by B cells can be promoted by IL-17A in addition to IL-4 and IL-13.¹ The presence of an IL-17–IgE–plasmacytoid dendritic cell axis may contribute to self-destructive autoimmune responses in psoriatic patients with high serum IgE levels.⁴

Ustekinumab is one of the most commonly used biologics in psoriatic patients. Its efficacy has been shown even for psoriatic patients with high total serum IgE levels and, indeed, UST lowered the number of IgE- and FcεRI-bearing cells in the lesional skin.⁵ However, previous case reports have also documented that UST provoked or exacerbated AD-like symptoms paradoxically while improving psoriatic symptoms.^{6,7} We also experienced a similar reciprocal phenomenon following UST administration in a couple of psoriatic patients. Elevation of total serum IgE and TARC levels occurred in parallel with the exacerbation of AD symptoms possibly due to the result of Th2 dominance. In addition to IgE, serum TARC level is known to reflect the Th2-dominant immune response and is markedly elevated in patients with AD but not in those with psoriasis,⁸ although its elevation is not necessarily specific to AD. The underlying mechanism is only speculative regarding the induction or aggravation of AD-like symptoms by UST. IL-17 has some protective roles in skin barrier functions and its inhibition may cause their dysfunction, leading to the development of Th2 dominance.⁹ Furthermore, the inhibition of the Th1 pathway by blocking IL-12 may create an immunological imbalance, favoring an increased activity of the opposing Th2 pathway.¹⁰ In either case, the resultant Th2-dominant inflammation may cause AD-like symptoms as well as an elevation of serum IgE and TARC levels in psoriatic patients irrespective of the presence of Th2-independent pathway.

In addition, tumor necrosis factor (TNF)- α inhibitors are known to induce a variety of cutaneous eruptions

paradoxically, such as eczematous reaction, psoriasiform drug eruption, interface dermatitis and palmoplantar pustular psoriasis.^{11,12} Considering that UST may act partly as a TNF- α inhibitor, this mechanism may serve as another explanation for the aggravation of AD-like symptoms by UST.¹³

Very interestingly, UST has recently been proposed as a potential treatment modality for AD.¹⁰ Indeed, several studies have shown an enhanced immune response of the Th17 axis in patients with specific subtypes of AD, especially in those of an Asian origin, intrinsic type or pediatric type.^{9,14} Nevertheless, we need to remember that the Th17 pathway is overall much less activated in AD patients compared with that in patients with psoriasis.⁹ Although beneficial clinical efficacy of UST has been reported in some severe AD patients, others including Japanese AD patients have shown only partial or even no efficacy.¹⁵ Based on our observation, the possible development of Th2 dominance induced by UST needs extreme caution, especially in patients with primarily Th2-skewed condition, such as extrinsic AD.¹⁵

In conclusion, we have reported two cases of psoriatic patients with high total serum IgE levels, in whom UST induced or exacerbated the AD-like symptoms despite complete improvement of psoriasis. It should be kept in mind that UST may induce eczematous eruptions or AD symptoms in psoriatic patients, especially in those with concomitant AD, a history of AD or high serum IgE levels. UST may not be applied to such psoriatic patients. In addition, PASI-75 response rates were significantly higher after treatment with UST in psoriatic patients with low total serum IgE levels compared with those in psoriatic patients with higher IgE levels (Dr Yoshinori Umezawa, 2018, unpubl. data). IgE-mediated mechanisms may somehow negatively interfere with the therapeutic benefit of UST for psoriasis. Further studies will be needed to elucidate the mechanism of IgE contribution to the pathogenesis of psoriasis.

CONFLICT OF INTEREST: H. N. has received consultant and/or speaker fees from Janssen Pharmaceuticals (Tokyo, Japan). Y. U. and N. A. have received speaker fees from Janssen Pharmaceuticals (Tokyo, Japan).

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