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Title: Flare of palmoplantar psoriasis with ustekinumab

Case Letter

Running head: Ustekinumab induced flare of PPP

Short running title: Ustekinumab induced flare of PPP

Authors: Benjamin S Daniel¹, Chris Baker^{1, 2, 3} Peter Foley^{1, 2, 3}

Affiliations:

1. St Vincent's Hospital, Melbourne, Australia
2. Skin and Cancer Foundation, Carlton, Melbourne, Australia
3. University of Melbourne, Melbourne, Australia

Word count: 498

References:3

Table: 1

Corresponding author:

Benjamin S Daniel

ben@drdaniel.com.au

Department of Dermatology, St Vincent's Hospital, Melbourne

41 Victoria St, Fitzroy

(03)92312211

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/AJD.13122](https://doi.org/10.1111/AJD.13122)

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Article type : Case Letter

Though there are countless reports of *de novo* and paradoxical worsening of palmoplantar pustular psoriasis (PPPP) and palmoplantar pustulosis (PPP) with TNF-inhibitors [1], these side effects are not well-recognised with ustekinumab. We report three cases of patients with palmoplantar psoriasis whose conditions worsened after commencing ustekinumab.

A 54-year-old male smoker with palmoplantar psoriasis consisting of erythema, scale and hyperkeratosis in the absence of pustules, noticed a flare after the initial dose of ustekinumab. After 2 years of ustekinumab, the patient reported ongoing worsening palmoplantar involvement within 4 weeks of every injection, so ustekinumab was ceased. The palmoplantar involvement completely resolved and he is maintained on acitretin 10mg/day alone.

A 64-year-old female non-smoker with biopsy proven pustular psoriasis involving the left sole had a flare of her disease within seven days of every ustekinumab administration. Other causes of plantar pustules were eliminated with biopsies, tissue culture, fungal scrapings and blood tests. She was diagnosed with breast cancer after the second dose of ustekinumab and underwent a lumpectomy and radiation therapy. Ustekinumab was ceased after the third injection. She is not currently on any immunosuppression and has persistent plantar pustules.

A 59-year-old male smoker with palmoplantar psoriasis with hyperkeratosis, fissures and erythema developed headaches, diaphoresis, tremors and corysal symptoms after the second dose of ustekinumab. These symptoms improved in the lead up to, but worsened again, after the third injection (week 16). He was thoroughly investigated for an underlying autoimmune, paraneoplastic and infectious cause of his presentation with no alternative precipitant identified. Ustekinumab was ceased and he was

commenced on a tapering dose of prednisolone. The systemic symptoms resolved but he still had marked palmoplantar involvement which is currently being treated with methotrexate and acitretin.

The pathophysiology of palmoplantar psoriasis, PPPP and PPP is thought to be different to chronic plaque type psoriasis with other cytokines such as IL-36 and IL-17 playing a role. Ustekinumab, an IL-12/23 inhibitor, is effective in treating PPP, PPPP and paradoxical reactions secondary to TNF-inhibitors [2] and can be used as a first line biological agent for PPP.

At least six cases have been published suggesting a temporal association of PPPP/PPP and ustekinumab [3]. (table 1) Pustules tend to form within days to months of starting ustekinumab. Another two reports describe worsening of CPP or development of inverse psoriasis with ustekinumab.

An increase in IFN-alpha due to blocking IL-23, TNF-alpha and the Th-17 pathway may be responsible for paradoxical reactions. Though alternative explanations for clinical deterioration such as infections (bacterial, viral), lack of response to biologic or natural disease fluctuation were considered in our three cases, temporality similar to the published case reports supports a paradoxical reaction. A preferred treatment option for paradoxical reactions cannot be extrapolated from the small number of case reports. Cases typically improved with switching biologic agent, or adding a topical or oral corticosteroid. Further research is required to determine why this paradoxical reaction occurs, which subsets of patients are at risk, the reason for a predominant pustular presentation, and appropriate therapy.

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Author/s:

Daniel, BS;Baker, C;Foley, P

Title:

Flare of palmoplantar psoriasis with ustekinumab

Date:

2019-08-01

Citation:

Daniel, B. S., Baker, C. & Foley, P. (2019). Flare of palmoplantar psoriasis with ustekinumab. AUSTRALASIAN JOURNAL OF DERMATOLOGY, 61 (1), pp.63-65. <https://doi.org/10.1111/ajd.13122>.

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