Title: Tildrakizumab for treatment of refractory pyoderma gangrenosum of the penis and polymyalgia rheumatica: Killing two birds with one stone.

Running title: Tildrakizumab for treatment of PG & PMR

Authors: John, Jared Marc [BBiomedSci, BSc (Hons), MBBS, MPH]¹
Sinclair, Rodney Daniel [MBBS, MD, FACD]

Corresponding Author: John, Jared Marc (ORCID: 0000-0002-3096-5562)

Institution: Sinclair Dermatology, 2 Wellington Parade, East Melbourne, VIC 3002, Australia

Tel: (613) 9013 0099

Email: jared.john@sinclairdermatology.com.au

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.13196](https://doi.org/10.1111/AJD.13196)

This article is protected by copyright. All rights reserved

DR. JARED MARC JOHN (Orcid ID : 0000-0002-3096-5562)

PROF. RODNEY SINCLAIR (Orcid ID : 0000-0001-6751-1428)

Article type : Case Letter

Tildrakizumab for treatment of refractory pyoderma gangrenosum of the penis and polymyalgia rheumatica: Killing two birds with one stone.

Pyoderma gangrenosum is an inflammatory dermatosis characterised by painful, non-healing skin ulceration. There are no evidence-based or expert consensus guidelines to direct management and treatment failure is common. Approximately 50% of pyoderma gangrenosum sufferers have a recognized disease association such as inflammatory bowel disease, or polymyalgia rheumatica (1).

Polymyalgia rheumatica is a chronic inflammatory condition characterised by fatigue, pain and stiffness in the neck and proximal joints. This second most common rheumatic disease in the elderly is associated with giant cell arteritis in about 20% of cases. Treatment is unsatisfactory with many patients experiencing corticosteroid toxicity from prolonged courses required to maintain remission (2).

A 69 year-old male with a history of gout, polymyalgia rheumatica and renal impairment presented with a sloughy painful penile ulcer along the inferior corona measuring 25x12mm which appeared 8 months ago and was enlarging progressively (Fig 1). Previous treatments included numerous courses of antibiotics and topical corticosteroids. Polymyalgia rheumatica medications of 3 years (since May 2016) included methotrexate (15mg/week) and prednisolone (6mg/day). Initial laboratory investigations revealed erythrocyte sedimentation rate (ESR) 38, C-reactive protein (CRP) 16 and rheumatoid factor 23. Immunoserology and sexual health screens were negative. Swabs from the ulcer base showed heavy growth of mixed flora.

Histopathology revealed ulceration with bland-appearing keratinocytes in the epithelium. The ulcer base contained a mixed inflammatory cell infiltrate, granulation tissue and ectatic vessels, but no granulomas. Viropathic changes were not observed and various pathogen stains were negative. A diagnosis of pyoderma gangrenosum was made based on clinico-pathological and microbiological correlation.

The patient was initially prescribed topical clobetasol. After 2 weeks the ulcer had expanded, so cyclosporine (100mg/day) was commenced. 5 weeks later, the lesions were 25% smaller but still very painful. There was no further response after 4 more weeks, so cyclosporine was ceased, prednisolone tapered, and he was commenced on tildrakizumab 100mg subcutaneously on a 0, 4, then 12-weekly schedule. After 2 doses (week 6), prednisolone was discontinued, and methotrexate was reduced to 10mg weekly. After 3 doses (week 24), the ulceration had almost completely re-epithelialized (Fig 2). Methotrexate was stopped without polymyalgia rheumatica relapse. He received the 4th dose at week 28. At this timepoint, ESR was 2 and CRP 8. The ulceration had healed completely at week 32. There were no adverse events and the patient discontinued topical treatment.

Elevated IL-23 expression, Th17-cell recruitment and IL-23/IL-17 inflammatory axis disturbance have been implicated in pyoderma gangrenosum pathogenesis (3). Tildrakizumab is a monoclonal antibody that neutralizes IL-23 activity through IL-23p19 receptor inactivation. While the IL-12/IL-23p40 inhibitor ustekinumab has been successfully used to treat pyoderma gangrenosum (3, 4), this is the first report of a selective anti-IL-23 biologic for refractory pyoderma gangrenosum treatment. The profound response seen justifies further clinical studies to investigate the efficacy and safety of tildrakizumab in pyoderma gangrenosum.

Interestingly, tildrakizumab enabled cessation of prednisolone and methotrexate without polymyalgia rheumatica relapse. A decreased regulatory T-cell count, and a markedly increased Th17-cell response is observed in polymyalgia rheumatica (2, 5). Tildrakizumab's inhibition of the IL-23/IL-17 axis and hence Th17-cell activity may explain its efficacy in polymyalgia rheumatica treatment and account for the clinical response seen. Further investigation of its use as either a stand-alone treatment or steroid sparing agent for polymyalgia rheumatica is also justified.

References

1. Ahn C, Negus D, Huang W. Pyoderma gangrenosum: a review of pathogenesis and treatment. *Expert Review of Clinical Immunology*. 2018;14(3):225-33.
2. González-Gay MA, Pina T, Prieto-Peña D, Calderon-Goercke M, Blanco R, Castañeda S. Drug therapies for polymyalgia rheumatica: a pharmacotherapeutic update. *Expert Opinion on Pharmacotherapy*. 2018;19(11):1235-44.
3. Guenova E, Teske A, Fehrenbacher B, Hoerber S, Adamczyk A, Schaller M, et al. Interleukin 23 Expression in Pyoderma Gangrenosum and Targeted Therapy With Ustekinumab. *Archives of Dermatology*. 2011;147(10):1203-5.
4. Goldminz AM, Botto NC, Gottlieb AB. Severely recalcitrant pyoderma gangrenosum successfully treated with ustekinumab. *Journal of the American Academy of Dermatology*. 2012;67(5):e237-8.
5. Castañeda S, García-Castañeda N, Prieto-Peña D, Martínez-Quintanilla D, Vicente EF, Blanco R, et al. Treatment of polymyalgia rheumatica. *Biochemical Pharmacology*. 2019.

Figure Legends

Figure 1: (a) Ulceration along the inferior penile corona. (b) Crusted erosion on central glans.

Figure 2: (a) At week-24 of tildrakizumab treatment, the ulceration had almost completely healed except for (b) 2 focal areas on left lateral aspect of the shaft (arrows).

ajd_13196_f1.jpg

ajd_13196_f2.jpg

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

John, JM;Sinclair, RD

Title:

Tildrakizumab for treatment of refractory pyoderma gangrenosum of the penis and polymyalgia rheumatica: Killing two birds with one stone

Date:

2019-11-14

Citation:

John, J. M. & Sinclair, R. D. (2019). Tildrakizumab for treatment of refractory pyoderma gangrenosum of the penis and polymyalgia rheumatica: Killing two birds with one stone. AUSTRALASIAN JOURNAL OF DERMATOLOGY, 61 (2), pp.170-171. <https://doi.org/10.1111/ajd.13196>.

Persistent Link:

<http://hdl.handle.net/11343/286616>