

Checkpoint inhibitor-induced polymyalgia rheumatica controlled by cobimetinib, a MEK 1/2 inhibitor

We read with great interest the recently published paper by Kostine *et al*¹ reporting on musculoskeletal immune-related adverse events (IRAE) related to cancer immunotherapy. We applaud the authors for being able to identify the incidence of these side effects and of their relation to tumour response.

Of particular interest to us is the fact that most of the musculoskeletal IRAE were polymyalgia-like. We are eager to add to that discussion by presenting this case of checkpoint inhibitor-induced polymyalgia rheumatica (PMR) that was partially treated by targeted therapy with a MEK 1/2 inhibitor.

A 70-year-old woman presented in November 2015 with rectal cancer that was locally invasive and metastatic to peritoneum and lung. She failed chemotherapy (5-fluorouracil, leucovorin and irinotecan) and in September 2016 was enrolled in a trial of atezolizumab (anti-PD-L1) every 2 weeks plus cobimetinib (a MEK 1/2 inhibitor). Cobimetinib was given daily for 3 weeks each month followed by a 1-week break.

In March 2017, the patient developed shoulder and hip girdle pain accompanied by prolonged morning stiffness. A reduction in the dose of cobimetinib made her feel worse. Lyrica and Oxycodone were added to her regimen without benefit. The patient noted that her symptoms were episodic, coming only during the week each month that she was off cobimetinib. Her symptoms would resolve promptly 2 days after she resumed cobimetinib.

The patient was referred to rheumatology in September 2017 and was thought to have checkpoint inhibitor-induced PMR. Laboratory evaluation performed when she was symptomatic (at the end of a week off of cobimetinib) revealed an erythrocyte sedimentation rate (ESR) 72. Because it appeared that her PMR was controlled by the MEK 1/2 inhibitor, prednisone 10 mg daily was added for only 5 days each month, starting on day 3 of the off-cobimetinib week. The patient did very well until January 2018 when her malignancy progressed. Atezolizumab and cobimetinib were discontinued; she was started on a different regimen. Following discontinuation of cobimetinib, her PMR symptoms recurred and she required daily prednisone.

Autoimmune diseases induced by checkpoint inhibitors may give insight into the pathogenesis of native autoimmune diseases such as PMR. This case of a patient with checkpoint inhibitor-induced PMR responding to a MEK 1/2 inhibitor suggests that there could be a role for MEK inhibition in the management of PMR.

The protein kinase cascade Raf/MEK/ERK regulates gene expression in response to stimuli such as extracellular mitogens, growth factors and cytokines. Downstream effects are important in cellular proliferation and apoptosis. Disordered activity of this pathway leads to uncontrolled tumour cell proliferation. The pathway has therefore become a useful therapeutic target in KRAS-mutated and BRAF-mutated cancers.

In addition to its role in cellular proliferation, the MEK/ERK cascade also plays a role in inflammatory responses. A number of studies have shown that the MEK/ERK cascade promotes the production of a variety of proinflammatory cytokines, and MEK inhibitors have been reported to impair T-lymphocyte function. For example, Vella *et al* demonstrated that the MEK inhibitor trametinib suppresses T-cell proliferation and cytokine production by CD4+ and CD8+ T cells.² Dumont *et al* showed that the MEK-inhibitor PD98059 inhibits, among other things, IL-6 production.³

In rheumatoid arthritis, the MEK/ERK pathway is upregulated in the synovial tissues.^{4,5} The MEK inhibitor PD184352 inhibited paw oedema and clinical arthritis scores and attenuated disease-induced weight loss in a collagen-induced arthritis mouse model.⁵ The MEK inhibitor JTP-74057 reduced TNF- α and interleukin 6 (IL-6) production in human, mouse and rat peripheral blood mononuclear cells and was equal to leflunomide in suppressing the development of both adjuvant-induced arthritis and collagen-induced arthritis mouse models.⁶

Patients with PMR have elevated circulating levels of IL-6; the anti-IL-6 receptor antibody tocilizumab has been used effectively in this condition. In our patient with checkpoint inhibitor-associated PMR, treatment with the MEK inhibitor cobimetinib suppressed inflammation, perhaps via suppression of IL-6. This case suggests that MEK inhibitors could be a promising steroid-sparing agent for PMR.

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Contributors Both KKC and ARB have a research interest in checkpoint inhibitor-associated rheumatic adverse events. This particular patient is followed by KKC. KKC identified the material and wrote the first draft of the case. ARB reviewed the material and provided editing support.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Ethics approval HSS IRB.

Provenance and peer review Not commissioned; internally peer reviewed.

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To cite Chan KK, Bass AR. *Ann Rheum Dis* 2019;**78**:e70.

Received 28 April 2018

Accepted 30 April 2018

Published Online First 14 May 2018



► <http://dx.doi.org/10.1136/annrheumdis-2018-213672>

Ann Rheum Dis 2019;**78**:e70. doi:10.1136/annrheumdis-2018-213672

REFERENCES

- Kostine M, Rouxel L, Barnette T, *et al*. Rheumatic disorders associated with immune checkpoint inhibitors in patients with cancer—clinical aspects and relationship with tumour response: a single-centre prospective cohort study. *Ann Rheum Dis* 2018;**77**:393–8.
- Vella LJ, Pasam A, Dimopoulos N, *et al*. MEK inhibition, alone or in combination with BRAF inhibition, impairs multiple functions of isolated normal human lymphocytes and dendritic cells. *J Immunother Cancer* 2013;**1**(Suppl 1):P93.
- Dumont FJ, Staruch MJ, Fischer P, *et al*. Inhibition of T cell activation by pharmacologic disruption of the MEK1/ERK MAP kinase or calcineurin signaling pathways results in differential modulation of cytokine production. *J Immunol* 1998;**160**:2579–89.
- Schett G, Tohidast-Akrad M, Smolen JS, *et al*. Activation, differential localization, and regulation of the stress-activated protein kinases, extracellular signal-regulated kinase, c-JUN N-terminal kinase, and p38 mitogen-activated protein kinase, in synovial tissue and cells in rheumatoid arthritis. *Arthritis Rheum* 2000;**43**:2501–12.

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- 5 Thiel MJ, Schaefer CJ, Lesch ME, *et al.* Central role of the MEK/ERK MAP kinase pathway in a mouse model of rheumatoid arthritis: potential proinflammatory mechanisms. *Arthritis Rheum* 2007;56:3347–57.
- 6 Yamaguchi T, Kakefuda R, Tanimoto A, *et al.* Suppressive effect of an orally active MEK1/2 inhibitor in two different animal models for rheumatoid arthritis: a comparison with leflunomide. *Inflamm Res* 2012;61:445–54.