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Author reply to “No live vaccines for people being treated with leflunomide”

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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/imj.14053](https://doi.org/10.1111/imj.14053)

We thank Dr Karin Batty for her comments regarding avoidance of live vaccines in people receiving leflunomide (LFN).¹ This is an area which remains unclear. Advice has usually been that live vaccines should be avoided in the presence of severe immunosuppression. Although LFN was not specifically mentioned², the degree of immunosuppression for which live virus vaccination is contraindicated was marked, and “low-to-moderate dose, ie < 20 mg/d of prednisone or equivalent” did not preclude live virus vaccination. We agree with the Advisory Committee on Immunization Practices (ACIP) to the Centres for Disease Control (CDC) that “Therapy with low-doses of methotrexate (MTX, <0.4 mg/kg/week), azathioprine (AZA, <3.0 mg/kg/day), or 6-mercaptopurine (<1.5 mg/Kg/day) are not contraindications for administration of zoster vaccine.”² We would consider LFN in this category, as its efficacy and toxicity when used in the treatment of inflammatory arthritis is similar to that of the above doses of MTX and AZA. Neither ACIP or the Infectious Diseases Society of North America view LFN as a strong immunosuppressant.^{2,3} Our extrapolation from these, while not erroneous, should have been clearer and we appreciate Batty pointing this out.

Reassuringly, no cases of varicella or herpes zoster (HZ) occurred within 42 days in a subset of 633 patients receiving “high level” immunosuppression with a tumour necrosis factor inhibitor (TNFi) or other biologic disease modifying anti-rheumatic drug (bDMARD) at time of Zostavax (ZVL) administration.⁴ However, a more cautious approach is probably preferable. There were no reported infectious complications following administration of ZVL to 142 patients aged $\geq$ 50 years receiving bDMARDs.⁵ All patients missed one dose of bDMARD prior to vaccination, with ZVL given at the time of the missed dose and the bDMARD restarted two weeks later. We would suggest this is appropriate management in the setting of “high level” immunosuppression with a bDMARD.

While disseminated HZ post-ZVL can occur, it is most often described in those with haematologic malignancy.^{6,7} A United States study of 14 554 people who had an immunosuppressive dispensed around the time of ZVL, reported no cases of disseminated VZV in the following 42 days.⁸ While most of the 4826 patients who were immunosuppressed around the time of ZVL had only low-dose prednisone, 126 of them were taking LFN.⁸ Analysis of all worldwide post-marketing adverse events (2006-2016) following ZVL found that disseminated HZ was reported in <1% of cases.⁹ This suggests that while such an event can occur, it is uncommon. Given the significant morbidity seen with HZ¹⁰, we would suggest the benefit of ZVL even in the setting of LFN is worth the risk – after discussion with the patient regarding the

benefit/risk ratio. In the unlikely event of post-ZVL HZ, prompt anti-viral treatment should be instituted.

We agree the long *in vivo* half-life of LFN metabolites means its cessation for a few weeks prior to ZVL is of no value.¹¹

The imminent availability of Shingrix, a recombinant zoster vaccine will probably mean the above issue will become a moot point.

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Title:

Author reply.

Date:

2018-10

Citation:

Wong, P. K. K., Hanrahan, P. & Johnson, D. F. (2018). Author reply.. Intern Med J, 48 (10), pp.1280-1281. <https://doi.org/10.1111/imj.14053>.

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