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Response to "Increased awareness of hypogammaglobulinemia after B-cell targeting therapies" by Karim MY

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Dr Md Yusof has no conflict of interest.

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**TEXT**

We thank Dr Karim, MY for his interest in and kind comments on our study (1), in which we reported a low rate (i.e. 7 out of 700; 1%) of patients who required immunoglobulin replacement therapy (IGRT) for recurrent infections despite treatment with prophylactic antibiotics and/or hypogammaglobulinemia during rituximab (RTX) therapy in our cohort. This rate was the lowest compared to other published cohorts, which predominantly comprised patients with ANCA-associated vasculitis (AAV), ranging from 4–21% (2-4). Indeed, this low rate of IGRT requirement in our cohort was contributed to the variability in the diagnoses of rheumatic and musculoskeletal diseases (RMDs) studied. Of 7 patients who required the IGRT in our cohort, the rates were higher in systemic lupus erythematosus (SLE) and AAV, 2/94 (2.1%) and 1/49 (2.0%) respectively compared to rheumatoid arthritis (RA), 3/504 (0.6%). We believe that the higher rates for low IgG level (<6 g/L) at RTX initiation and subsequent requirement for IGRT during RTX therapy in SLE and AAV compared to RA were contributed by the intensity of previous remission induction agents including cyclophosphamide as depicted in Figure 1 of our paper (1). In comparison to cohorts from Roberts et al. (2, 5), Besada et al. (3) and Venhoff et al. (4) of which their rates for IGRT requirement for AAV indication were 8/288 (2.8%), 5/35 (14%) and 7/33 (21%), the low rate for IGRT requirement in our cohort was likely due to the difference in RTX retreatment strategy. We employed retreatment on clinical relapse (i.e. relapse was defined as an increase in the Birmingham Vasculitis Activity Score (BVAS) ≥1) compared to the fixed retreatment intervals i.e. every 6-12 months as per cohorts above. One concern using this re-treatment strategy was that allowing relapse might result in organ-threatening flares or necessitated exposure to further high dose of glucocorticoids. However, we previously reported that re-treatment on clinical relapse was effective with no patients discontinued RTX therapy at 7 years due to loss of efficacy, disease activity at each subsequent relapse was less severe than that at RTX initiation, the mean daily

oral prednisolone dose requirement was significantly reduced with more than a third of patients discontinued corticosteroid at the last follow-up, as well as none of our patient had progressed to severe organ damage (i.e. Vasculitis Damage Index (VDI) score of ≥ 5) (6). Additionally, results from the MAINRITSAN2 randomised controlled trial demonstrated AAV relapse rates did not differ significantly between individually tailored and fixed-schedule RTX regimens at 28 months and with fewer RTX cycles using the former strategy (7).

Although the rate for IGRT was the lowest in RA, we agree this is not a reason to be complacent since patients with RA need more frequent cycles for life-long therapy with median duration of response to RTX in RA, SLE and AAV were 10 months (8), 12 months (9) and 18 months (6) respectively. In those with low IgG either at baseline or at ≥4 months' duration of RTX therapy (N=110), there were 10/110 (9.1%) infection-associated deaths. Moreover, only 4/11 (36%) RA patients had their IgG normalized after at least 2 years post-bDMARDs switch, thus posing a treatment dilemma in the management of difficult to treat RA from the perspective of infection once RTX is discontinued (1). Therefore, our data strongly advocate that regardless RMD diagnoses, immunoglobulin levels should be monitored at baseline and before each RTX cycle, particularly in patients with comorbidities and low baseline immunoglobulin levels, in order to discern those at risk of serious infection events (SIEs).

Lastly, we agree with Karim MY that measurement of specific antibody responses to tetanus, hemophilus and pneumococcus should be measured more widely in clinical practice in patients with low IgG and/or an SIE in the previous RTX cycle in order to facilitate effective pre-RTX vaccination, as well as to identify those who fail to response after an appropriate vaccination challenge and may require treatment with IGRT.

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