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CORRESPONDENCE

Epstein-Barr virus-positive mucocutaneous ulcer is characterized by relatively low serum soluble IL-2 receptor levels regardless of methotrexate use; Reply to Ramia de Cap and Michaels

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TO THE EDITOR:

We appreciate the comments by Ramia de Cap et al.[1] regarding our recent article, 'Clinicopathological analysis of 34 Japanese patients with EBV-positive mucocutaneous ulcer (EBVMCU)'[2]. They expressed concerns that high prevalence of rheumatoid arthritis (RA) and methotrexate (MTX) use might have been a confounder to cause lower soluble IL-2 receptor (sIL-2R) levels in patients with EBVMCU, compared to those with de novo diffuse large B-cell lymphoma (DLBCL).

We excluded the patients with autoimmune diseases, such as RA, or on immunosuppressants including MTX from the comparative DLBCL group in our previous report[2]. However, the effect MTX to reduce serum sIL-2R levels in RA is unclear, or may be transient. A study by Salaffi et al.[3] is an open randomized study to see the changes of serum sIL-2R levels in RA patients treated with either MTX, sulphasalazine, or hydroxychroloquine. Only 29 patients with MTX were included in the study, and there were no statistically significant changes in serum sIL-2R levels after 24 weeks of treatment with MTX compared to the baseline (week 0). Barrera et al.[4] also performed a randomized trial to see the changes in various cytokine levels in RA patients on MTX or azathioprine. While there were statistically significant differences in serum sIL-2R levels in those on MTX after 24 and 48 weeks of treatment compared to the baseline, the extent of sIL-2R were only −24.1% (IQR, −51.1–6.5) and −28.2% (IQR, −55–−5.6), respectively, with a considerable rate of missing data (17.2% in MTX group at week 48). Also, Crilly et al.[5], who also measured serum sIL-2R levels in RA patients on MTX, noted that serum sIL-2R levels were significantly different from the baseline at week 12 only; there were no statistically significant differences in serum sIL-2R levels compared to week 0 and week 24. As above, all the studies that Ramia de Cap et al. cited, unfortunately, may not be reliable evidence to support their arguments.

To strengthen our position that patients with EBVMCU have low serum sIL-2R regardless of MTX use, we performed an additional analysis using methotrexate-associated lymphoproliferative disorders (MTX-LPD) patients as a comparative group. We analyzed serum sIL-2R levels of 45 patients with MTX-LPD (DLBCL-type [$n = 30$] and classic Hodgkin lymphoma-type [$n = 15$]) using data from previous our report[6] and 22 patients with EBVMCU whose serum sIL-2R levels were available[2]. We excluded one case that overlapped the disease concepts in EBVMCU and MTX-LPD from CHL-type MTX-LPD. As a result, those with EBVMCU had significantly lower serum sIL-2R levels than those with MTX-LPD, except for patients with Ann Arbor Stage I or II (Table 1). These data suggest that EBVMCU patients are characterized by relatively low serum sIL-2R levels regardless of MTX use.

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Table 1. Comparison of sIL-2R levels in EBVMCU and MTX-LPD.

	EBVMCU	MTX-LPD				
		All patients	DLBCL-type	CHL-type	Ann Arbor Stage I, II	Ann Arbor Stage III, IV
	$n = 22$	$n = 45$	$n = 30$	$n = 15$	$n = 12$	$n = 33$
sIL-2R (U/ml)	652 (263–2786)	2710 (252–40,727)	2748 (252–40,727)	2450 (363–11,000)	1028 (363–5800)	3470 (252–40,727)
		$P < 0.001$[a]	$P < 0.001$[a]	$P = 0.001$[a]	$P = 0.102$	$P = 0.001$[a]

All statistical analyses were conducted with the Mann–Whitney U test using SPSS for Windows software version 14.0 (SPSS Inc., Chicago, IL, USA).
CHL-type classic Hodgkin lymphoma-type, *DLBCL-type* diffuse large B-cell lymphoma-type, *EBVMCU* Epstein-Barr virus-positive mucocutaneous ulcer, *MTX-LPD* methotrexate-associated lymphoproliferative disorders, *sIL-2R* soluble interleukin 2 receptor.
[a]Compared to EBVMCU group.

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AUTHOR CONTRIBUTIONS

Study design: I.T., Y.G., and Y.S. Data analysis: I.T., A.N., M.F.N., and Y.G. Wrote the paper: I.T., Y.N., T.Y., and Y.S. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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