

Towards standardisation of histopathological assessments of germinal centres and lymphoid structures in primary Sjögren's syndrome

We read with great interest the study by Delli *et al*,¹ indicating the potential value of baseline salivary gland histopathology to predict response to rituximab (RTX) therapy. In their study, the authors report that RTX treatment significantly affects local inflammation at different levels, including a decrease in numbers of lymphoepithelial lesions, area of focal infiltrates, numbers of B cells and germinal centres (GCs). Interestingly, the presence of a high number of CD20-expressing B cells in parotid gland biopsy at baseline predicted response to RTX treatment. We agree that these observations may facilitate personalised medicine in patients with primary Sjögren's syndrome (pSS). Importantly, the results from this study emphasise the relevance of detailed analysis of salivary gland biopsy tissue. In this respect, we would argue for joint efforts to standardise measurements of local disease parameters. This is particularly relevant because the inhibition of GC may be of pivotal importance for patients for prevention of lymphoma development.

The absence of GC was previously reported to have a very strong negative predictive value for lymphoma development in patients with pSS.² As the absence of a high (at least 3) focus score has similarly high negative predictive value for lymphoma development,³ the exact contributions of focus score, focus size and GC formation to lymphoma development need to be further clarified. In this study, a striking 67% and 68% of patients in the placebo and RTX group, respectively, presented with GC at baseline. This is much higher than the 25.1% \pm 5.0% reported in a meta-analysis from 2013.⁴ Even in groups of selected patients with high focus scores, GCs were present in only 35.3% \pm 14.8% of patients.⁴ Of note is the use of parotid gland biopsy samples in this study, while the meta-analysis refers to minor salivary gland measurements, which may partly explain the difference. As described in the methods section, the authors defined GC as a clearly visible lighter area in a lymphocytic infiltrate. A more exhaustive analysis of these structures by staining for markers of follicular dendritic cells (long isoform of CD21 or CD35), follicular T helper cells (PD-1, Bcl-6, CXCL13, SAP), B cells (CD20, Pax-5), proliferation and functional markers (Ki-67 and activation-induced cytidine deaminase) should be used to properly identify these structures.^{5 6} As RTX treatment resulted in a clear decrease in local B cell numbers, it stands to reason that the area of focal infiltrates as well as the number of GCs would also be different between responders and non-responders. The absence of differences in these parameters may be related to the different methods used for analysis of these parameters. There are currently no standardised protocols and guidelines for distinguishing GCs in salivary gland biopsies and only the focus score is used in the classification criteria, while aggregate size and the analysed tissue surface are disregarded. However, the inclusion of these parameters in

the outcome measures is already in place in several early-phase clinical trials.⁷

The rheumatologic community should search for guidelines to standardise these important measurements in order to properly dissect the contribution of these parameters to local inflammation, in particular lymphoma development, and effective disease management.

Maarten R Hillen,^{1,2} Francesca Barone,² Timothy RDJ Radstake,¹ Joel AG van Roon¹

¹Rheumatology & Clinical Immunology/Laboratory of Translational Immunology, UMC Utrecht, Utrecht, the Netherlands

²School of Immunity and Infection, University of Birmingham, Birmingham, UK

Correspondence to Dr Joel A van Roon, Rheumatology & Clinical Immunology/Lab Translational Immunology, UMC Utrecht, Heidelberglaan 100, Utrecht 3584CX, The Netherlands; j.vanroon@umcutrecht.nl

Competing interests None declared.

Provenance and peer review Not commissioned; internally peer reviewed.



CrossMark

To cite Hillen MR, Barone F, Radstake T RDJ, *et al*. *Ann Rheum Dis* 2016;**75**:e31.

Received 2 March 2016

Accepted 3 March 2016

Published Online First 23 March 2016



► <http://dx.doi.org/10.1136/annrheumdis-2016-209480>

Ann Rheum Dis 2016;**75**:e31. doi:10.1136/annrheumdis-2016-209475

REFERENCES

- Delli K, Haacke EA, Kroese FG, *et al*. Towards personalized treatment in primary Sjögren's syndrome: baseline parotid histopathology predicts responsiveness to rituximab treatment. *Ann Rheum Dis* 2016; Published Online First: 12 Jan 2016. <http://dx.doi.org/10.1136/annrheumdis-2015-208304>
- Theander E, Vasaitis L, Baecklund E, *et al*. Lymphoid organisation in labial salivary gland biopsies is a possible predictor for the development of malignant lymphoma in primary Sjögren's syndrome. *Ann Rheum Dis* 2011;**70**:1363–8.
- Risselada AP, Kruize AA, Goldschmeding R, *et al*. The prognostic value of routinely performed minor salivary gland assessments in primary Sjögren's syndrome. *Ann Rheum Dis* 2014;**73**:1537–40.
- Risselada AP, Looije MF, Kruize AA, *et al*. The role of ectopic germinal centers in the immunopathology of primary Sjögren's syndrome: a systematic review. *Semin Arthritis Rheum* 2013;**42**:368–76.
- Jonsson MV, Skarstein K. Follicular dendritic cells confirm lymphoid organization in the minor salivary glands of primary Sjögren's syndrome. *J Oral Pathol Med* 2008;**37**:515–21.
- Bombardieri M, Barone F, Humby F, *et al*. Activation-induced cytidine deaminase expression in follicular dendritic cell networks and interfollicular large B cells supports functionality of ectopic lymphoid neogenesis in autoimmune sialoadenitis and MALT lymphoma in Sjögren's syndrome. *J Immunol* 2007;**179**:4929–38.
- Fisher BA, Brown RM, Bowman SJ, *et al*. A review of salivary gland histopathology in primary Sjögren's syndrome with a focus on its potential as a clinical trials biomarker. *Ann Rheum Dis* 2015;**74**:1645–50.



Towards standardisation of histopathological assessments of germinal centres and lymphoid structures in primary Sjögren's syndrome

Maarten R Hillen, Francesca Barone, Timothy RDJ Radstake and Joel AG van Roon

Ann Rheum Dis 2016 75: e31 originally published online March 23, 2016
doi: 10.1136/annrheumdis-2016-209475

Updated information and services can be found at:
<http://ard.bmj.com/content/75/6/e31>

References

These include:

This article cites 6 articles, 4 of which you can access for free at:
<http://ard.bmj.com/content/75/6/e31#BIBL>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>