University of Groningen

Serum levels of BAFF, but not APRIL, are increased after rituximab treatment in patients with primary Sjogren's syndrome

Pollard, Rodney P. E.; Abdulahad, Wayel H.; Vissink, Arjan; Hamza, Nishath; Burgerhof, Johannes G. M.; Meijer, Jiska M.; Visser, Annie; Huitema, Minke G.; Spijkervet, Fred K. L.; Kallenberg, Cees G. M.

Published in:
Annals of the Rheumatic Diseases

DOI:
[10.1136/annrheumdis-2012-202071](https://doi.org/10.1136/annrheumdis-2012-202071)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2013

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Pollard, R. P. E., Abdulahad, W. H., Vissink, A., Hamza, N., Burgerhof, J. G. M., Meijer, J. M., Visser, A., Huitema, M. G., Spijkervet, F. K. L., Kallenberg, C. G. M., Bootsma, H., & Kroese, F. G. M. (2013). Serum levels of BAFF, but not APRIL, are increased after rituximab treatment in patients with primary Sjogren's syndrome: data from a placebo-controlled clinical trial. *Annals of the Rheumatic Diseases*, 72(1), 146-148. <https://doi.org/10.1136/annrheumdis-2012-202071>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Serum levels of BAFF, but not APRIL, are increased after rituximab treatment in patients with primary Sjögren's syndrome: data from a placebo-controlled clinical trial

B cell depletion therapy with rituximab (RTX; 2 weekly infusions of 1000 mg, premedication: 100 mg prednisolone) in primary Sjögren's syndrome (pSS) patients is effective in reducing subjective and objective symptoms.¹ As B cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) are important cytokines involved in B cell survival and activation, we assessed in pSS patients included in a double-blind, randomised, placebo-controlled trial¹ the effects of RTX on serum BAFF and APRIL levels up to 48 weeks after RTX.

Serum concentrations of BAFF and APRIL were measured by ELISA using kits from R&D systems (Minneapolis, Minnesota, USA) and Bender Med Systems (San Diego, California, USA), respectively. At baseline serum BAFF levels were significantly higher in pSS patients (n=28; median 1277 pg/ml (range 907–3802 pg/ml)) compared with healthy controls (n=10; median 983 pg/ml (range 600–1564 pg/ml)); $p<0.01$; figure 1A). Also, baseline serum APRIL levels were significantly higher in pSS patients (median 15 098 pg/ml (range 1891–228 591 pg/ml)) than in healthy controls (median 1965 pg/ml (range 889–4567 pg/ml)); $p<0.05$; figure 1B). After RTX, serum BAFF levels in pSS patients further increased when B cells were depleted from the circulation. When B cells reappeared, BAFF levels declined (figure 2A). In marked contrast, APRIL levels, which partly target the same receptors as BAFF, remained unaltered (figure 2B).

Binding of BAFF to the BAFF receptor (BAFF-R) plays a critical role in B cell homeostasis because binding of BAFF to the BAFF-R prevents apoptosis of the cells.² Mature B cells excessively express BAFF-R; a decrease in B cell numbers will therefore lead to higher levels of unbound BAFF in serum and may favour survival of newly generated B cells. Upregulation of BAFF production by monocytes has been proposed as another mechanism for the rise in serum BAFF levels after RTX.³ In line with these findings, we observed an inverse relationship between serum BAFF levels and B cell numbers in patients after RTX. Furthermore, Pers *et al*⁴ demonstrated that higher baseline BAFF levels lead to a shorter period of B cell depletion after RTX. Elevated BAFF levels may also influence the stringency of B cell selection.⁵ Generation of B cells in an environment with high BAFF levels may therefore lead to more newly generated autoreactive cells.⁶ Moreover, BAFF is also involved in B cell activation and may lead to higher IgG levels. However, after RTX IgG levels decrease, although they remain elevated in comparison with healthy controls,¹ while BAFF levels increase. Therefore, we consider it unlikely that higher BAFF levels, seen after RTX, result in hyperactivation of persisting B cells.

In contrast to BAFF, APRIL levels remained unchanged after RTX. This can be explained by the notion that the major receptors for APRIL, that is, transmembrane activator and calcium modulator and cyclophilin ligand interactor and B-cell maturation antigen, are largely restricted to activated B cells and to

Figure 1 B cell activating factor (BAFF) (A) and a proliferation-inducing ligand (APRIL) (B) levels in healthy controls (HCs) (n=10) and primary Sjögren's syndrome (pSS) patients (placebo n=9; rituximab n=19) at baseline. Both BAFF and APRIL levels are higher in pSS patients compared with HCs. *Indicates significant differences between HCs and pSS subjects ($p<0.05$). The horizontal lines indicate the median values. No association was found between BAFF and APRIL levels.

plasma cells, respectively.^{7 8} Numbers of activated B cells are relatively low, and plasma cells are largely unaffected by RTX. The persistently high APRIL levels may be involved in B cell activation of (activated) B cells and survival of plasma cells, herewith contributing to the elevated serum IgG levels in pSS patients, even after RTX.

To conclude, RTX has differential effects on BAFF and APRIL levels in pSS patients. In patients with systemic lupus

Figure 2 Effect of placebo and rituximab (RTX) treatment on B cell activating factor (BAFF) (A) and a proliferation-inducing ligand (APRIL) (B) levels in Sjögren's syndrome patients (placebo n=9; RTX n=19). BAFF levels increase after RTX, but not after placebo, whereas APRIL levels remain high after treatment. *Indicates significant differences compared with baseline values ($p < 0.05$). The horizontal lines indicate median values.

Letters

erythematosus, rheumatoid arthritis and pemphigus vulgaris, BAFF levels also increase, while APRIL levels remain stable (rheumatoid arthritis, pemphigus vulgaris) or decrease (systemic lupus erythematosus).^{9 10} This suggests that increase in BAFF is a general phenomenon and not specific for pSS. Given the potential role of BAFF in pSS, combination of anti-BAFF treatment with RTX may lead to a prolonged reduction of (autoreactive) B cells. Since B cell reappearance after RTX correlates well with clinical relapse¹ such an approach might be an appropriate treatment modality.

Rodney P E Pollard,¹ Wayel H Abdulahad,² Arjan Vissink,¹ Nishath Hamza,² Johannes G M Burgerhof,³ Jiska M Meijer,¹ Annie Visser,² Minke G Huitema,² Fred K L Spijkervet,¹ Cees G M Kallenberg,² Hendrika Bootsma,² Frans G M Kroese²

¹Department of Oral and Maxillofacial Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

²Department of Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

³Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Correspondence to Arjan Vissink, Department of Oral and Maxillofacial Surgery, University of Groningen, University Medical Center Groningen, PO-Box 30.001, Groningen 9700 RB, The Netherlands; a.vissink@umcg.nl

Funding Supported by Roche, Woerden, The Netherlands.

Competing interests None.

Patient consent Obtained.

Ethics approval The ethics committee of the University Medical Center Groningen (METC approval: 05.229).

Provenance and peer review Not commissioned; externally peer reviewed.

Accepted 3 July 2012

Published Online First 31 July 2012

Ann Rheum Dis 2013;**72**:146–148.

doi:10.1136/annrheumdis-2012-202071

REFERENCES

1. **Meijer JM**, Meiners PM, Vissink A, *et al*. Effectiveness of rituximab treatment in primary Sjögren's syndrome. A randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2010;**62**:960–8.
2. **Schneider P**. The role of APRIL and BAFF in lymphocyte activation. *Curr Opin Immunol* 2005;**17**:282–9.
3. **Lavie F**, Miceli-Richard C, Ittah M, *et al*. Increase of B cell-activating factor of the TNF family (BAFF) after rituximab treatment: insights into a new regulating system of BAFF production. *Ann Rheum Dis* 2007;**66**:700–3.
4. **Pers J**, Devauchelle V, Daridon C, *et al*. BAFF-modulated repopulation of B lymphocytes in the blood and salivary glands of rituximab-treated patients with Sjögren's syndrome. *Arthritis Rheum* 2007;**56**:1464–77.
5. **Ota M**, Duong BH, Torkamani A, *et al*. Regulation of the B cell receptor repertoire and self-reactivity by BAFF. *J Immunol* 2010;**185**:4128–36.
6. **Lesley R**, Xu Y, Kalled SL, *et al*. Reduced competitiveness of autoantigen-engaged B cells due to increased dependence on BAFF. *Immunity* 2004;**20**:441–53.
7. **Moreaux J**, Legouffe E, Jourdan E, *et al*. BAFF and APRIL protect myeloma cells from apoptosis induced by interleukin 6 deprivation and dexamethasone. *Blood* 2004;**103**:3148–57.
8. **Laabi Y**, Gras MP, Brouet JC, *et al*. The BCMA gene, preferentially expressed during B-lymphoid maturation, is bidirectionally transcribed. *Nucleic Acids Res* 1994;**22**:1147–54.
9. **Vallerskog T**, Heimbürger M, Gunnarsson I, *et al*. Differential effects on BAFF and APRIL levels in rituximab-treated patients with systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Res Ther* 2006;**8**:R167.
10. **Nagel A**, Podstawa E, Eickmann M, *et al*. Rituximab mediates a strong elevation of B-cell-activating factor associated with increased pathogen-specific IgG but not autoantibodies in pemphigus vulgaris. *J Invest Dermatol* 2009;**129**:2202–10.

Serum levels of BAFF, but not APRIL, are increased after rituximab treatment in patients with primary Sjögren's syndrome: data from a placebo-controlled clinical trial

Rodney P E Pollard, Wayel H Abdulahad, Arjan Vissink, et al.

Ann Rheum Dis 2013 72: 146-148 originally published online July 31, 2012

doi: 10.1136/annrheumdis-2012-202071

Updated information and services can be found at:

<http://ard.bmj.com/content/72/1/146.full.html>

These include:

References

This article cites 10 articles, 4 of which can be accessed free at:

<http://ard.bmj.com/content/72/1/146.full.html#ref-list-1>

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/>