Author's response to reviews

Title: Clinical impact of B-cell depletion with the anti-CD20 antibody Rituximab in chronic fatigue syndrome: a preliminary case series

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Author's response to reviews: see over
Bergen, 16th June 2009

Dear Dr. Robin Cassady-Cain,

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Thank you for your response and for allowing us to submit a second revised version of the manuscript, taking into account the new comments by the reviewers. The specific comments are discussed in this covering letter point-by point.

Reviewer 1:
His first review, of May 6th, was indeed very thorough and helpful in preparing the revised manuscript. We have responded to all the comments. Reviewer 1 had no further comments to the revised version.

Reviewer 2:
As a minor essential revision he suggests that we state what special toxicity was seen after rituximab treatment. This has now been stated, page 11, section Results, subheading Toxicity: “No other toxicity was seen during follow-up.”

As a minor essential revision, reviewer 2 suggests that the discussion should be shortened by ½.
We made a major modification of the discussion in the first revision, taking into account all the specific points made by the reviewers. We removed parts of the discussion which could be considered speculative, and which were not adequately supported by the observations. Specifically, the reviewers asked for details regarding the presence of other autoimmune diseases among the patients, comments to the use of steroids as premedication before rituximab treatment, and to the fact that all three patients had mononucleosis prior to developing CFS. In the first revised version, we discussed and cited the works of reviewer 2 describing the presence of IgM antibodies to Epstein-Barr virus or cytomegalovirus in a subset of CFS patients. We believe that it is difficult to shorten the discussion without compromising the information added (and requested by the reviewers).
Indeed, reviewer 1 states that: “The authors have done a great job in responding to all
the comments….”

As a minor discretionary revision, reviewer 2 states that the study would be
strengthened by serum assay titres for EBV, CMV, and HHV6, according to his
previous publications. We performed standard serologic tests, and also PCR analyses,
for EBV and CMV during follow-up. We did not have the possibility to perform these
described additional assays during follow-up.

Reviewer 2 also believes that the study could be strengthened by measuring the
severity of fatigue with the EIPS TM. We do not have the possibility to express the
fatigue as metric EIPS TM, as this cannot be performed retrospectively. As explained
in the covering letter to the first revised version, we have tried to be more precise in
the description of fatigue status of the three patients, so that the readers may get an
impression of their significant improvement.

Ethical considerations:
We have added information about ethical approval. The manuscript text (Section
Methods, subheading Patients, page 5) now reads:
“After response was seen in the first patient, the concept was discussed with the
chairman of the Regional Ethical Committee, and permission was given for open-
label treatment of two additional patients while awaiting the formalities of a planned
randomized study. This study (NCT00848692) has been approved by the Regional
Ethical Committee in Norway (200800657-6/MRO/400) and is recruiting. Written
consent was obtained from the three patients for treatment and for publication of this
case series.”

To verify that we had such approval, we include a signed statement from the chairman
of the Regional Ethical Committee, professor Jon Lekven (uploaded as an additional
file).

We have moved the statement about consent from the Acknowledgements section to
the Methods section, and included that they also consented to be given the treatment.
“Written consent was obtained from the three patients for treatment and for
publication of this case series.”

Except for these comments and responses, we have changed two sentences for clarity:
Results section, page 7, now reads:
“The serum levels of IgG were slightly reduced from inclusion to the end of follow-up (12.1 – 5.8, 9.5 – 8.5, 12.5 – 11.6 g/L for patients 1, 2, and 3, respectively, normal range 6.0 – 15.3 g/L).”

-In the Discussion section, we have deleted part of one sentence (page 9), which should have been modified in the first revision with the update of patient histories with extended follow-up:
“Fifty weeks after the first Rituximab infusion (30 weeks after the second) he started treatment with weekly oral Mtx with no clinical improvement yet (after 10 weeks observation).”

Please notify us if the editorial office prefers that we send the signed patient consents. We will send these on request (either by fax, as e-mail attachments as scanned jpg-files, or uploaded as additional files).

This concludes our second revision.

Yours sincerely,

Øystein Fluge and Olav Mella