Efficacy of retreatment with rituximab in patients with primary Sjögren's syndrome

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In primary Sjögren's syndrome (pSS), the majority of open-label studies and randomised controlled trials (RCT) showed the efficacy of rituximab in improving objective signs of disease activity, patients' symptoms, and health-related quality of life. Most alleviation of symptoms was observed within 24 weeks of treatment (1, 2). The beneficial effect on salivary flow seemed to be dependent on the residual function of the glands (1). Recently, Gottenberg *et al.* found good physician-reported efficacy and tolerance during retreatment with rituximab in 41 initially responding pSS patients (3). Furthermore, Carubbi *et al.* showed sustained clinical response and a good safety profile during 6 courses of rituximab (given every 24 weeks) in 19 early pSS patients with active disease (4).

To add to these two studies on the efficacy of retreatment, we analysed data of pSS patients who received their first two courses of rituximab within our previously reported RCT (5) and extension study (6). From these studies, 15 pSS patients (14 female)

Table I. Clinical and laboratory parameters during the first and second course of rituximab in patients with pSS.

Parameter	Course	Week 0		Week 24		*p*-value*	Week 48		*p*-value**
ESSDAI	First	9.0	(4.0-13.0)	2.5	(0.0-9.0)	0.006	8.0	(2.0-17.0)	0.009
ESSDAI	Second	8.0	(2.0-18.0)	3.0	(0.0-10.0)	0.005	5.0	(1.0-26.0)	0.028
SWS (ml/minute)	First	0.47	(0.11-2.49)	0.52	(0.07-2.24)	0.694	0.37	(0.07-2.95)	0.048
SWS (ml/minute)	Second	0.40	(0.02-1.47)	0.35	(0.06-1.72)	0.320	0.34	(0.04-1.69)	0.691
B-cells (10^9/l)	First	0.20	(0.01-0.40)	0.05	(0.00-0.31)	0.002	0.16	(0.05-0.31)	0.011
B-cells (10^9/l)	Second	0.22	(0.02-0.52)	0.00	(0.00-0.24)	0.001	0.15	(0.01-0.41)	0.002
RF (kI U/l)	First	88	(8-241)	30	(10-120)	0.001	72	(8-400)	0.003
RF (kI U/l)	Second	95	(12-230)	37	(13-160)	0.002	43	(11-354)	0.056
IgG (g/l)	First	22.9	(13.0-44.3)	19.3	(13.9-26.1)	0.001	21.4	(14.1-35.6)	0.004
IgG (g/l)	Second	22.2	(13.7-41.5)	18.9	(12.1-25.0)	0.002	18.3	(11.5-33.3)	0.320
Patient GDA	First	62	(43-74)	25	(0-61)	0.011	53	(4-84)	0.037
Patient GDA	Second	52	(15-93)	38	(0-85)	0.060	37	(3-82)	0.410
MFI-GF	First	16	(4-20)	12	(5-20)	0.016	16	(4-20)	0.081
MFI-GF	Second	16	(4-20)	13	(7-20)	0.019	15	(10-20)	0.168
VAS oral dryness	First	58	(0-91)	25	(0-67)	0.021	50	(0-88)	0.010
VAS oral dryness	Second	60	(1-92)	37	(0-84)	0.053	65	(1-88)	0.115
VAS ocular dryness	First	63	(0-88)	33	(0-89)	0.041	55	(0-90)	0.624
VAS ocular dryness	Second	55	(0-91)	53	(0-94)	0.802	59	(4-87)	0.463

Values are presented as median (range).
**p*-value compared with values recorded at baseline.
***p*-value compared with values recorded at week 24.
pSS: primary Sjögren's syndrome; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; SWS: stimulated whole salivary flow rate; RF: rheumatoid factor; GDA: global disease activity; MFI-GF: multidimensional fatigue inventory general fatigue; VAS: visual analogue scale.

could be included. Patients had median age of 39 years (range 27–65) and median disease duration of 37 months (range 3–154). Each course consisted of 1000 mg rituximab intravenously (given with 100 mg methylprednisolone) on days 1 and 15. Median interval between courses was 103 weeks (range 60–136).
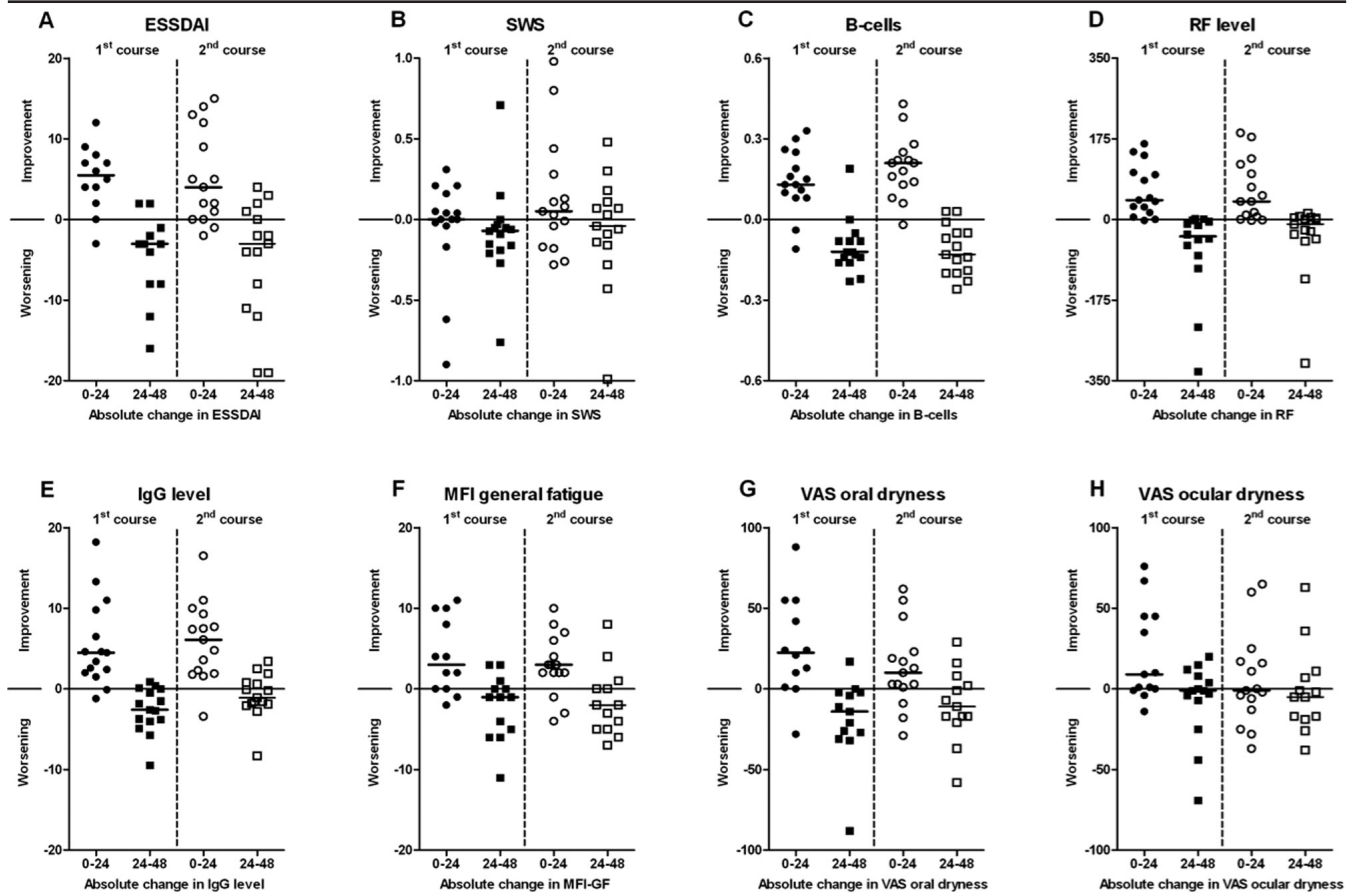

Fig. 1. Absolute change over time during the first and second course of rituximab in patients with pSS. **A**: ESSDAI, **B**: stimulated whole saliva **C**: CD19+ B-cells, **D**: rheumatoid factor, **E**: IgG level, **F**: MFI general fatigue, **G**: VAS oral dryness, **H**: VAS ocular dryness. Values for change from baseline to week 24 and from week 24 to week 48 of individual patients are presented, together with the median of all patients.

Letters to the Editors

During both courses, patients were evaluated at baseline and 24 and 48 weeks after rituximab treatment. Assessments included EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) (7), stimulated whole saliva (SWS), B-cells, rheumatoid factor (RF), IgG levels, patient global disease activity (GDA), multidimensional fatigue inventory general fatigue (MFI-GF) and visual analogue scale (VAS) for oral and ocular dryness (see references 5, 6 and 8 for details). Variables within patients were analysed using the Wilcoxon signed-rank test.

Retreatment with rituximab was well-tolerated. One patient developed mild serum-sickness-like disease after the first infusion of both courses (second infusions were not administered). Both courses of rituximab resulted in significant improvement of ESSDAI, B-cells, RF, IgG and MFI-GF at week 24 compared with baseline. Patient GDA and VAS oral dryness improved significantly during the first course and showed a trend for improvement during the second course. Improvement in VAS ocular dryness was observed only during the first course. All these variables, except for VAS ocular dryness, showed significant deterioration at week 48 compared with week 24 during the first course. The same pattern was found during the second course, although deterioration seemed less pronounced. SWS remained stable during the first 24 weeks of both courses, but a significant decrease was seen at week 48 of the first course (Table I). Absolute changes per patient over time during both courses are shown in Figure 1.

The main strength of this analysis is no selection regarding initial response to rituximab. Our group consisted of 15 well-characterised pSS patients in whom a variety of objective and subjective parameters was assessed in a standardised way at fixed times after administration of rituximab during both courses. The main limitations are the small sample size and the varying time between courses, because retreatment was started after completion of the entire RCT and after recurrence of symptoms. No relation was found between the interval between courses and the effect of the second course.

In conclusion, retreatment with rituximab after recurrence of symptoms resulted in comparable beneficial effects as initial treatment on objective parameters, including ESSDAI, whereas the effect on patient-reported parameters was somewhat less pronounced. The latter finding is in line with an earlier study in pSS (9). Because goals of retreatment include maintenance of efficacy and prevention of flare, further studies are needed to investigate optimal timing of retreatment of rituximab in pSS patients. Furthermore, it would be of interest to investigate the clinical value of a combination therapy of biological agents (10).

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References

1. MEINERS PM, VISSINK A, KALLENBERG CGM et al.: Treatment of primary Sjögren's syndrome with anti-CD20 therapy (rituximab). A feasible approach or just a starting point? Expert Opin Biol Ther 2011; 11: 1381-94.
2. DEVAUCHELLE-PENSEC V, MARIETTE X, JOUSSE-JOUILIN S et al.: Treatment of primary Sjögren syndrome with rituximab: a randomized trial. Ann Intern Med 2014; 160: 233-42.
3. GOTTENBERG JE, CINQUETTI G, LARROCHE C et al.: Efficacy of rituximab in systemic manifestations of primary Sjögren's syndrome: Results in 78 patients of the AutoImmune and rituximab registry. Ann Rheum Dis 2013; 72: 1026-31.
4. CARUBBI F, CIPRIANI P, MARRELI A et al.: Efficacy and safety of rituximab treatment in early primary Sjögren's syndrome: a prospective, multi-center, follow-up study. Arthritis Res Ther 2013; 15: R172.
5. 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.
6. MEINERS PM, ARENDS S, BROUWER E, SPIJKERVET FK, VISSINK A, BOOTSMA H: Responsiveness of disease activity indices ESSPRI and ESSDAI in patients with primary Sjögren's syndrome treated with rituximab. Ann Rheum Dis 2012; 71: 1297-302.
7. SEROR R, RAVAUD P, BOWMAN SJ et al.: EULAR Sjögren's syndrome disease activity index: Development of a consensus systemic disease activity index for primary Sjögren's syndrome. Ann Rheum Dis 2010; 69: 1103-9.
8. MOERMAN RV, ARENDS S, MEINERS PM et al.: EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) is sensitive to show efficacy of rituximab treatment in a randomized controlled trial. Ann Rheum Dis 2014; 73: 472-4.
9. SEROR R, GOTTENBERG JE, DEVAUCHELLE-PENSEC V et al.: ESSDAI and ESSPRI: EULAR indexes for a complete picture of primary Sjögren's syndrome patients. Arthritis Care Res 2013; 65: 1358-64.
10. DE VITA S, QUARTUCCIO L, SALVIN S et al.: Sequential therapy with belimumab followed by rituximab in Sjögren's syndrome associated with B-cell lymphoproliferation and overexpression of BAFF: evidence for long-term efficacy. Clin Exp Rheumatol 2014; 32: 490-4.