



5. van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, et al. Test-retest reliability of the food allergy quality of life questionnaires (FAQLQ) for children, adolescents and adults. *Qual Life Res.* 2009;18: 245-251.
6. van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, et al. Development, validity and reliability of the food allergy independent measure (FAIM). *Allergy.* 2010;65:630-635.
7. DunnGalvin A, Cullinane C, Daly DA, Flokstra-de Blok BM, Dubois AE, Hourihane JO. Longitudinal validity and responsiveness of the food allergy quality of life questionnaire - parent form in children 6-12 years following positive and negative food challenges. *Clin Exp Allergy.* 2010;40:476-485.
8. Factor JM, Mendelson L, Lee J, Nouman G, Lester MR. Effect of oral immunotherapy to peanut on food-specific quality of life. *Ann Allergy Asthma Immunol.* 2012;109:348-352.
9. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. *J Clin Epidemiol.* 1994;47:81-87.

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Long-term effects upon rituximab treatment of acquired angioedema due to C1-inhibitor deficiency

To the Editor,

Acquired angioedema due to deficiency of C1-inhibitor is a relatively infrequent but serious disorder, resulting in severe, sometimes life-threatening, angioedema.^{1,2} Most cases of acquired C1-inhibitor deficiency are associated with an underlying B-cell disorder, ranging from autoimmune anti-C1-inhibitor antibodies to lymphoproliferative disease with excessive activation of the classic complement pathway due

to anti-idiotypic antibodies directed to monoclonal antibodies produced by the malignant clone with consequent consumption of C1 inhibitor.^{3,4} In view of the central role of B cells in this condition, anti-CD20 treatment seems a rational strategy. Since the initial publication of successful treatment of acquired angioedema due to C1-inhibitor deficiency with rituximab was published in 2005,^{5,6} several case reports have confirmed the efficacy of this approach.⁷⁻⁹ Most reports

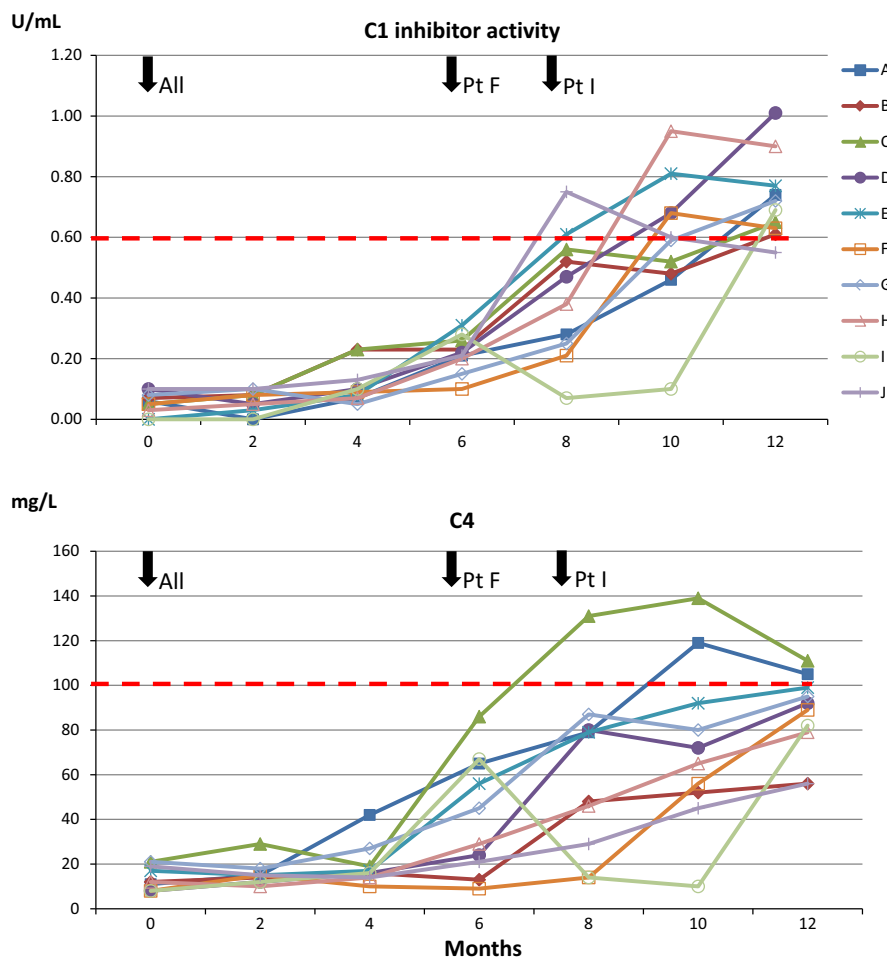


FIGURE 1 Effect of the administration of anti-CD20 monoclonal antibodies (rituximab) in ten patients with acquired angioedema due to C1-inhibitor deficiency on plasma levels of C1-inhibitor and C4. Each line represents one patient, and patients are labeled A-J (see table in Data S1). The arrow indicates rituximab treatment, in all patients at the beginning of the observation period and a second cycle in patient F and I, respectively. The striped red line represents the lower level of normal values [Colour figure can be viewed at wileyonlinelibrary.com]

so far are anecdotal and present short-term follow-up only. Here, we demonstrate efficacy of rituximab in a consecutive series of 10 patients with acquired angioedema due to C1-inhibitor deficiency that was followed for 8.5–10 years after treatment with rituximab.

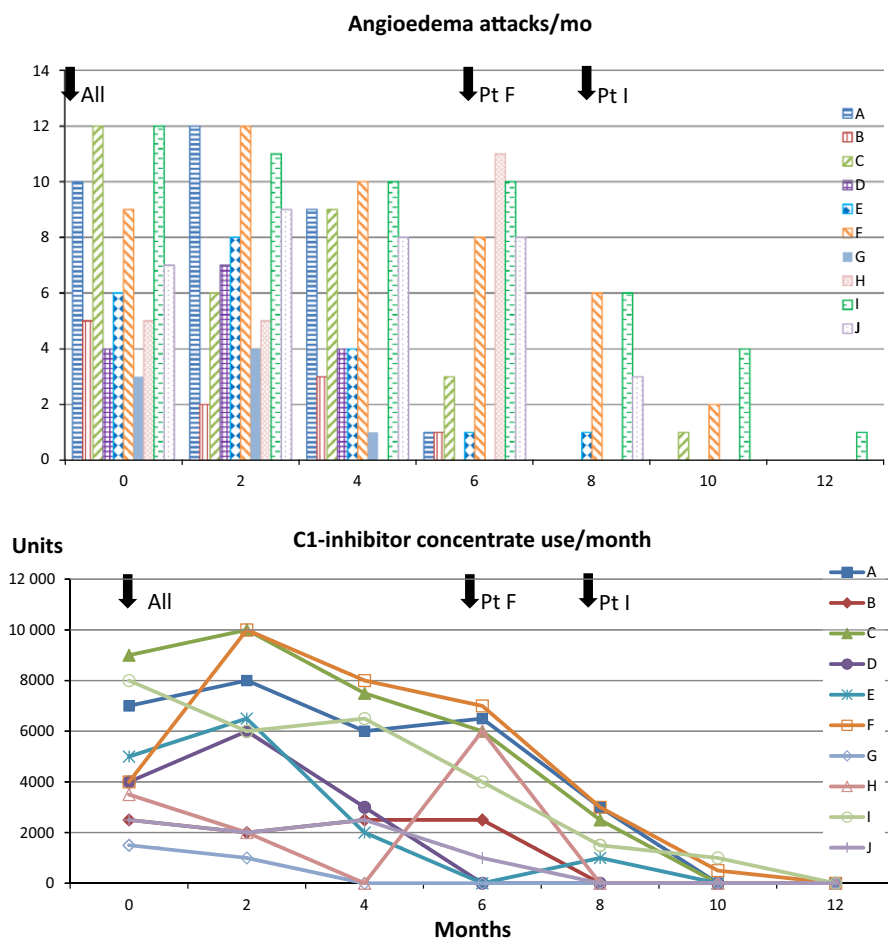
Between 2004 and 2007, we managed 10 patients with acquired angioedema due to C1-inhibitor deficiency and subjects. Clinical and laboratory characteristics of patients are given in the Data S1. All patients had initially very low levels of C1-inhibitor activity (≤ 0.1 U/mL) and low levels of C4 and C1q (mean level 26 ± 5.3 , and 47 ± 15.2 mg/L, respectively). In 50% of patients, an antibody against C1-inhibitor could be detected. Three out of 10 patients were diagnosed with lymphoproliferative disease (1x indolent follicular B-cell lymphoma and 2x splenic marginal zone lymphoma). Interestingly, in two of these patients, the clinical presentation of angioedema preceded the diagnosis of lymphoma, whereby in one of these patients, angioedema episodes were present 8 years before the diagnosis of lymphoma. Patients were initially treated with danazol (150–400 mg daily), if tolerated. Some patients reported to respond well to tranexamic acid and were treated with doses between 1 and 3 g daily. Severe episodes of angioedema (abdominal attacks, swelling of the tongue, or oropharyngeal region) were treated with C1-inhibitor concentrate (Cinryze, Sanquin, the Netherlands) at a dose of 1000–1500 U intravenously. Criteria for treatment with rituximab consisted of persistent and/or treatment-resistant

angioedema (>1 severe episode per month) and repeated requirement for C1-inhibitor concentrate treatment. Rituximab (Roche, Woerden, the Netherlands) was administered intravenously at a dose of 375 mg/m^2 , once weekly for a total of 4 doses. In patients with lymphoproliferative disease, treatment consisted of 6–8 courses of CVP chemotherapy (cyclophosphamide, vincristine, and prednisone) combined with rituximab (R-CVP).

Plasma levels of C1 inhibitor activity and C4 in the first year after initiation of treatment with rituximab are presented in Figure 1. A significant increase in C1 inhibitor activity was noted 6 months after initiation of treatment in the 8 responders after the first cycle ($P < 0.01$). Two patients required a second cycle of rituximab. Patients had angioedema symptoms for 4–144 months before a decision to treat with rituximab. Eight patients (including the three patients treated with R-CVP) had a complete remission of angioedema after one cycle of rituximab (Figure 2). The decrease in angioedema attacks occurred 3–4 months after initiation of rituximab, and after 8 months, all these patients were completely free from angioedema attacks. After 12 months, all patients showed a complete response with resolution of angioedema. The reduction in angioedema activity was associated with a reduction in the requirement for C1-inhibitor concentrate (Figure 2).

In 8 of 10 patients, the complete remission of acquired angioedema in the first year after initiation of treatment was sustained

FIGURE 2 Clinical effect of the administration of anti-CD20 antibodies (rituximab) in ten patients with acquired angioedema due to C1-inhibitor deficiency on frequency of serious angioedema attacks (upper airway edema, facial edema, severe edema of extremities or genitals, and severe abdominal attacks) and the monthly requirement for C1-inhibitor concentrate (in units). Each line represents one patient, and patients are labeled A–J (see table in Data S1). The arrow indicates rituximab treatment, in all patients at the beginning of the observation period and a second cycle in patient F and I, respectively [Colour figure can be viewed at wileyonlinelibrary.com]



over the entire follow-up period (8.5-10 years) (see Figure in Data S1). In one patient, a recurrence of acquired angioedema occurred at 2 years after the initial cycle of rituximab with a drop in the level of C1-inhibitor activity below 0.2 U/mL and angioedema attacks in the abdomen. After a second cycle of rituximab at that point, a rapid remission was achieved that remained present during the further follow-up period. One patient remarkably developed autoimmune thrombocytopenia in the second year after treatment with rituximab whereas there were no signs of recurrent angioedema or C1-inhibitor deficiency. This patient was treated with steroids and a second cycle of rituximab, with good result (sustained remission of autoimmune thrombocytopenia).

In conclusion, we here present long-term complete remission of treatment-resistant acquired angioedema due to deficiency of C1-inhibitor upon treatment with anti-CD20 antibodies. The treatment was shown to be equally effective in patients with anti-C1-inhibitor antibodies and patients with acquired angioedema due to lymphoproliferative disease (in the latter cases in combination with CVP chemotherapy). We appreciate that a case series with successful outcome but without a control group does not provide conclusive proof of efficacy of this treatment for patients with acquired angioedema due to C1-inhibitor deficiency. However, many of our patients had angioedema symptoms for a long time despite other treatment modalities (making spontaneous remission less likely) and they were all cured upon administration of rituximab. Therefore, we think these results in combination with other published reports are rather convincing and suggest that there is a definitive role for anti-CD20 treatment in this disease. The treatment was well tolerated by patients and resulted in a sustained restoration of C1-inhibitor and C4 plasma levels at 8½- to 10-year follow-up.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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REFERENCES

1. Markovic SN, Inwards DJ, Frigas EA, Phyllyk RP. Acquired C1 esterase inhibitor deficiency. *Ann Intern Med.* 2000;132:144-150.
2. Agostoni A, Aygoren-Pursun E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol.* 2004;114(3 suppl):S51-S131.
3. Zuraw BL, Altman LC. Acute consumption of C1 inhibitor in a patient with acquired C1-inhibitor deficiency syndrome. *J Allergy Clin Immunol.* 1991;88:908-918.
4. Cugno M, Castelli R, Cicardi M. Angioedema due to acquired C1-inhibitor deficiency: a bridging condition between autoimmunity and lymphoproliferation. *Autoimmun Rev.* 2008;8:156-159.
5. Levi M, Hack CE, van Oers MH. Rituximab-induced elimination of acquired angioedema due to C1-inhibitor deficiency. *Am J Med.* 2006;119:3-5.
6. Ziakas PD, Giannouli S, Psimenou E, Evangelia K, Tzioufas AG, Voulgarelis M. Acquired angioedema: a new target for rituximab? *Haematologica.* 2004;89(8):E113.
7. Motosue MS, Howard MT, Butterfield JH. Rituximab in a patient with splenic marginal zone lymphoma and acquired angioedema. *Ann Allergy Asthma Immunol.* 2016;116:472-473.
8. Branellec A, Bouillet L, Javaud N, et al. Acquired C1-inhibitor deficiency: 7 patients treated with rituximab. *J Clin Immunol.* 2012;32:936-941.
9. Doshi A, Tse K, Riedl M, Zuraw B, Christiansen S. Cases of acquired C1 inhibitor deficiency treated with rituximab. *J Allergy Clin Immunol Pract.* 2016;4:987-988.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Online Supplement

LONG TERM EFFECTS UPON RITUXIMAB TREATMENT OF ACQUIRED ANGIO-EDEMA DUE TO C1-INHIBITOR DEFICIENCY

METHODS

Patients

We studied patients with acquired angio-edema due to C1-inhibitor deficiency. This diagnosis was based on (1) a clinical presentation with angio-edema in patients older than 25 years; (2) a level of C1-inhibitor activity < 0.2 U/ml (normal value 0.6-0.8 U/ml); (3) a low level of C4 (< 50 mg/L) (normal value 100-150 mg/L); (4) decreased levels of C1q (< 80 mg/L) (normal value 100-150 mg/L); and (5) the absence of genetic mutations in the C1-inhibitor gene. All patients had a negative family history for angio-edema. In all patients anti-C1 inhibitor antibodies were assayed but the presence of these antibodies was not an essential requirement to make a diagnosis of acquired C1-inhibitor deficiency. All patients were screened for lymphoproliferative disease by physical examination, routine laboratory testing including a full blood cell count, liver enzymes, lactate dehydrogenase, immunoglobulins and paraproteins and imaging (computer tomography of chest, abdomen, and pelvis).

Treatment

Patients were initially treated with danazol (150-400 mg daily), if tolerated. Some patients reported to respond well to tranexamic acid and were treated with doses between 1-3 gram daily. Severe episodes of angio-edema (abdominal attacks, swelling of the tongue or oropharyngeal region) were treated with C1-inhibitor concentrate (Cinryze, Sanquin, the Netherlands) at a dose of 1000-1500 U intravenously. Criteria for treatment with rituximab consisted of persistent and/or treatment-resistant angio-edema (>1 severe episode per month) and repeated requirement for C1-inhibitor concentrate treatment. Rituximab (Roche, the Netherlands) was administered intravenously at a dose of 375 mg/m^2 , once weekly for a total of 4 doses.

Follow-up

Patients were seen monthly for the first year after administration of rituximab and thereafter (at least) once every year. Seven patients were followed up for 10 years after treatment with rituximab, and three patients were followed for a period between $8\frac{1}{2}$ and 9 years. At each visit clinical episodes of angio-edema and requirement for the administration of C1 inhibitor

concentrate were noted and blood samples for measurement of C1-inhibitor activity and C4 were collected. Anti-C1 inhibitor antibodies (if detected at baseline) were monitored every 3 months in the first year and yearly thereafter until negative at three consecutive occasions.

Assays and statistics

C1 inhibitor activity was measured by means of a chromogenic assay (Dade Behring, Marburg, Germany). Plasma levels of C4 and C1q were quantitated by nephelometric assays (Sanquin, Amsterdam, the Netherlands). Anti-C1-inhibitor antibodies were assayed by ELISA.

Data are presented as median (with range) or means with standard deviation. Statistical analysis was done by analysis of variance (ANOVA) and Mann-Whitney-U test.

DETAILED RESULTS

Patients and treatment

Between 2004 and 2007 we managed 10 patients with acquired angio-edema due to C1-inhibitor deficiency and subjects. Clinical and laboratory characteristics of patients are given in the supplement table. The median age was 58 year (range 45-70 year) and the male:female ratio was 6:4. Patients had angio-edema localised to the abdomen, extremities, face and oropharynx, and the genital region. Two patients needed admission to the intensive care unit because of threatening airway obstruction but no patients required intubation.

Initial treatment was with danazol in 6 out of 10 patients, combined with tranexamic acid in 2 patients. Two patients were treated with tranexamic acid alone. Median monthly dose of C1 inhibitor concentrate was 4000 U/month (range 1500-9000 U/month). In patients with lymphoproliferative disease treatment consisted of 6-8 courses of CVP chemotherapy (cyclophosphamide, vincristine, and prednisone) combined with rituximab (R-CVP).

Short-term outcome of rituximab treatment

A significant increase in C1 inhibitor activity was noted 6 months after initiation of treatment in the 8 responders after the first cycle ($p < 0.01$). One patient (patient F) did not show any response in C1 inhibitor activity levels at 6 months after the first cycle of rituximab and continued to experience significant angio-edema activity; hence, it was decided to administer a second cycle at 6 months. In patient I levels of C1 inhibitor activity dropped after an initial moderate response. The low C1 inhibitor activity was associated with significant angio-edema activity, and this patient also received a second cycle of rituximab. The increase in plasma levels of C1 inhibitor activity was associated with increases in C4 plasma concentrations (Figure 1).

Patients had angio-edema symptoms for 4-144 months before a decision to treat with rituximab. Eight patients (including the three patients treated with R-CVP) had a complete remission of angio-edema after one cycle of rituximab (Figure 2). The decrease in angio-edema attacks occurred 3-4 months after initiation of rituximab and after 8 months all these patients were completely free from angio-edema attacks. Two patients (patient F and patient I) had no significant response after one cycle of rituximab (see above) and were treated with another cycle at month 6 and month 8, respectively. Hereafter they also responded with a marked reduction in angio-edema attacks. After 12 months all patients showed a complete response with resolution of angio-edema.

The reduction in angio-edema activity was associated with a reduction in the requirement for C1-inhibitor concentrate (Figure 2). In the good responders after one cycle of rituximab the use of C1-inhibitor concentrate was significantly lower at 6 months after the initiation of treatment. In the two patients that required a second cycle of rituximab, C1-inhibitor concentrate requirement significantly lessened at 2 months after the second cycle. After 12 months after the initiation of rituximab, all patients were free from use of C1-inhibitor concentrate.

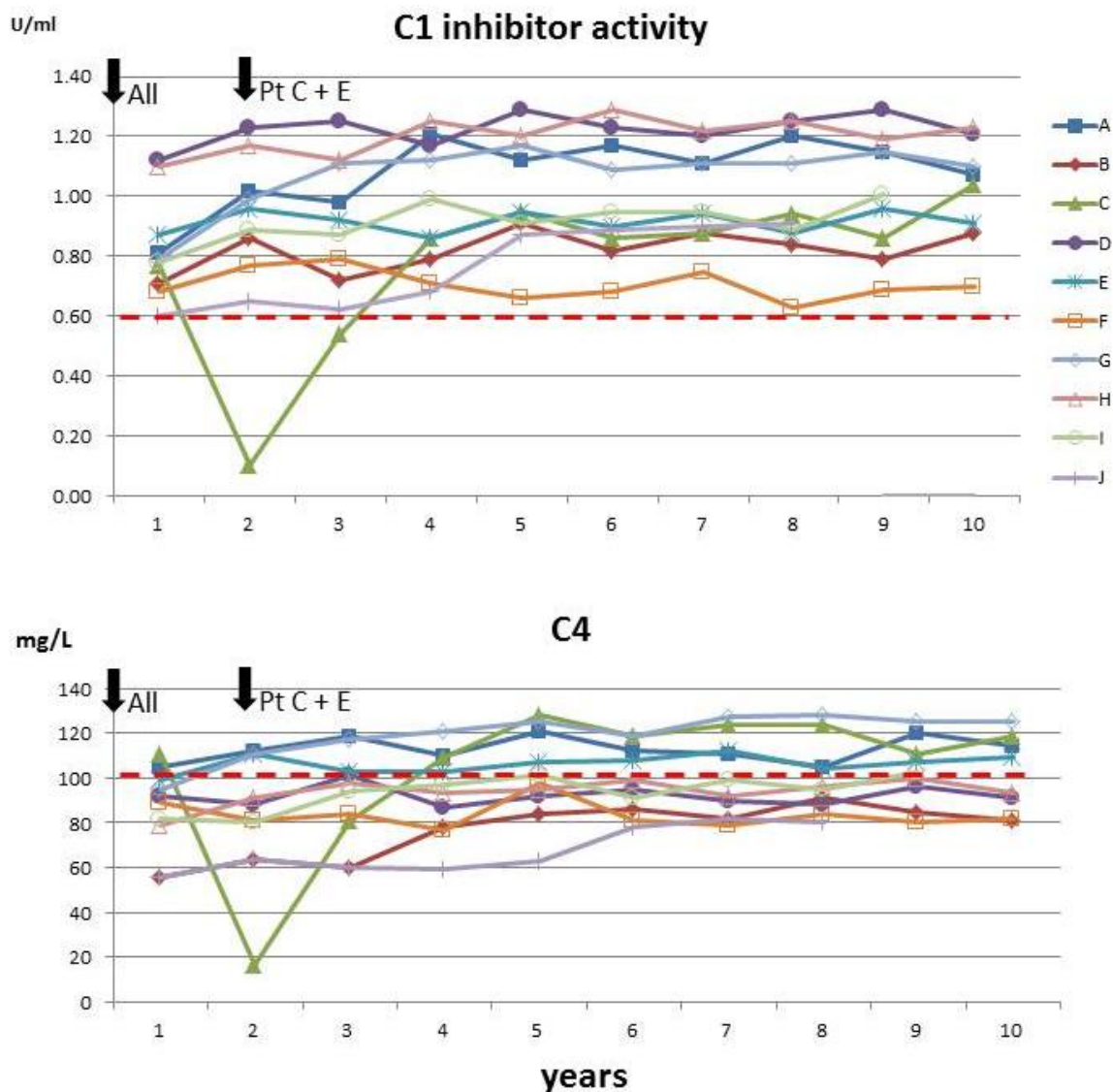
In 2 of 5 patients with a positive anti-C1 inhibitor antibody, the antibody became undetectable at 6 months after the initiation of rituximab (patient A and D). Another 2 patients (patient F and I), who required a second cycle of rituximab, showed disappearance of the anti-C1 inhibitor antibody at 12 and 16 months after the first cycle of rituximab. In patient J the anti-C1 inhibitor antibody remained borderline throughout the study.

Treatment with rituximab was tolerated well in all patients and we did not observe significant adverse events upon the administration of this agent.

Long-term outcome of rituximab treatment

In 8 of 10 patients the complete remission of acquired angio-edema in the first year after initiation of treatment was sustained over the entire follow-up period (8½ -10 years) (Supplement Figure). In one patient (patient C) a recurrence of acquired angio-edema occurred at 2 years after the initial cycle of rituximab with a drop in the level of C1-inhibitor activity below 0.2 U/mL and angio-edema attacks in the abdomen. After a second cycle of rituximab at that point a rapid remission was achieved that remained present during the further follow-up period. One patient (patient E) remarkably developed auto-immune thrombocytopenia in the second year after treatment with rituximab whereas there were no signs of recurrent angio-edema or C1-inhibitor deficiency. This patient was treated with steroids and a second cycle of rituximab, with good result (sustained remission of auto-immune thrombocytopenia).

Supplement Figure



Long-term effect of the administration of anti-CD20 antibodies (rituximab) in ten patients with acquired angio-edema due to C1-inhibitor deficiency on plasma levels of C1-inhibitor and C4. Each line represents one patient and patients are labelled A-I. The arrow indicates rituximab treatment, in all patients at the beginning of the observation period and a second cycle (in the 2nd year after the initial treatment) in patient C and E, respectively. The striped red line represents the lower level of normal values.

Supplement Table

	Age	M/F	Co-morbidity	Angio-edema location(s)	Duration of symptoms before rituximab treatment (months)	Angio-edema frequency (per month)	C1-inhibitor activity (U/ml)	C4 (mg/L)	C1q (mg/L)	Anti-C1 inhibitor antibody	Treatment	Follow-up (months)
A	45	F	-	abdomen, hands	144	10	0.05	11	59	+	Danazol + 1 cycle rituximab	120
B	70	M	Indolent follicular B-cel lymphoma	hands, feet, genital	6	5	0.07	12	43	-	CVP (x6) + rituximab	120
C	68	M	-	abdomen	84	12	0.05	21	41	-	Danazol, tranexamic acid, rituximab (2 cycles, 2 nd after 2 years)	120
D	56	M	-	face, tongue	14	4	0.10	8	27	+	Danazol + 1 cycle rituximab	120
E	65	M		abdomen, lips, hands, feet	24	6	0	17	60	-	Danazol + 2 cycles rituximab (2 nd after 1 year for ITP)	120
F	55	M	-	face, abdomen	4	9	0.05	8	37	+	Danazol, tranexamic acid + 2 cycles rituximab	120
G	46	F	Splenic marginal zone lymphoma	hands, feet, genitals	36	3	0.08	21	48	-	Tranexamic acid, CVP (x6) + 1 cycle rituximab	120
H	60	F	Splenic marginal zone lymphoma	abdomen	96	5	0.03	12	38	-	CVP (x6) + 1 cycle rituximab	108
I	70	M	-	lips, tongue, throat	4	12	0	8	25	+	Danazol + 2 cycles rituximab	110
J	49	F	SLE	abdomen, hands, feet	12	7	0.10	19	44	+/-	Tranexamic acid + prednisolone + 1 cycle rituximab	98