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Rituximab Therapy of Recalcitrant Bullous Dermatoses

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Abstract

Background: Rituximab is a monoclonal antibody directed against CD20 cell surface antigen of B-lymphocytes. Recent studies have demonstrated effectivity in recalcitrant bullous pemphigoid. The data available on other types of autoimmune bullous disease is more scant.

Main observation: Here we report on the successful adjuvant use of rituximab in mucous membrane pemphigoid and pemphigus vulgaris in two patients with the most refractory course of disease. Both patients achieved a good clinical response.

Conclusion: Rituximab is a third line treatment of patients with pemphigus vulgaris and mucous membrane pemphigoid. In contrast to bullous pemphigoid, other bullous diseases do not always respond to a monotherapy with this monoclonal antibody. Nevertheless, biological therapy seems to work faster than established treatment in such cases. Risks and benefits of the treatment are discussed.

Introduction

Pemphigus is a life-threatening autoimmune bullous disease mediated by pathogenic antibodies against epidermal desmoglein 1 and 3. Bullous pemphigoid often has a more benign course when treated early. Mucous membrane pemphigoid (cicatrical pemphigoid), however, often runs a severe course of eye affection leading to severe vision impairment and blindness.[1]

The disease often requires a long-term immunosuppressive treatment. Immunosuppressive drugs employed include corticosteroids, azathioprine, methotrexate, ciclosporin A, mycophenolate mofetil, cyclophosphamide, and intravenous immunoglobulins. Such treatment may lead to severe adverse effects in some patients.

Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 antibody directed against CD20, a B-lymphocyte specific cell surface antigen. Once bound, the Fc portion of the antibody recruits immune effector cells leading to a lysis of pre-B and B-lymphocytes.[2] In adults the standard dosage is 375 mg/m^2 once per week for 4 consecutive weeks.[3]

Adverse effects are mostly mild infusion-related, such as headaches, fever, chills, nausea, pruritus and rash, usually seen with the first treatment. Such events can be minimized giving antihistamines and antipyretics before the infusion. Severe adverse effects are rare but may be fatal. Stevens-Johnson syndrome, anaphylaxis, bacterial sepsis or viral infections of the central nervous system have been reported.[3,4]

Initially approved for the treatment of relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma, the drug has since been used to treat a wide variety of autoimmune disease like rheumatoid arthritis, lupus erythematosus, and idiopathic thrombocytopenic purpura.[3]

We report two patients treated with rituximab as adjuvant drug, one with mucous membrane pemphigoid and one with severe pemphigus vulgaris.

Case 1

A 41-year-old male patient with a progressive eye disease since 2003, was initially treated Vidisic eye gel drops. The disease led over years to symblepharon and severe visual impairment. Upon admission, ophthalmologic consultants suggested the diagnosis of a mucous membrane pemphigoid although pemphigoid antibodies were negative. The patient received a combination of oral therapy with dapsone, cyclophosphamide and prednisolone. Because the treatment was not effective to stop disease progression mycophenolic acid at the dose of 2x720 mg/d p.o. and 100 mg of predisolone i.v. per day was introduced and a partial remission was achieved after 8 weeks. The corticosteroid dosage was reduced to 40 mg methyprednisolone per day and continued until 2006.

In 2006, after a viral upper respiratory infection he had his first eruption of bullous oral mucous membrane lesions. Now skin biopsies were taken and histology and immunofluorescence was consistent with mucous membrane pemphigoid. During follow-up the prednisolone dosage was reduced because of the development of a type IIa diabetes mellitus.

In March 2007 the eye involvement showed progression with vascularization and scar formation (Fig. 1a). At that time he got 10 mg prednisolone/ day and 2x2 mycophenolic acid 360 mg tablets/ day. Topical therapy for the eyes included eye drops (ciclosporin A, ofloxacine, and dexamethasone).

Because of progression we decided to treat him with rituximab (MabThera®; Roche) 375 mg/m^2 i.v. once a week with a total of 4 infusions in an adjuvant fasion. The treatment was well tolerated and no unwanted side effects were noted. The percentage of CD20-positive cells dropped from 20% before to zero after rituximab infusion.

We achieved a stable ocular disease. The follow-up period is now 8 months (Fig. 1b).

Case 2

A 79-year old woman with cardiac disease and relapsing tachyarrhythmia came to the department with a history of three months of severe mucous membrane lesions and fever of up to 40 degrees Celcius. On examination she had a severely reduced general health status. The oral mucosa including the tongue showed large, painful erosions. Oral and esophageal candidosis had been diagnosed and treatment was started with amphotericine suspension. The eyes had a marked conjuctival injection and redness. Bullae and crusted erosions were seen on the trunk and upper legs. A diagnostic biopsy was taken that revealed a pemphigus vulgaris with typical histopathology and direct immunofluorescence. Pemphigus vulgaris antibodies were positive 1:640.

Treatment was started with 120 mg prednisolone per day i.v. in combination with azathioprine 150 mg/ d p.o. A partial remission was achieved with complete remission of mucous membrane lesions and marked reduction of skin lesions within a months. The dosage was tapered down to 50 mg/d prednisolone and 100 mg/d azathioprine. The treatment was continued until two years later she had a severe relapse with painful mucosal and generalized cutaneous involvement (>80% body surface) (Fig. 2a).

The initial treatment consisted of prednisolone 125 mg/ day i.v. and mycophenolic acid 2x 720 mg/ d p.o. The treatment showed only a marginal improvement. Therefore we decided to treat her with rituximab 375 mg/m^2 i.v. once a week for 4 weeks in an adjuvant setting. Staphylococcal and E. coli skin infections and mucosal candidiasis needed antibiosis (levofloxacine) and antifungal treatment (diflucan oral suspension). The disease showed an almost complete clinical response, i.e. complete remission of mucosal lesions and residual superficial erosions of less than 1% body surface (Fig. 2b). Pemphigus antibodies were reduced from 1:320 to 1:40. Predisolone could be reduced

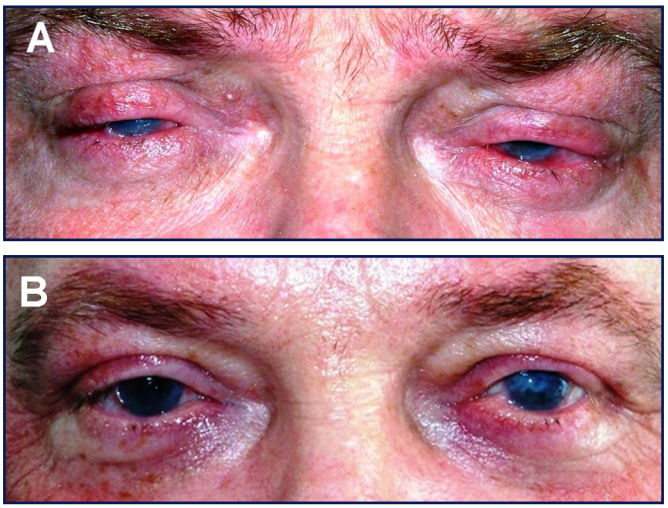

Figure 1

Male patient with severe eye involvement by mucous membrane pemphigoid. (A) Before rituximab and (B) at the end of rituximab therapy.

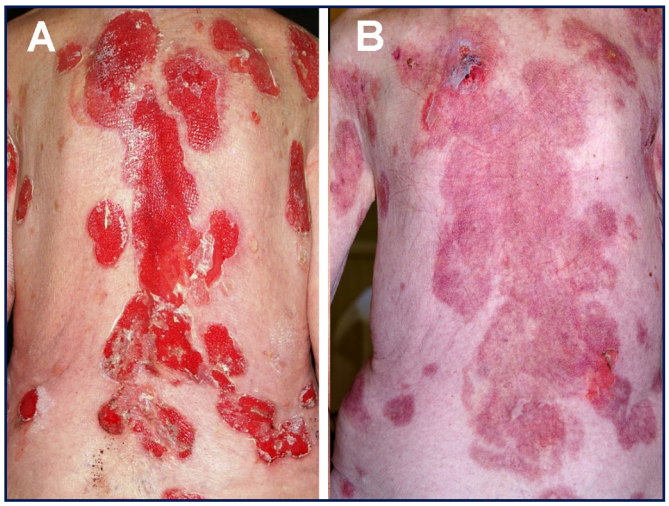

Figure 2

Female patient with severe, recalcitrant pemphigus vulgaris. (A) Before rituximab and (B) at the end of rituximab therapy. A further improvement was noted thereafter.

Table 1: Rituximab therapy in pemphigus vulgaris (PV) and mucous membrane pemphigoid (MMP)

Reference	Type of study	Number of patients	Diagnoses	Treatment	Outcome	Follow-up (mena in months)	Time to response (months)	Duration of response	Severe adverse effects
Joly *et al.* (2007)	multicenter, prospective, open-label	21 (including 7 patients with pemphigus foliaceus)	PV and pemphigus foliaceus	four weekly infusions of rituximab plus prednisolone	CR in 18 patients	34	3	mean 18.9	pyelonephritis (1), death due to septicaemia (1)
Schmidt *et al.* (2006)	two centers, open-label	7	PV (4), bullous pephigoid (2), MMP (1)	(four weekly infusions in 5 patients, two infusions in 1 and 4 + 5 infusions in 1 patient, concomintant immunosuppression	CR (3)	7 to 21	6 to 26	up to 10	bilateral blindness (MMP), fatal pneumonia (1)
Goh *et al.* (2007)	single center, open-label prospective pilot study	5	PV	four weekly infusions, concurrent immunosuppression	CR (3), PD (2)	?	2 to 8	13 to 18	pneumonia with neutropenia (1), cytomegalovirus infection (1)
Marzano *et al.* (2007)	single center, open-label	6	PV (2), pemphigus foliaceus (3), MMP (1)	four weekly infusions, in one patient 6 infusions; concomitant immunosuppression	CR 6 (including MMP)	up to 18	?	?	?
Cianchini *et al.* (2007)	single center, open-label	12	PV (10), pemphigus foliaceus (2)	four weekly infusions	CR (9), PR (3)	6 to 18	3 to 6	up to 12	none
Ziai *et al.* (2007)	single center	5	PV	four to six weekly infusions	CR (1), PR (3)	?	?	?	none
Ahmed *et al.* (2006)	single center, open-label	11	PV	two cycles of weekly rituximab infusions followed by intravenous immunoglobulin for 4 consecutive months, concomitant immunosuppression	CR (9)	15 to 37	4	mean 31.1	none
Fatourechi *et al.* (2006)	review	12	PV (11), pemphigus foliaceus (1)	four weekly infusions (single cases with a second course), concurrent immunosuppression, intravenous immunoglobulins and/or plasmapheresis	CR (8), PR (3)	?	1 to 10	up to 18	pneumonia (1), sepsis (1) fatal pneumocystis carinii infection (1)
Arin *et al.* (2005)	single center, open-label	5	PV (4), pemphigus foliaceus (1)	four weekly infusions, concomitant immunosuppression	CR (3), PR (2)	10 to 36	?	10 to 36	none
Weger & Aberer (2008)	single center, open label	1	PV (1)	four weekly infusions, concomitant immunosuppression	progression				none
Present paper	single center, open label	2	PV (1), MMP (1)	four wekly intervals	PR (2)	4 to 8	4	2 to 6	none

to 15 mg/ d, mycophenolic acid was continued with 720 mg twice a day. CD20-positive cells dropped from 16% to zero. The treatment was well tolerated. The only side-effect noted was a mild phlebitis of the arm used for infusions. The follow-up is four months.

Discussion

Rituximab has shown clinical efficacy in small series of autoimmune bullous disease.[3] Most experience has been gained in pemphigus vulgaris. In one review covering 18 refractory patients and a standard dosing schedule of rituximab, 3 patients achieved a complete remission (CR, no further treatment needed), 4 patients achieved a clinical remission (complete healing of lesions but further treatment needed), and 11 patients experienced a partial remission (PR).[5] In 11 patients with refractory pemphigus vulgaris rituximab was used once a week for three weeks only followed by intravenous immunoglobulins 2g/kg in the fourth week. The cycle was repeated once and followed by monthly rituximab and intravenous immunoglobulins for another 4 months. 9 patients achieved a clinical remission lasting between 22-27 months without severe adverse effects.[6] Recently Joly *et al*.[4] investigated 21 pemphigus vulgaris patients who had not responded to an 8-week course of prednisolone. The patients were treated with a single 4-week cycle of rituximab therapy. The primary endpoint of this study was CR 3 months after rituximab therapy. 8 patients had a CR at three months, after a median follow-up of 34 months 18 patients were free of disease with 10 CR and 8 clinical responses, treated with prednisolone.[4] In mucous membrane pemphigoid, only case reports have been published (Table 1).[7,8]

Here we described two patients with a severe and progressive disease, one with a mucous membrane pemphigoid, one with a relapsed generalized pemphigus vulgaris, using the standard dosing schedule for rituximab adjuvant to the previous immunosuppressive therapy in each patient. In patient 1 a stable disease was achieved after he had experienced progressive disease over years and serious side-effects such as a diabetes induction by corticosteroid therapy. In the second patient risk factors for fatal outcome of pemphigus such as old age (79 years), cardiac disease, and a severe relapse with a body surface area involvement of more than 80% were evident. Nevertheless, we gained a clinical remission without severe adverse effects and the drug worked fast compared to established immunosuppressive treatment.

In conclusion, rituximab is an effective third-line therapy in severe and potentially life-threatening autoimmune bullous diseases with best evidence available in pemphigus vulgaris. There is only limited evidence until now for other types like mucous membrane pemphigoid. Since fatal adverse effects may occur, the use of rituximab should be limited to the most severe types of autoimmune bullous disease only.

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