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Letter to the Editor

Rituximab off-label use for immune diseases: assessing adverse events in a single-centre drug-utilization survey

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Rituximab is an anti-CD20 autoantibody approved for rheumatoid arthritis. It induces deep and prolonged depletion of CD20-bearing lymphocytes. Rituximab is increasingly used off-label for autoimmune diseases (AIDs) in immunocompromised patients (ICP), whereas its safety is not well documented in this setting. We assessed off-label rituximab use in AIDs through a drug-utilization survey in Toulouse University Hospital (2834 beds) from January 2004 to December 2005.

Patients who had received at least one rituximab infusion for AIDs were identified from the pharmacy department database. We used the World Health Organization definition for serious adverse events (SAEs) [1]. Patients taking >20 mg day^{-1} prednisone and/or an immunosuppressive drug at the time of first rituximab infusion were considered immunocompromised. All patients were followed 1 year after the first rituximab infusion.

Thirty-seven patients (18 women), mean age 51.7 years (95% confidence interval ±17.6) were included in the study. Median disease duration was 87 months (range 1–396). Diagnostic groups were: autoimmune cytopenia ($n = 19$), autoimmune coagulation disorder ($n = 5$), cryoglobulinaemia ($n = 7$), Wegener's granulomatosis ($n = 3$), pemphigus ($n = 2$) and lupus erythematosus ($n = 1$). The mean daily corticosteroid dosage at the time of rituximab first infusion was 35.2 mg day^{-1} (median 30; range 0–60). There was 30 ICPs (81.1 ± 12.6%); 75.7% (±13.8) of the patients received a complete cycle of four 375 mg kg^{-1} day^{-1} infusions. Eight then had maintenance therapy.

We estimated that the complete remission rate after rituximab was 20/37 (54 ± 16.1%) according to criteria used in major international publications. One patient had a partial response. Rituximab was the main contributor to complete remission in 14 patients (37.8 ± 15.6) who had no intensification of other therapies. Among 20 complete responders, three were treated again because of relapse between 12 and 13 months after the first infusion.

SAEs occurred in 14/37 patients (37.8 ± 15.6%) (Table 1), including death in six with uncontrolled disease. Seven (18.9 ± 12.6%) had serious infections, of whom two had pneumocystosis. Six of these seven patients were immunocompromised and another had undergone splenectomy 3 months earlier. The estimated incidence rate of infectious SAEs was 20.7 (±14.5) per 100 patient-years in ICPs.

To our knowledge, this is the first report of a systematic hospital-based safety survey of rituximab off-label utilization for AIDs. Incidence of SAE, especially infectious, was much higher than in another study including adult patients with various AIDs [2]. In this retrospective study, 1/3 of patients had rheumatoid arthritis, some had a short follow-up, and patients were included on a voluntary basis by their attending physician. We cannot exactly determine the contribution of rituximab to infectious SAEs, as SAEs occur in about 13.5 per 100 years in patients receiving chronic immunosuppressive therapy for various AIDs [3]. Given a large confidence interval, this may not be very different from the 20.7 (±14.5) per 100 years infection rate we have found. However, hypogammaglobulinaemia occurring in some patients [4], loss of IgM-only producing memory B cells that are crucial for defence against bacteria [5], alteration of antigen-presenting cell function due to B-cell depletion [6] and the possibility of delayed neutropenia [7] may worsen susceptibility to infection in previously immunocompromised patients exposed to rituximab.

Table 1

Serious adverse events (SAE) among 37 patients treated by Rituximab for AIDs

Age	Gender	Disease	Drugs at the time of AE	Co-morbidity	Adverse event	Time of AE	B cell %	Evolution	Response to RTX
51	F	MPG-cryoglobulinaemic vasculitis	Prednisone 60 mg Interferon-ribavirin	HCV infection	Cutaneous necrosis over a catheter port	M2	0	Resolved	Yes
47	M	MPG-cryoglobulinaemia-HCV	Ciclosporin 100 mg MMF 2 g Prednisone 5 mg	Renal engraftment	Staphylococcal cellulitis CMV reactivation	M12	3	Resolved	Yes
56	F	MPG-VHC	Prednisone 5 mg MMF 1000 mg Tacrolimus 3 mg	Renal engraftment	*Staphylococcus aureus* *Pseudomonas aeruginosa* pneumopathy Disseminated HSV2	M5	1	Resolved	No
40	M	TTP	Prednisone 60 mg	Urinary catheter	*Escherichia coli* septicaemia	M2	0	Resolved	No
52	M	WG	Prednisone 60 mg CPM 100 mg day^{-1}	Renal dialysis	Haemorrhagic collapse	M1	0	Resolved	Yes
53	M	WG Digestive and lung haemorrhage	Prednisone 60 mg	Renal dialysis	Pneumocystosis Severe lymphopenia neutropenia anemia	M2	0	Resolved Resolved Resolved Resolved	Yes
57	F	AIHA	Prednisone 15 mg		Pleuro-pneumopathy	M10	ND	Resolved	No
85	H	ITP	Prednisone 60 mg	Waldenström's gammaglobulinaemia	Bacterial pneumopathy	M2	ND	Resolved	Yes
70	F	Pure red cell aplasia	Prednisone 30 mg	Chronic malnutrition	Shock and epidermolysis	M1	ND	Died	No
73	F	AIHA	Prednisone 1 mg kg^{-1} day^{-1} IV CPM		Uncontrolled haemolysis	M5	ND	Died	No
72	M	AIHA	Methylprednisolone 60–120 mg day^{-1}	Undiagnosed AIL-like T-lymphoma	Septic choc Pneumocystosis Uncontrolled haemolysis	M2	0	Died	No
50	M	Wegener's	I.v. methylprednisolone, i.v. CPM		Uncontrolled cerebral vasculitis	D3	ND	Died	NE
80	M	Acquired anti-Willebrand	IV-Ig (inefficacy)	End-stage renal disease	Undefined	M3	ND	Died	No
77	F	ITP	Prednisone 2 mg kg^{-1} IV-Ig	Splenectomy	Cerebral bleeding	D7	ND	Died	No

One Wegener's patient had SAE in 2004 and in 2005 after re-treatment. AE, adverse event; AIHA, autoimmune haemolytic anemia; CPM, cyclophosphamide; D, day; HCV, hepatitis C virus; HSV, herpes simplex virus; ITP, immune thrombocytopenic purpura; IV-Ig, intravenous immunoglobulins; M, month; MMF, mycophenolate mophetil; MPG, membranoproliferative glomerulonephritis; ND, not done; NE, not evaluable; RTX, rituximab; TTP, thrombotic thrombocytopenic purpura; WG, Wegener's granulomatosis.

In conclusion, in this study SAEs were frequent among patients treated off-label by rituximab for AIDs. The infection rate was perhaps abnormally high. Benefit-to-risk ratio of rituximab off-label use for immune diseases in real life should be further systematically assessed.

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