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Preliminary report

Unexpected worsening of pemphigus vulgaris after rituximab: A report of three cases

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ABSTRACT

During the recent decade, several studies have confirmed the high efficacy of targeting the CD20 molecules using rituximab (RTX). Recently, RTX has been suggested as the first-line treatment of pemphigus vulgaris (PV). In this study, the records of all the PV patients, who had received RTX in Autoimmune Bullous Diseases Research Center, Tehran University of Medical Sciences between the 2009 and 2017, have been reviewed for any sign of disease worsening within three months after treatment. We have observed three PV patients from 612 RTX-exposed patients, who had experienced worsening of disease more than one time after discrete RTX cycles after the first infusion of RTX. All patients were successfully managed with different strategies (e.g., increase in steroid dosag intravenous immunoglobulin [IVIg], and plasmapheresis). In conclusion, despite the high efficacy of RTX therapy in PV patients, the exceptional risk of post-RTX disease worsening exists. Further studies are encouraged to develop (bio)markers to predict possible unexpected worsening of PV patients exposed to RTX.

1. Introduction

Rituximab (RTX) is a newly emerged drug that targets the CD20 molecule on B cells. It is a very potent alternative drug for patients with pemphigus vulgaris (PV), who do not tolerate conventional treatments or do not respond well and still flare despite the combination therapy [1]. Using RTX has also led to reasonable outcomes in patients with refractory pemphigus [1]. Recently, Joly et al. [2] have suggested first-line RTX therapy in patients with moderate-to-severe pemphigus. However, there are rare reports showing worsening of pemphigus in the literature. Additionally, some reports of disease exacerbation in patients with neuromyelitis optica [3,4], ulcerative colitis [5], lymphomatoid papulosis [6] and pemphigoid [7], few weeks/months following RTX have also been published. To our best knowledge, five papers have reported similar unexpected phenomenon in pemphigus (total 16 patients). Leshem et al. [8] the evaluated response rate in 47 pemphigus patients. Four (8.5%) of them exacerbated immediately after infusion. Years later, another report of pemphigus exacerbation was noted in two of 25 (8%) pemphigus patients after the first dose of RTX [9]. Feldman also reported a case of PV exacerbation who received RTX as monotherapy in an RA protocol [10]. Around five weeks after the RTX infusion, the oral erosions worsened [10]. In another report, a six-year-old boy with refractory pemphigus foliaceus (PF) experienced exacerbation following RTX administration [11]. Bhattacharjee et al. [12] reported disease flare in 8 out of 17 severe pemphigus patients who received monotherapy with RTX. Here we report three PV patients, who had received RTX but failed to respond and experienced disease relapse more than one time within the first three months of injection.

2. Patients and methods

The medical records of the PV patients, who had received RTX in Autoimmune Bullous Diseases Research Center, Tehran University of Medical Sciences within nine years (2009–2017) were reviewed. Those who experienced at least two episodes of disease worsening after receiving different cycles of RTX have been included. Disease worsening was defined as at least increasing 10 points in Pemphigus Disease Area Index (PDAI) score and the new lesions persisting > 2 weeks within the first three-month following receiving the RTX. Disease worsening should occur at least twice during different cycles of RTX in each patient to distinguish disease worsening from disease fluctuation. Other disease phases, such as relapse and remission were defined according to consensus [13]. All the patients had received a premedication of chlorphenamine (10 mg IV), hydrocortisone, 100 mg IV, and two acetaminophen tablets (325 mg) and RTX was administered intravenously at the dose of 500 mg weekly for four weeks. After receiving RTX,

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Table 1
Summary of patients' characteristics, treatment strategies, and outcomes. Abbreviations: AZA, azathioprine; MMF, mycophenolate mofetil; IVIg, intravenous immunoglobulin; MTX, methotrexate.

Patient number	Sex and age	Treatment at the time of PV worsening (dosage)	Drugs before first rituximab therapy	Total number of rituximab cycles	Number of exacerbation after rituximab	Time to exacerbate	Strategies to control	Outcome
Case 1	Female, 44-year-old	Cycles 1: Prednisolone (dosage was not available) Cycle 2: Prednisolone (32.5 mg/d), Cycle 3: Prednisolone (10 mg/d),	Prednisolone, AZA, MMF, IVIg	3	3	Cycle 1: Some days after the first infusion. Cycle 2: One week after the first infusion. Cycle 3: Some days after the third infusion.	Cycles 1: Increasing prednisolone dosage (up to 50 mg/g) Cycle 2: Prednisolone (up to 70 mg/d), IVIg (2 g/kg) Cycle 3: IVIg (2 g/kg)	Partial remission
Case 2	Male, 32-year-old	Cycle 1: Prednisolone (25 mg/d) Cycle 2: Prednisolone (12.5 mg/d)	Prednisolone, AZA, MMF	2	2	Cycle 1: Less than one week after the first infusion Cycle 2: and fourth infusion	Cycle Prednisolone (50 mg/d), MTX (20 mg/w) Cycle 2: IVIg (4 cycles at the dose of 2 g/kg), plasmapheresis	Partial remission
Case 3	Male, 35-year-old	Cycle 1: Prednisolone (35 mg/d) Cycle 2: Prednisolone (7.5 mg/d)	Prednisolone	2	2	Cycle 1: Some days after the second infusion. Cycle 2: Some days after the first infusion.	Cycle 1: Increasing prednisolone dosage (45 mg/d) Cycle 2: Increasing prednisolone dosage (15 mg/d)	Complete remission

patients continued prednisolone in tapering dose, depending on the response to the treatment.

3. Results

3.1. Patients' characteristics

The study includes three patients out of 612 RTX-treated patients, who did not respond to RTX and developed numerous new erosions on the skin and/or mucous membranes, considered as disease worsening according to the definition within 3 months after RTX infusion.

3.2. Cases synopsis

3.2.1. Case 1

A 44-year-old woman, non-responder to conventional treatments with a three-year history of mucocutaneous PV had received RTX in June 2008. The patient experienced an unexpected flare of disease some days after receiving the first infusion of RTX but controlled by a combination of high dose steroid and IVIg (2 g/kg within 5 days). After less than one year (November 2009), she received the second cycle of RTX resulting in immediate disease worsening, which was controlled by an increase in prednisolone dose and initiation of IVIg therapy (2 g/kg within 5 days). After six years on minimal therapy with occasional minor relapses, disease flared again leading to an increase in the prednisolone dose up to 70 mg/d, and a new RTX cycle was planned. Similar to 6 years ago, she developed erythema of face, neck, and breast as well as mucosal lesions following the third infusion. Evaluation of anti-Dsg1 and anti-Dsg3 ELISA revealed positive values (> 200 U/mL). The patient had been given IVIg infusions (2 g/kg), which were effective.

3.2.2. Case 2

A 32-year-old male, who was diagnosed with mucocutaneous PV in July 2012, did not respond well to prednisolone (40 mg/d) and MMF (2 g/d). The patient had received RTX in August 2014, which caused a disease flare (appearance of bullae on hands and feet), less than one week after the first infusion. With a one-week delay, the second infusion also led to the development of new bullae in addition to herpetic lesions. Doubling prednisolone dose (50 mg/d) was decided, followed by IVIg infusion within the second month of patient's hospitalization. With a three-month delay, the third and fourth 500 mg of RTX were infused, which were not effective. After controlling the disease with prednisolone and methotrexate (MTX), another cycle of RTX was tried one year later (December 2015). However, the disease exacerbated one week after the fourth infusion. Moreover, the results of tests for anti-Dsg1 and anti-Dsg3 ELISA were positive (> 200 U/mL). After four monthly cycles of IVIg therapy, deep venous thrombosis (DVT) developed, and IVIg therapy was stopped, and plasmapheresis was planned for September 2016. Interestingly, his lesions started to heal following six sessions of plasmapheresis.

3.2.3. Case 3

A 35-year-old man with a more than two-year history of mucocutaneous PV had received four infusions of RTX at the dose of 500 mg in four consecutive weeks. However, he did not respond and the disease exacerbation was noted with the development of new blisters on the skin as well as mucous membranes after the second infusion, which resolved by increasing prednisolone dosage (up to 45 mg/d). After approximately 11 months, considering multiple transient lesions and a significant rise in anti-Dsg3 (> 200 U/mL), we decided to start a new cycle of RTX. Exacerbation of disease was observed similarly after the first infusion (1000 mg) and then prednisolone dosage was doubled (15 mg/d). Immediately after the disease worsening, evaluation of both CD19 and CD20 revealed a complete B-cell depletion. Following partial control of the disease through the escalation of prednisolone dosage, we

decided to continue the second infusion at the dose of 1000 mg after two weeks. Interestingly, we did not detect any new lesion after these infusions, and the patient went into complete remission on minimal therapy (5 mg/d prednisolone). Table 1 summarizes the patients' characteristics and treatment strategies for the three patients.

4. Discussion

Increased use of RTX shed light on some unexpected outcomes in patients with different autoimmune diseases. Recently, some authors have reported paradoxical worsening of PV patients, who were under RTX therapy [8–10]. However, there is no exact explanation for this unusual occurrence. During this study, because of diversity in the severity of relapse and difference in interval between the clinical flare and RTX exposure as well as the low number of detected patients, no trustable correlation was found. The mechanisms of this phenomenon in PV patients are not clear. However, some speculations could be released, including (1) B cell escaping from rapid apoptosis, for example through overexpression of anti-apoptotic gene products [14]; (2) increased antibody production by anti-Dsg clonal plasma cells following total immunoglubin decrease as a consequence of B cell depletion; (3) mutation (s) or polymorphisms in genes encoding the receptor or even enzymes involved in RTX action, such as FcγRIIIa [15] and CD20 [16]; (4) incomplete B-cell depletion in the peripheral blood, which could be rejected based on our case with CD19 and CD20 depleted cells after disease exacerbation; (5) development of inhibitory human anti-chimeric antibodies to the RTX [17]; (6) alternative CD20 transcript variant [18], lack of whose expression in circulating B cells from PV patients has been reported [19]; and (7) the promotion of T cells' roles. Bhattachajee et al. [12] could find any trend in CD4+ CD25+ FoxP3+ and IL-10-secreting Tr1 Tregs in their patients following RTX monotherapy.

In such patients with worsening of their PV after RTX therapy with either an increase in prednisolone dosage or adding IVIg to the treatment, delaying and even canceling the rest of RTX injections may be a suitable management protocol. After controlling the relapse, the remaining RTX infusions could be continued safely. According to our observations, it is plausible that treatments with either IVIg or escalation in steroid dosage after the paradoxical worsening following RTX infusion(s) in PV patients are even more effective than these therapies without RTX treatment. IVIg was found to be an effective treatment in pemphigus, which may act through different mechanisms [20]. Moreover, IVIg was reported to selectively decrease circulating autoantibodies in pemphigus [21]. Thus, it could be expected that patients may benefit from treatment with RTX in combination with IVIg, as Ahmed et al. [22] have reported previously. This protocol could also decrease the risk of infection.

In conclusion, exceptional PV patients might experience disease worsening after RTX. IVIg and/or increasing in prednisolone dosage were found practical approaches to control disease after such event. However, more studies are needed to determine the mechanism of this disease worsening and to detect possible (bio)markers predicting this phenomenon.

Conflict of interest

None.

Financial disclosure

None.

References

[1] S. Tavakolpour, H. Mahmoudi, K. Balighi, R. Abedini, M. Daneshpazhooh, Sixteen-year history of rituximab therapy for 1085 pemphigus vulgaris patients: a systematic review, Int. Immunopharmacol. 54 (2017) 131–138.

[2] P. Joly, M. Maho-Vaillant, C. Prost-Squarcioni, V. Hebert, E. Houivet, S. Calbo, F. Caillot, M.L. Golinski, B. Labeille, C. Picard-Dahan, C. Paul, M.A. Richard, J.D. Bouaziz, S. Duvert-Lehembre, P. Bernard, F. Caux, M. Alexandre, S. Ingen-Housz-Oro, P. Vabres, E. Delaporte, G. Quereux, A. Dupuy, S. Debarbieux, M. Avenel-Audran, M. D'Incan, C. Bedane, N. Beneton, D. Jullien, N. Dupin, L. Misery, L. Machet, M. Beylot-Barry, O. Dereure, B. Sassolas, T. Vermeulin, J. Benichou, P. Musette, First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial, Lancet (London, England) 389 (10083) (2017) 2031–2040.

[3] J.S. Perumal, I. Kister, J. Howard, J. Herbert, Disease exacerbation after rituximab induction in neuromyelitis optica, Neurology® Neuroimmunology & Neuroinflammation 2 (1) (2015) e61.

[4] Y. Dai, T. Lu, Y. Wang, L. Fang, R. Li, A.G. Kermode, W. Qiu, Rapid exacerbation of neuromyelitis optica after rituximab treatment, Journal of clinical neuroscience: official journal of the Neurosurgical Society of Australasia 26 (2016) 168–170.

[5] M. Goetz, R. Atreya, M. Ghalibafian, P.R. Galle, M.F. Neurath, Exacerbation of ulcerative colitis after rituximab salvage therapy, Inflamm. Bowel Dis. 13 (11) (2007) 1365–1368.

[6] O. McCurdy, C. McCormack, D. Ritchie, H.M. Prince, Exacerbation of lymphomatoid papulosis during rituximab therapy, The Australasian Journal of Dermatology 55 (1) (2014) e1–e3.

[7] A.F. Batts, S.Z. Jalalat, L. Hunter-Ellul, M.G. Wilkerson, Exacerbation of bullous pemphigoid after hand, foot, and mouth disease treated with rituximab, JAAD Case Reports 2 (1) (2016) 7–9.

[8] Y.A. Leshem, E. Hodak, M. David, G.J. Anhalt, D. Mimouni, Successful treatment of pemphigus with biweekly 1-g infusions of rituximab: a retrospective study of 47 patients, J. Am. Acad. Dermatol. 68 (3) (2013) 404–411.

[9] V.K. Sharma, N. Bhari, S. Gupta, K. Sahni, N. Khanna, M. Ramam, G. Sethuraman, Clinical efficacy of rituximab in the treatment of pemphigus: a retrospective study, Indian Journal of Dermatology, Venereology and Leprology 82 (4) (2016) 389–394.

[10] R.J. Feldman, Paradoxical worsening of pemphigus vulgaris following rituximab therapy, Br. J. Dermatol. 173 (3) (2015) 858–859.

[11] P. M, A. HA, T. DQ, Exacerbation of pemphigus foliaceus in a child after rituximab treatment, Transl, Science 2 (8) (2016) e05.

[12] R. Bhattacharjee, D. De, S. Handa, R.W. Minz, B. Saikia, N. Joshi, Assessment of the effects of rituximab monotherapy on different subsets of circulating T-regulatory cells and clinical disease severity in severe pemphigus vulgaris, Dermatology (Basel, Switzerland) 232 (5) (2016) 572–577.

[13] D.F. Murrell, S. Dick, A.R. Ahmed, M. Amagai, M.A. Barnadas, L. Borradori, J.C. Bystryn, G. Cianchini, L. Diaz, D. Fivenson, R. Hall, K.E. Harman, T. Hashimoto, M. Hertl, N. Hunzelmann, P. Iranzo, P. Joly, M.F. Jonkman, Y. Kitajima, N.J. Korman, L.K. Martin, D. Mimouni, A.G. Pandya, A.S. Payne, D. Rubenstein, H. Shimizu, A.A. Sinha, D. Sirois, D. Zillikens, V.P. Werth, Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus, J. Am. Acad. Dermatol. 58 (6) (2008) 1043–1046.

[14] A.R. Jazirehi, M.I. Vega, B. Bonavida, Development of rituximab-resistant lymphoma clones with altered cell signaling and cross-resistance to chemotherapy, Cancer Res. 67 (3) (2007) 1270–1281.

[15] I. Pál, S. Szamosi, K. Hodosi, Z. Szekanecz, L. Váróczy, Effect of Fcγ-receptor 3a (FCGR3A) gene polymorphisms on rituximab therapy in Hungarian patients with rheumatoid arthritis, RMD Open 3 (2) (2017).

[16] Y. Terui, Y. Mishima, N. Sugimura, K. Kojima, T. Sakurai, Y. Mishima, R. Kuniyoshi, A. Taniyama, M. Yokoyama, S. Sakajiri, K. Takeuchi, C. Watanabe, S. Takahashi, Y. Ito, K. Hatake, Identification of CD20 C-terminal deletion mutations associated with loss of CD20 expression in non-Hodgkin's lymphoma, Clinical Cancer Research: An Official Journal of the American Association for Cancer Research 15 (7) (2009) 2523–2530.

[17] L. Lunardon, A.S. Payne, Inhibitory human anti-chimeric antibodies to rituximab in a pemphigus patient, J. Allergy Clin. Immunol. 130 (3) (2012) 800–803.

[18] C. Henry, M. Deschamps, P.S. Rohrlich, J.R. Pallandre, J.P. Remy-Martin, M. Callanan, A. Traverse-Glehen, C. GrandClement, F. Garnache-Ottou, R. Gressin, E. Deconinck, G. Salles, E. Robinet, P. Tiberghien, C. Borg, C. Ferrand, Identification of an alternative CD20 transcript variant in B-cell malignancies coding for a novel protein associated to rituximab resistance, Blood 115 (12) (2010) 2420–2429.

[19] C. Gamonet, C. Ferrand, N. Colliou, P. Musette, P. Joly, M. Girardin, P. Humbert, F. Aubin, Lack of expression of an alternative CD20 transcript variant in circulating B cells from patients with pemphigus, Exp. Dermatol. 23 (1) (2014) 66–67.

[20] B. Chaigne, L. Mouthon, Mechanisms of action of intravenous immunoglobulin, Transfusion and Apheresis Science: Official Journal of the World Apheresis Association: Official Journal of the European Society for Haemapheresis 56 (1) (2017) 45–49.

[21] A. Czernik, E.H. Beutner, J.C. Bystryn, Intravenous immunoglobulin selectively decreases circulating autoantibodies in pemphigus, J. Am. Acad. Dermatol. 58 (5) (2008) 796–801.

[22] A.R. Ahmed, Z. Spigelman, L.A. Cavacini, M.R. Posner, Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin, N. Engl. J. Med. 355 (17) (2006) 1772–1779.