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First line treatment of pemphigus vulgaris with a novel protocol in patients with contraindications to systemic corticosteroids and immunosuppressive agents: Preliminary retrospective study with a seven year follow-up☆,☆☆

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ABSTRACT

Background: Conventional therapy for pemphigus vulgaris (PV) consists of high-dose systemic corticosteroids (CS) and immunosuppressive agents (ISA). This combination may be ineffective, cause serious adverse events or relapses in some patients.
Objective: To determine if the combination of intravenous immunoglobulin (IVIg) therapy and rituximab (RTX) can be used as first-line therapy in PV patients in whom systemic CS and ISA are contraindicated and evaluate its ability to produce long-term sustained remissions.
Method: This a retrospective study of five male and five female patients (mean age 47.87 years). RTX was administered once weekly for eight consecutive weeks, followed by once monthly for four months (dose 375 mg/m^2). Since CD20$^+$ B cells were undetectable, IVIg was infused until they reached normal levels (dose 2 g/kg/cycle). IVIg was then continued according to published protocol.
Results: Initial clinical response and complete disease resolution occurred in a mean of 3.2 weeks and 7.4 weeks, respectively. Mean duration of rituximab therapy was 6.09 months and 33.7 months for IVIg therapy. Mean duration of follow-up after the last dose of rituximab was 86.08 months, during which all patients remained in complete remission. Mean length of total follow-up was 103.99 months. No relapses, infections, or hospitalizations were reported.
Conclusions: When systemic CS and ISA are contraindicated in PV patients, combination RTX and IVIg therapy can produce a prolonged, sustained remission without additional systemic therapy. This positive clinical outcome could be the consequence of pathogenic B cell depletion and restoration of immune regulation.

1. Introduction

Pemphigus vulgaris (PV), a potentially fatal autoimmune blistering disease that affects the skin and mucous membranes [1], is characterized by autoantibodies against desmoglein (Dsg) 1 and 3 [1]. Rituximab (RTX), a chimeric monoclonal antibody, targets the CD20 molecule on B cells but not on plasma cells [1]. Rapid improvement is observed in PV patients treated with RTX [1]. Initially, the lymphoma protocol was used. Now, the rheumatoid arthritis protocol is popular. In both protocols, systemic corticosteroids (CS) and immunosuppressive agents (ISA) were used as concomitant therapy [1]. After discontinuation of RTX, some patients required CS and/or ISA to maintain remission. Approximately 95% achieved rapid clinical remission and some achieved remission off therapy. However, the cumulative data from case reports and series indicate that approximately 50% to 80% experience relapses [2]. The immunosuppression from RTX combined with the "concomitant" ISA produces several side effects, notably infection, which may proceed to septicaemia and in some cases death [1].

In 2006, a protocol combining intravenous immunoglobulin (IVIg) and RTX was used to treat severe, recalcitrant PV [3]. Patients had failed to achieve remission despite systemic CS, multiple ISA, and IVIg [3]. This combination protocol resulted in complete remission, off all systemic therapy, sustained for over three years.

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Ten PV patients, in whom systemic CS and ISA were contraindicated, were treated with a combination of RTX and IVIg as first-line therapy. Their clinical outcomes and relevant immunologic studies are described in this report.

2. Material and methods

2.1. Patient demographics

Ten patients (5 males, 5 females) were treated between 2002 and 2007. The mean age at onset was 47.87 years (range 35–64). Data from the patients presented in this study have not been previously published and were not included in earlier studies [3,4].

2.2. Clinical presentation

The clinical features of the patients are presented in Table 1. Eight patients had mucocutaneous and two had only mucosal disease. The pemphigus disease area index (PDAI) described by the International Pemphigus Definition Committee could not be used because it was unavailable when patients were treated [5]. The patients had moderate to severe PV as described earlier [3].

2.3. Inclusion criteria

All 10 patients met the following inclusion criteria: 1) presence of intraepidermal vesicle with acantholysis on routine histology and IgG on the keratinocyte cell surface in the epidermis/epithelium on direct immunofluorescence (DIF); 2) normal lymphocyte panel and serum immunoglobulin levels; 3) normal CT scan of the neck, chest, abdomen, and pelvis; 4) absence of any detectable infection, especially hepatitis; and 5) normal cardiac function.

2.4. Treatment protocol

Topical and systemic therapies prior to initiating this novel protocol were noted.

The treatment protocol consisted of three phases and was modified from a previously published protocol [6].

In phase 1, prior to the initiation of RTX therapy, patients received one cycle of IVIg for the purpose of immunoprophylaxis. The dose of IVIg was 2 g/kg/cycle, divided into two or three equal parts, each given on two or three consecutive days, during a 4.5–6 h slow infusion. Thereafter, they received an infusion of RTX once weekly for 8 consecutive weeks. The dose was 375 mg/m^2. Additional RTX infusions were given once monthly for four consecutive months. Thus 12 infusions of RTX were given in 6 months. The purpose was to eliminate pathogenic autoantibody producing B cells. Since the CD20$^+$ B cells level was zero, IVIg was continued for immunoprophylaxis. Duration of phase 1 was relatively constant in most patients.

In phase 2, once monthly infusions of IVIg (2 g/kg/cycle) was continued until the CD20$^+$ B cell level was 15% or higher for continued immunoprophylaxis. Duration of phase 2 was variable due to differences in duration to re-populate B cells.

Phase 3 was based on a published protocol [6]. It was consistent in all patients who received IVIg at 6, 8, 10, 12, 14, and 16 weeks intervals. This was the end of the protocol. Its intended purpose was to facilitate and promote the restoration of immune regulation.

2.5. End points

End points were based on guidelines established by an international panel of experts [7]. Control of disease activity was defined as the interval between the beginning of the protocol and the cessation of new lesions and healing of previous lesions [7]. Clinical remission on therapy was defined as the time interval from the beginning of the protocol to the absence of active lesions and complete resolution of previous lesions while on therapy [7]. Complete remission was time between initiation of protocol and discontinuation of all systemic therapy and absence of all disease [7]. This protocol was approved by the Institutional Review Board. Each patient signed a consent form.

2.6. Follow-up

At the conclusion of this protocol, patients were followed at 6 month intervals for three years. Thereafter at 9-, 12-, and 18-month intervals until October 2015. Although a specific quality of life assessment analysis was not performed, the patients had a high quality of life based on several factors, notably brief duration of disease, no relapses, and no significant adverse events from the therapy.

2.7. Laboratory studies

Prior to initiation of the protocol, before each infusion and follow-up visit, the following laboratory studies were performed: 1) autoantibody profiles by indirect immunofluorescence (IIF) using monkey oesophagus as substrate; 2) ELISA for anti-Dsg-1 and -3 autoantibodies; and 3) peripheral blood lymphocyte panel (CD19, CD4, CD8, CD3, CD56, CD16).

2.8. Post-therapy tissue immunopathology

Five years after the last infusion of RTX, biopsy for DIF was done from a site adjacent to the original biopsy for diagnosis.

Table 1
Clinical profiles and data on response to treatment with RTX in combination with IVIg in ten patients with pemphigus vulgaris.

Patient number	Sex	Age onset	Clinical profile	Duration of disease prior to RTX (months)	Duration of RTX (months)	Duration of IVIG (months)	Duration of post RTX follow-up (months)	Total duration follow-up (months)
1	F	61	Skin/oral cavity/nasal	1	5.83	32.63	87.4	96.0
2	F	64	Skin/oral cavity/pharynx	6.3	5.5	33.13	89.4	97.1
3	F	40	Skin/oral cavity/nasal	4.9	6.4	38.67	90.4	114.8
4	M	35	Skin/oral cavity/laryngeal	3.2	6.7	17.8	83.2	94.7
5	M	50	Skin/oral cavity/penis	5.3	5.6	24.7	84.7	95.7
6	F	44	Skin/oral cavity/vagina	3.5	5.7	52.57	84.9	112.8
7	M	52	Skin/anal/oral cavity	6.1	6.4	41.1	86.8	119.9
8	M	44	Skin/oral cavity/nasal	1.7	6.3	34.34	84.7	96.9
9	F	49	Oral cavity/vaginal/conjunctiva	3.2	6.3	29.3	84.5	111.0
10	M	47	Oral cavity/nasal/pharyngeal	4.8	6.2	33.17	84.8	101.0
Mean		48.6		4.0	6.09	33.7	86.08	103.99

IVIg — intravenous immunoglobulin; RTX — rituximab.