Rituximab in Pemphigus: Road Covered and Challenges Ahead

Pemphigus is a group of autoimmune blistering disorders, clinically characterized by mucocutaneous blisters and erosions and histopathologically by intraepidermal acantholysis. It is caused due to autoantibodies directed against the cell surface proteins, desmogleins. Pemphigus was traditionally associated with high mortality and morbidity. However, advent of corticosteroids dramatically changed the outlook of this invariably fatal disease and reduced the mortality rate to <10%.[1] Another milestone in the therapeutics of pemphigus in India was the use of dexamethasone cyclophosphamide pulse (DCP) therapy by Pasricha and Ramji in 1984.[2] Since then, DCP and oral corticosteroids have been the backbone of pemphigus treatment in India.[3] This has been reiterated by a number of publications.[4-6] However, long-term corticosteroid intake is associated with various metabolic complications, global immunosuppression, and an antecedent risk of serious infections. Thus, there was a continuous search for a safer, more targeted therapeutic option, especially in patients in whom corticosteroids were contraindicated. Thus came the use of intravenous immunoglobulin (IVIg) and plasmapheresis, which differed from the commonly used corticosteroids by their immunomodulatory action compared to the global immunosuppression achieved by corticosteroids.[7,8]

The next major development in pemphigus treatment was the use of rituximab in 2001 by Heizmann *et al*.[9] This serendipitous discovery of improvement in mucocutaneous lesions of paraneoplastic pemphigus when rituximab was used to treat non-Hodgkin's lymphoma dawned upon a new era of targeted therapy to treat autoimmune blistering diseases. Rituximab, a chimeric monoclonal antibody, selectively acts on the CD20 expressing B cells, which are known to secrete autoantibodies targeting the epidermal desmogleins. In the Indian scenario, rituximab was first used by Kanwar and colleagues in 2010 and the promising findings were first published in 2012.[10] Since then its use has increased exponentially with reports from various parts of the country. In this review, we briefly discuss the road covered, way ahead, and future challenges in the biological treatment of pemphigus.

Rituximab in Pemphigus

Indian scenario

Rituximab is a chimeric monoclonal antibody, which acts against the cell surface CD20 antigen (a calcium channel in cell membrane) expressed on B cells. It acts by causing direct induction of apoptosis, complement-dependent cytotoxicity (CMC), and antibody-dependent cellular cytotoxicity (ADCC).[11] The usage of rituximab has increased many folds over the recent years with availability of rituximab biosimilars, which has drastically cut down the marketing cost of the drug.[12] Though concerns have been raised on the efficacy of these biosimilars *vis-à-vis* the reference molecule,[13] these have now been allayed with biosimilars showing similar efficiency as the reference molecule.[14]

Rituximab has been used in various protocols and in combination with other immunomodulators in treatment of pemphigus. Currently, the two commonly used protocols in India are the lymphoma protocol (LP) and the rheumatoid arthritis (RA) protocol. The various regimes were summarized in a previous review.[15] Kanwar *et al*.[10] treated 10 pemphigus patients by RA protocol [Table 1]. At a mean follow-up of 33.4 weeks, three patients had achieved complete remission off all treatment [CR(off)] and four patients had achieved complete remission on minimal therapy [CR(on)]. One patient died of sepsis. In this study the mean time to disease control (TDC) was 8 weeks. In a retrospective review, Sharma *et al*.[16] reported the treatment outcome of 25 pemphigus patients treated with rituximab mostly by RA protocol [Table 1]. At a mean follow-up of 18 months, CR was noted in 22 patients and PR in 3 patients with a mean TDC of 5 weeks. Relapse was seen in four patients after a mean duration of 11.75 months. Adverse events included disease exacerbation in two patients, acute respiratory distress syndrome and cellulitis in one patient each.

Londhe *et al*.[17] treated 24 pemphigus patients with a modified version of LP [Table 1]. At a mean follow-up of 18 months, all 24 patients had responded to treatment with 9 patients achieving CR(off), 10 achieving CR(on), and 5 patients achieving partial remission (PR). Adverse effects were limited to infusion reactions. In a follow-up publication of this cohort Khopkar and colleagues reported the outcome of 114 pemphigus patients (including the 24 cases reported by the authors in 2014) receiving rituximab.[18] Fourty-nine (43%) cases had achieved CR(off), 32 (28%) patients had achieved CR(on), and 12 patients had achieved PR at the end of 24 months. Relapse was noted in 13 (11.4%) patients. There was no remarkable difference in the clinical outcome between the patients treated with RA protocol (n = 66) and LP (n = 48). In the systematic analysis of published literature by Ahmed and Shetty, the authors found CR in a statistically higher number of patients receiving RA protocol.[19] Also, patients receiving RA protocol were more likely to be off all treatment during post-treatment follow-up.[19]

The common variation in the RA protocol was the high- and low-dose rituximab administration. The

Table 1: Overview of the major Indian studies reporting rituximab use in pemphigus

Author	Number of patients	Study design	Follow-up duration (months)	Rituximab dose	Other therapies	Adverse effect	Clinical outcome*	
							Short term	Long term
Kanwar *et al*.[10]	10 (9 PV + 1 PF)	Open label	6-12	1 g × 2	PRE, DCP, CP, AZA	Infusion reaction (30%); sepsis (20%)	Mean TDC was 8 weeks	At the end of study period 30% had CR (off), 40% had CR (on), and 20% had PR
Sharma *et al*.[16]	25 (21 PV + 4 PF)	Retrospective	12-32	1 g × 2 500 mg × 3-4 (4)	PRE, DCP, CP, MMF, AZA, MTX, DAP	Disease exacerbation (8%); pneumonia (4%); cellulitis (4%)	TDC 1.1 month and time to complete remission 4.36 months	At the end of study period CR (88%), PR (12%), relapse (16%)
Londhe *et al*.[17]	24 (23 PV + 1 PF)	Open label	7-24	375 mg/m^2 BSA × 4	PRE, DCP, CP, MMF, AZA, MTX	Infusion reaction (37.5%); pulmonary embolism (4%); herpes zoster (8%); Tinea corporis (4%); Isospora diarrhea (4%)	At 6 months CR (79%) and PR (21%)	At 24 months CR (79%); PR (21%); relapse (8%)
Khopkar *et al*.[18]	114 (99 PV + 15 PF)	Retrospective	Mean of 29.3 months	375 mg/m^2 BSA × 4 (48) 1 g × 2 (66)	PRE, DCP, CP, MMF, AZA, MTX	Infusion reaction (25%); infections (15%)	At 6 months CR (79%) and PR (21%)	At 6-24 months CR (71%); PR (10.5%); relapse (11.4%)
Vinay *et al*.[23]	10 (7 PV + 3 PF)	Retrospective review of childhood and juvenile pemphigus	8-36	500 mg × 2 *375 mg/m^2 BSA × 2 (2)	PRE, AZA	Infusion reaction (20%); angioedema (20%); URTI (10%)	Not mentioned	At the end of study period 70% had CR, 10% had PR, and 20% had control of disease activity. Two relapses were noted
Bhattacharjee *et al*.[30]	18 (18 PV)	Prospective	6.5	1 g × 2	PRE	Infusion reaction (5.5%); disease flare (47%)	At 14 weeks 59% had achieved cutaneous ABSIS of 0	At 26 weeks 89% had achieved cutaneous ABSIS of 0
Kanwar *et al*.[26]	11 (7 PV + 4 PF)	Randomized control trial	12	1 g × 2	PRE, AZA	Infusion reactions; URTI; diarrhea; striae; acneiform erup- tions	TDC: 7.1 weeks ECP: 9.1 weeks	PR: 14.5 weeks CR: 25.2 weeks relapses 4
	11 (8 PV + 3 PF)		12	500 mg × 2	PRE, AZA, MMF		TDC: 7.4 weeks ECP: 9.8 weeks	PR: 12 weeks CR: 28.1 weeks relapse 7

ABSIS: Autoimmune bullous skin disorder intensity score, AZA: Azathioprine, BSA: Body surface area, CR (off): Complete remission off treatment, CR (on): Complete remission on treatment, CP: Cyclophosphamide, DAP: Dapsone, DCP: Dexamethasone cyclophosphamide pulse therapy, ECP: End of consolidation phase, MTX: Methotrexate, MMF: Mycophenolate mofetil, PR: Partial remission, PRE: Prednisolone, PV: Pemphigus vulgaris, PF: Pemphigus foliaceus, TDC: Time to disease control, URTI: Upper respiratory tract infection. *As per international consensus conference definitions

high-dose regimen involved administration of two doses of 1000 mg of rituximab 2 weeks apart. Whereas, in low-dose regimen, two doses of 500 mg rituximab was administered 2 weeks apart. In a prospective study, Gupta and colleagues treated 50 pemphigus patients with low-dose RA protocol. At 6 months follow-up 20/50 (40%) patients were in CR(off).[20] In a randomized control trial, Kanwar *et al.* compared the clinical and immunological outcome of pemphigus patients treated with high- and low-dose RA protocol.[21] The clinical response as evident by the fall in the disease severity scale was significantly more in the high-dose group. Additionally, the immunological parameters assessed by fall in the anti-desmoglein antibody titer and B cell repopulation was significantly better in patients receiving the high-dose regimen. The meta-analysis of low- and high-dose regimen by Wang and colleagues also reported longer duration of CR with high-dose regimen.[22]

In a retrospective review of patient records, Vinay *et al.*[23] reported the encouraging results of rituximab treatment (two doses of 500 mg 15 days apart) in childhood and juvenile pemphigus patients. CR(off) treatment was achieved in 7/10 patients at a median follow-up period of 16 months. Relapse was seen in six patients by a mean of 13 months, which showed good treatment response to repeat infusions of rituximab and/or conventional immunosuppressants. Oral lesions of pemphigus show treatment refractoriness in comparison to cutaneous lesions.[24] Vinay *et al.*[25] treated three pemphigus patients with refractory oral ulcers using intralesional rituximab (5 mg/cm^2 two injections 15 days apart) with a good response in all. Rituximab has also been used in special situations in treating paraneoplastic pemphigus and in pemphigus patients with hepatitis B and C infection.[26-28]

Various studies have analyzed the immunological changes after rituximab treatment. Post-rituximab treatment, a gradual fall in anti-desmoglein antibody titers is generally observed.[10,17,21] In the study by Kanwar *et al*.[10] the clinical response paralleled the fall in anti-desmoglein 1 antibody indices, whereas there was only a partial reduction in anti-desmoglein 3 titers. The fall in CD19 cell count is dramatic after rituximab infusion and is seen as early as 2 weeks.[21] Even low-dose RA protocol and intralesional rituximab injection successfully reduced CD19 cell count.[21,25] However, CD19 cell repopulation is earlier in patients receiving low-dose rituximab regimens compared to patients receiving high-dose regimen.[21] Since relapses are associated with B cell repopulation, low-dose regimens may have a higher relapse rate compared to high-dose regimens.[29] Bhattacharjee *et al*.[30] studied the effect of rituximab on circulating T regulatory cells in 18 pemphigus patients. No direct relationship was found between the disease severity/clinical response and circulating T regulatory cells. In the seminal study by Colliou *et al*.[31] increased CD19+CD27 − naïve B cells to CD19+CD27+ memory B cells ratio, increased transitional B cells and interleukin-10 – secreting regulatory B cells were associated with complete remission. Delayed appearance of memory B cells and the disappearance of desmoglein-specific circulating immunoglobulin G-positive (IgG+) B-lymphocytes were also associated with long-lasting remission with rituximab.

Global scenario

In a landmark randomized controlled trial, Joly and colleagues compared clinical outcome of patients receiving rituximab and low-dose corticosteroids compared to corticosteroids alone.[32] The study recruited 91 treatment naïve pemphigus patients and randomized them in 1:1 ratio to rituximab or corticosteroid group. At the end of 36 months of follow-up, 41/46 (86%) of patients in rituximab arm were in CR compared to 15/44 (34%) patients in prednisolone only arm. The adverse effects were common and more severe in the prednisolone only group.

The noted deviation by Joly *et al.* was the use of rituximab as a first line adjuvant in treatment naïve patients.[32] Though many authors have previously suggested using rituximab as a first line adjuvant,[30,33,34] most of the current treatment guidelines recommend rituximab as a second or third line drug after failing conventional immunosuppressants.[35] The trial by Joly *et al*.[32] has paved way for considering rituximab treatment earlier in the disease course. Using rituximab early in the disease course has added advantage. Cho *et al*.[36] suggested that relapse after rituximab treatment was associated with prior long-term use of conventional immunosuppressive agents. Also, the probability of achieving CR(off) is more in pemphigus patients receiving rituximab within 6 months of disease onset.[37-39] The United States Food and Drug Administration has now approved rituximab for the treatment of adults with moderate-to-severe pemphigus vulgaris, which makes the drug the first biologic approved for the treatment of pemphigus vulgaris. The most recent guidelines by the international panel of experts recommend rituximab as a first line treatment option for pemphigus.[40]

Questions Unanswered

Though rituximab has now been firmly established as a treatment modality of pemphigus, many questions still remain unanswered. Important among these is the indication to use rituximab. Should rituximab be the first line therapy for all pemphigus patients irrespective of disease severity or disease duration? Should rituximab treatment be guided by immunological parameters like desmoglein indices, CD19, and CD4 cell counts? Is there a sub-set of patients who benefit from starting rituximab early in the disease course? Future studies are required to answer these questions for a patient-tailored treatment approach.

Rituximab is generally used in combination with low-dose corticosteroids. Ahmed and colleagues strongly advocate

using IVIg in combination with rituximab.[41,42] Few authors have used azathioprine, cyclophosphamide, and mycophenolate mofetil as adjuvants in addition to rituximab. However, there is no consensus on use of other immunosuppressants and immunomodulators along with rituximab.[40] Questions regarding optimal dose, frequency, total number of maintenance infusions to use, and treatment schedule for relapses also needs to be answered.

The literature on vaccination for patients receiving rituximab is blurred. Live vaccines such as influenza and varicella-zoster vaccine are contraindicated while on immunosuppression.[43] Whereas killed vaccine, sub-unit vaccine, and other non-live inactivated vaccines can be safely administered. The literature-based immunization recommendations for immunosuppressed autoimmune bullous dermatoses patients recommend vaccination with non-live vaccines of pneumococcal, hepatitis B, and inactivated influenza vaccine (annually).[44] The same can be currently followed for patients receiving rituximab; however, specific data on immune conversion and complications after vaccination are required.

Future Prospects

Rituximab for maintenance therapy

Many long-term case series and a few randomized control trials have now clearly established the efficacy of rituximab to induce remission.[10,32,45] However, these studies and systematic analysis consistently report a relapse rate of 40–60%.[19,22,45] Interestingly, in their randomized control trial, Joly *et al.*[32] administered 500 mg rituximab at 12 and 18 months irrespective of the disease activity. This was based on the author's observation that the desmoglein indices increase 12 months after rituximab infusion following the initial fall in its titers.[32] It is also supplemented by the observation that the CD19 repopulation and relapses are common after 12 months and usually occur at a median of 15 months.[32,45] Therefore, few authors recommend additional rituximab infusions every 6 monthly to maintain clinical remission.[46,47] A previous study by Gregoriou *et al.*[48] found no additional benefit from prophylactic infusions of rituximab. However, many recent studies have reported low or no relapse rate with maintenance rituximab infusions.[32,49] However, there is uncertainty on the optimal dose (500 mg or 1 g) to be used and frequency of administration (every 6 months or 1 year) when used for maintenance therapy. Many immunologic markers can be used to predict disease relapse including desmoglein indices, CD19, and CD4 cell counts. Future studies are needed to assess these markers as criteria to administer or withdraw rituximab maintenance.[29,50]

Ultra low-dose rituximab

Rituximab acts by depletion of CD20 expressing circulating B cells, but has no action on CD20 negative early pre B cells and terminally differentiated plasma cells.[15] The B cell burden in autoimmune blistering diseases is much lower than in lymphoproliferative diseases. Recent studies have found 97% of circulating B cell depletion with rituximab dose as less as 1 mg/m^2 (contrasting to 375 mg/m^2 in lymphoma).[51] We previously reported similar findings with intralesional injection of ultra low-dose rituximab injection (30–40 mg) wherein CD19 B cell suppression was seen within 2 weeks.[22] There has been a suggestion that 100 mg rituximab may be sufficient to induce depletion of B cells for 3 months and, consequently, two doses of 100 mg every 3 months could deplete the B cell population for 6 months.[52] However, well-designed clinical trials are warranted to determine its efficacy in the context of treating autoimmune blistering disorders.

Future strategies beyond rituximab

Use of newer generation anti-CD20 monoclonal antibodies are being explored to treat B cell mediated diseases including pemphigus.[53] Anti-CD20 antibodies are categorized into Type I (including rituximab, ofatumumab, veltuzumab, and ocrelizumab) and Type II (including tositumomab or obinutuzumab), depending on mechanism of action.[54] Type I antibodies cause a clustering of CD20 that enhances the recruitment and activation of complement for a potent CDC response. On the other hand, Type II antibodies exhibit stronger homotypic adhesion and induction of direct cell death but with a minimal CDC response.

The newer generation anti-CD20 monoclonal antibodies have added advantage.[55] Humanized monoclonal antibodies are less immunogenic than mouse-derived proteins. Few of these antibodies can be injected subcutaneously, obviating the need for hospitalization for intravenous infusions. Increased binding to the affinity effector cells leads to increased B cell depletion, which may translate to better/prolonged clinical efficacy. Veltuzumab, a second generation Type 1 anti-CD20 antibody has been reported useful in inducing remission in a treatment resistant case of pemphigus.[56] Phase III studies are currently being conducted for ofatumumab and anti-BAFF antibodies in pemphigus patients.[53] Monoclonal antibodies targeting CD19 and CD22 are being explored in multiple sclerosis and systemic lupus erythematosus, which may in future be evaluated in treating autoimmune blistering diseases. Another interesting strategy is the antigen-specific B cell depletion using chimeric autoantibody receptor (CAAR) T cells.[47,51,55] In this strategy, biochemically engineered T cells specifically recognize and deplete anti-desmoglein 1 and anti-desmoglein 3 secreting B cells.[57] CAAR T cells have the ability to proliferate and expand *in vivo*, which may lead to long-lasting effect.

Conclusion

In the era of evidence-based medicine, it is essential to provide customized treatment options, balancing its

efficacy, tolerance, adverse effect profile, and patients co-morbidity. It is true in the therapeutics of pemphigus too. The established use of rituximab has heralded a new era in this regard and the horizon looks bright with an armory of new monoclonal antibodies. Future studies will pave way in providing the tailor made patient care for this orphan disease.

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Quick Response Code

DOI: 10.4103/idoj.IDOJ_290_18

How to cite this article: Vinay K, Dogra S. Rituximab in pemphigus: Road covered and challenges ahead. Indian Dermatol Online J 2018;9:367-72.

Received: September, 2018. **Accepted:** September, 2018.