■ REVIEW ARTICLES

Adjuvant Therapies of Pemphigus Vulgaris: A Review

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ABSTRACT

Despite the reduction in mortality since the use of corticosteroids, pemphigus vulgaris still carries significant morbidity. This article reviewed recent studies on the use of available adjuvant therapies, including azathioprine, pulse cyclophosphamide, cyclosporine, methotrexate, anti-inflammatory agents, plasmapheresis, mycophenolate mofetil and intravenous immunoglobulins.

Keywords: *Adjuvant therapies, pemphigus vulgaris, review*

INTRODUCTION

Pemphigus vulgaris (PV) is an autoimmune disease characterized by blistering and erosions on skin and mucous membranes due to acantholysis. It is caused by autoantibodies against desmosomal caderins desmoglein 3 (Dsg 3) which are calcium dependent cell adhesion molecules.[1] The measurement of Dsg 3-ELISA had been shown to be a sensitive and specific test for the diagnosis of PV in addition to the traditional indirect immunofluorescence autoantibodies titre.[2] The incidence of the disease in the United States is about 0.42 per 100,000, equally affecting males and females.[3] The exact incidence in Hong Kong is unknown. According to a study in Hong Kong Social Hygiene Service between 1985-1992, it was the second most common chronic bullous dermatosis; second to bullous pemphigoid.[4] There were 38 cases of pemphigus vulgaris, which composed of 16.2% of all chronic bullous dermatoses. The male to female ratio was 1.4:1 and the majority of patients were between 50 to 69 years old.[4]

The use of corticosteroids in the 1950s had reduced mortality from 60% to 90% to about 30%.[1,5] The current mortality was about 6.2% (range 0 to 10%) and did not show further significant reduction.[5] This may in part be related to the side effects of the immunosuppressive treatments used. The disease still carries significant morbidity. The complete remission rate was about 20.5% in the 1950s when only corticosteroids was used and improved only to about 28.9% in the 1990s.[5]

The mainstay of treatment remains to be corticosteroids with or without another adjuvant therapy. The adjuvant therapies include steroid sparing agents (immunosuppressive agents and anti-inflammatory agents) and immunomodulatory procedures. Due to the variations in severity, the rarity of the disease, and the great differences in treatment protocols, large scale randomized control trials are difficult to carry out. Hence comparisons and interpretation of studies results are often difficult. A search in recent literature regarding the use of adjuvant therapies in PV was performed. The use of new treatment modalities including myco-phenolate mofetil and intravenous immunoglobulins will also be discussed.

AZATHIOPRINE

Azathioprine is metabolized to 6-thioguanine, which produces DNA strand breaks and blocks DNA synthesis.[6] It is probably the most commonly used immunosuppressive agent.[7] It appeared to be the case in Hong Kong also.[4] Summarizing seven studies in the 1970s and 1980s, remissions were induced in 28% of patients and mortality rate was 1.9%.[5] Azathioprine also allowed reduction in the dose of the steroid used and hence its side-effects.[7] In a long-term study by Aberer,

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29 patients treated with combined steroid-azathioprine regimen were available for complete follow-up lasting 4 to 16 years.[8] Thirteen (45%) patients were free of disease and had not received treatment for up to 132 months; eleven (38%) of the patients were clinically well but still had low titers of antibodies and required low-dose maintenance therapy. Side effects were rare and mostly related to corticosteroids and there was only one death (pulmonary tuberculosis) in the study. It was concluded that azathioprine-corticosteroid treatment of PV was effective and safe enabling long-term remissions in most patients and possibly to a cure in some.[8]

The side effects of azathioprine include bone marrow suppression, liver dysfunction and increased incidence of malignancy. Azathioprine is metabolized by thiopurine methyltransferase (TPMT). Low enzyme activity leads to accumulation of cytotoxic thiopurine metabolites which increase the risk of toxicity. On the other hand, patients with high activity may require a higher dose. Genetically homozygotes with low activity account for approximately 0.3% and homozygotes with high activity account for approximately 88.6% of population in the West. Screening for TPMT activity would therefore be helpful in guiding therapy.[6]

PULSE CYCLOPHOSPHAMIDE

Though some authors feel that cyclophosphamide is more effective compared to azathioprine, it is more difficult to use and has more toxic effects.[5] Cyclophosphamide is an alkylating agent that disrupts cell growth and mitotic activity by cross-linking DNA. Daily oral cyclophosphamide may lead to haemorrhagic cystitis, myelosuppression, alopecia, azospermia, ovarian failure, teratogenicity and is associated with an increased risk of malignancy in prolonged use. It is important to keep a good hydration state while on cyclophosphamide. Cumulative dose of cyclophosphamide with monthly pulse doses is lower than continuous therapy and this may account for the lower incidence of secondary malignancies.[9] Two-third (six out of nine) of patients showed good response to pulse cyclophosphamide and low dose oral cyclophosphamide in a recent retrospective study.[9] These patients had failed to respond to azathioprine, gold and dapsone previously. They were put on monthly cyclophosphamide 0.5-1 g/m^2 body surface area (starting dose 500-1000 mg and maximum dose 750-2000 mg) for 3 to 24 pulses. However, one patient died of heart failure before effects of treatment could be established and was thought to be partly related to the treatment. Another patient died of myocardial infarction after the last dose while PV was in remission.

CYCLOSPORINE

Cyclosporine inhibits production of interleukin-2 and interferon-gamma by lymphocytes. It is metabolized by hepatic cytochrome P-450 enzyme and its blood level is increased by drugs metabolized by the same enzymatic pathway (for example diltiazem, azole antifungal agents and erythromycin).[6]

Some recent studies on cyclosporine produced conflicting results. In one report, six patients who relapsed on azathioprine were given cyclosporine 1-3 mg/kg to reach a serum level of 100-125 mg/ml.[10] Total treatment period was 13 to 20 months. There was no recurrence during the 3.5 to 5 years follow-up period in all. On the other hand, a randomized trial showed that there was no significant difference in terms of response, time required to control the disease and proportion of flare between two groups of patients taking steroid versus steroid plus cyclosporine.[11] The dose of prednisolone used in this study was 1 mg/kg and increased by 50% every five to ten days based on the persistence of the disease. It was tapered when lesions were 80-90% cleared every two weeks. Dose of cyclosporine was 5 mg/kg. All patient achieved complete or partial remission (average prednisolone dose 2.5 mg/d) in the four to six years follow up. However, one must take into consideration of the high dose of steroid used while interpreting the data. When there were concomitant modalities of treatment, it would be difficult to distinguish between the true effects of the two drugs.

Side effects of cyclosporine include renal function impairment (dose dependent increase in urea and creatinine in the first week), hypertension, hypertrichosis, gingival hypertrophy, tremor, gastrointestinal symptoms, hepatic dysfunction, hyperkalemia and hyperuricaemia.

Topical cyclosporine solution had been used in oral lesions using cotton swab or swished for five minutes. This is not commonly employed as it is less effective and expensive.[5]

METHOTREXATE

The use of low dose methotrexate (10-17.5 mg/week, mean 12.2 mg/week) was studied in nine patients.[12] They were also on prednisolone (3-40 mg/day, mean 20 mg/day) and were unable to taper the dose for an average of 27 months before the study. Six patients were able to stop the systemic steroid within six months without a flare-up. However, all of them flared when methotrexate was stopped after an average of 23 days. The adverse effects reported were nausea in one and mild elevation of transaminase levels in two patients. The authors concluded that methotrexate was a useful adjuvant as it enabled steroid to be discontinued in about two third of the patients, and disease flared shortly after it was stopped. They compared the result with 40 chronic PV patients on conventional therapy of steroid with or without azathioprine or cyclophosphamide in which steroid could only be discontinued in 5 to 7% within six months period. However, the matching of the two groups of patients was not stated. The use of methotrexate was again often limited by its toxicity. Well known side effects of methotrexate include liver toxicity, myelosuppression, pulmonary toxicity, stomatitis and gastrointestinal upset.

ANTI-INFLAMMATORY AGENTS

Dapsone was suggested to be an effective adjuvant to corticosteroids in PV.[7] Dapsone exhibits antibiotic effect, interferes with neutrophil chemotactic migration, reduces the release of prostaglandins and leukotrienes, inhibits neutrophil adherence to basement membranes, inhibits the generation of toxic radicals and protect cells from neutrophil- and eosinophil-mediated injuries. It does not stop the initial pathogenesis process but exhibits anti-inflammatory effects.[13] Some of the more common side effects of dapsone includes haemolysis, methaemoglobinaemia, neuropathy and allergic dermatitis.

Gold was first described in the treatment of PV since 1973. Intramuscular gold injections were given to 26 patients over a 10-year period as steroid-sparing agent.[14] Gold 50 mg was given weekly after test dose, and was reduced to monthly when prednisolone was taken off. Sixteen (62%) patients responded without significant toxic effect. The rest did not respond or had to discontinue treatment due to toxicity. Its use appeared to be lessened recently due to concerns of its efficacy and safety. Side effects of gold are dermatitis, pigmentation, diarrhoea, oral ulcers, proteinuria, blood disorders, alopecia, peripheral neuritis, pulmonary fibrosis, cholestatic jaundice and rarely colitis.

Although there was no controlled study in the use of tetracycline in PV, further study is worthwhile due to its relatively safety. In an uncontrolled trial, 11 patients with immune blistering disease were given tetracycline 2 g/day and nicotinamide 1.5 g/day.[15] There were six PV patients and among them, three achieved complete remission and two partial remissions. The side effects reported were mild gastrointestinal upset in one and allergy to tetracycline in another. It was important to note that patients with less severe PV were studied: three patients were not on systemic steroids, two of which were put on topical steroid only.

PLASMAPHERESIS

As the disease activity of PV generally correlates with the level of circulating autoantibodies, their removal seems a reasonable therapeutic approach. However, the use of plasmapheresis fails to control the rebound synthesis of antibodies due to a negative feedback mechanism. Pathogenic B cells are triggered with sudden drop in the circulating level of autoantibodies and secrete even more antibodies. The level of circulating antibodies was shown to increase as early as three hours after plasmapheresis. Therefore immunosuppression is administered immediately after plasmapheresis to help achieve complete remission.[16,17]

Turner reviewed seven patients who were treated with plasmapheresis followed by pulse cyclophosphamide (five patients) or pulse methylprednisolone with azathioprine (two patients).[16] The circulating intercellular antibodies titres decreased on average by threefold 60 days after plasmapheresis. They were put on immunosuppressants for two months and corticosteroids were tapered on average three months after plasmapheresis. Four patients remained well and among them, two had undetectable titres. Two patients had partial remission and one had only temporary effect. There was no data comparing the choice of immunosuppressive agents but the results suggested that the timing and the individual's responsiveness to the agent was the key to reduce antibodies level.

MYCOPHENOLATE MOFETIL

Mycophenolate mofetil (MMF) is a relatively new immunosuppressive agent used in bullous dermatoses. It is rapidly absorbed in its oral form and metabolized into the active metabolite mycophenolic acid (MPA). It inhibits the de novo pathway of purine synthesis in T and B-lymphocytes selectively and reversibly. It may also modulate the recruitment of leukocytes into sites of inflammation.

There were a number of recent studies showing favorable results in its use in PV. In one with 12 patients who relapsed on steroid and azathioprine, MMF of 2 g/day was kept for 12 months.[3] Prednisolone 2 mg/kg was initiated and the dose was halved when new blistered ceased then tapered till below 5 mg/day. Eleven out of 12 patients were free of disease clinically within two months with no relapse during the follow up period of 12 months. PV antibodies were undetectable by indirect immunofluorescence by two months. One patient relapsed when the dose of steroid was reduced. Main side effects included mild lymphopenia of 250-300/microlitres (9/11 patients), moderate gastrointestinal symptoms (5/11 patients), and transient rises in transaminase (3/11 patients).[3] In another study, four patients who either failed the combination of steroid and azathioprine, or had experienced significant side effects were put on MMF 1000-1250 mg bd. All showed good response and were able to tapere the dose of prednisolone.[18] Another report on MMF and autoimmune blistering disease showed that it may be useful as a monotherapy.[19]

The adverse effects of MMF are mainly gastrointestinal (diarrhoea, dyspepsia, abdominal pain, nausea), myelosuppressive and those due to immunosuppression. It has fewer toxic effects on liver compared to azathioprine. However, it is more costly than the conventional immunosuppressive agents. Its use in the future is promising especially for the patient who cannot tolerate azathioprine or cyclophosphamide.

INTRAVENOUS IMMUNOGLOBULIN

Intravenous immunoglobulin (IVIG) is being increasingly used in immune-mediated diseases. Postulated mechanisms include: functional blockade of Fc receptor, elimination of immune complexes, anti-idiotypic suppression of autoantibodies, inhibition of complement-mediated damage, modulatory effects on cytokines release and cellular response, and blockade of cell surface death receptor Fas and its ligand.[20] IVIG is usually well tolerated. Side effects include vasomotor symptoms such as headache, myalgia, flushing, nausea, tachycardia, usually in the first hour after infusion. Anaphylactic reactions may occur in patients with IgA deficiency. Uncommonly, acute renal failure and haemolysis had been reported.[20]

IVIG has been used in autoimmune blistering disorder in recent years. Leela et al. reviewed its use retrospectively based on nine reports during 1985-1999 on 21 patients.[21] The patients ranged from 35 to 73 years old and all had severe disease ranged from one month to 12 years. All patients had received systemic steroids with a mean dose of oral prednisolone of 120 mg/d and four also had intravenous pulse therapy. Azathioprine was used in 12, cyclosporine in four, dapsone in three, methotrexate in two, intravenous cyclophosphamide in four and oral dapsone in five. Despite the above treatments, significant remission was not achieved or relapses occurred on lowering steroid dosage. Various doses and regimes of IVIG were tried, eight patients had one cycle only, six had regular monthly cycle (ranged 3 to 16 months), two had bi-weekly cycle, and five had IVIG during disease flare. All but three patients were kept on steroid (mean prednisolone 68 mg/d) with or without other conventional adjuvant agents. IVIG was demonstrated to be beneficial in 17 out of 21 patients with rapid improvement (before end of second cycle) and steroid sparing effect (mean dose of prednisolone reduced to 8 mg/d). However, five out of 17 failed to have sustained improvement. Follow up period was 2.5 to 16 months. No significant side effects were observed. Mild headache was the most common problem reported.

The observations obtained from these results were: firstly, IVIG had a rapid onset of action. Secondly, remission lasted longest in patients receiving multiple regular monthly treatments (at least 3 cycles). In those cases where IVIG was clinically ineffective, single infusion of IVIG appeared to be the primary reason. Thirdly, a minimum dose of 2 g/kg per cycle (usually three to five days) was recommended. Fourthly, IVIG appeared to be most effective when used in conjunction with other drugs. It also showed a steroid sparing effect in almost all the patients and was helpful in inducing a rapid remission. Lastly, it was safe and well tolerated.[21]

There is no local data on the use of IVIG in bullous dermatosis. The following is the report of one patient treated in the Prince of Wales Hospital. A female patient aged 66 was diagnosed to have PV in 1997. She had severe (predominantly oral) disease resistant to treatment. She had been put on a combination of high dose oral prednisolone and azathioprine initially and required repeated pulse methylprednisolone to control the disease. Topical cyclosporine mouthwash gave limited benefit. Eventually she gained partial remission after one year and remained stable for another two years on maintenance low dose prednisolone and azathioprine. She suffered from multiple side effects of chronic steroid including cataract, proximal myopathy and osteoporotic collapse of spine. She had a major flare in early 2001 with marked oral erosions and antibodies titre was raised to 320. The dose of prednisolone was increased from 10 mg/d to 40 mg/d and azathioprine from 100 mg/d to 150 mg/d. Pulse methylprednisolone was repeated twice. Antibodies titre dropped to 80 temporarily but returned to 320 shortly afterwards. There was no significant response clinically despite increasing prednisolone to 60 mg/d. Oral methotrexate was added later for four weeks without satisfactory response. Cyclophosphamide was not attempted in view of her past history of interstitial cystitis. She was put on IVIG at 21 g/day (body weight 50 kg) for three-days monthly cycle. After the first two cycles, there was significant improvement. The oral lesion improved clinically and the antibodies titres reduced from 320 to 20. However, the condition became static after the third cycle and it was decided not to continue further IVIG. There was no side effect reported. There were mild residual oral lesions and she was maintained on prednisolone 40 mg/d immediately after the IVIG with the same dose of azathioprine. Her condition had remained stable on the last follow up, almost six months after the last dose of IVIG. The dose of prednisolone was tapered to 20 mg/d.

There are important considerations for the use of IVIG. The drug is costly and often requires hospitalization for intravenous administration. Intragam 6% 50 ml costs approximately HK$500 in a public hospital. For example, 40 mg/kg/day infusion for one three-days cycle in a 50 kg patient costs approximately $10500 in drug alone. There is no randomized control trial and the optimal dosage and regime is yet to be determined. Long-term follow up data is important in defining its benefits. Local data and experience is important. However, it provides a promising and safe adjuvant therapy for the recalcitrant cases of pemphigus vulgaris.

CONCLUSION

The use of adjuvant agents in treatment of PV is often limited by its toxicity. The choice of the adjuvant therapies needs to be individualized. The past medical history, severity and course of the disease, possible side effects of the therapy and availability of resources are all important considerations. The results of the various studies are summarized in Table 1. With the development of the new agents, the morbidity of the disease can hopefully be reduced. More local experience on the use of MMF or IVIG will be helpful in the management of severe recalcitrant cases.

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Table 1. Table summarizing various studies discussed

Therapy	Study	Year	Patient No.	Remission (%)	Remarks
Cyclophosphamide	Fleischli[9]	1999	9	6 (67%)	Mortality: 1 CHF 1 AMI
Cyclosporine	Mobini[10]	1997	6	6 (100%)	
	Ioannides[11]	2000	29		Randomized. No difference between steroid alone and combination.
Methotrexate	Smith[12]	1999	9	6 (67%)	All flare when MTX stopped
Gold	Pandya[14]	1998	26	16 (62%)	Only 7 patients able to stop steroid
Tetracycline/nicotinamide	Chaffins[15]	1993	6	3 (50%)	2 patients who responded on topical steroid only
Plasmapheresis	Turner[16]	2000	7	4 (57%)	5 on pulse CP, 2 on pulse steroid + Aza
MMF	Enk[3]	1999	12	11 (92%)	
	Grundmann-Kollmann[19]	1999	2	2 (100%)	Monotherapy in one
	Nousari[18]	1999	4	4 (100%)	
IVIG	Leela[21]	2000	21	17 (81%)	5 no sustained effect

Note :

Aza : azathioprine

Cys A : cyclosporine

CP : cyclophosphamide

MTX : methotrexate

MMF : mycophenolate mofetil

IVIG : intravenous immunoglobulins

CHF : congestive heart failure

AMI : acute myocardial infarction

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