

Combination of Intravenous Methylprednisolone and Cyclophosphamide Pulse Therapy Weekly in Severe Autoimmune Bullous Disease: A Preliminary Report

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Abstract: Pemphigus vulgaris (PV), pemphigus foliaceus (PF), and bullous pemphigoid (BP) are amongst autoimmune bullous skin diseases that are characterized by bullae formation at different levels of the skin. The mainstay treatment is still by systemic corticosteroids, but the outcome is not satisfying with many side effects and frequent relapse. One of the drugs that can be used as steroid-sparing agent is cyclophosphamide. In this report, we evaluate the therapy outcome of intravenous methylprednisolone and cyclophosphamide pulsed therapy (MCP) weekly in 6 patients with severe PV, PF, and BP who have completed six MCP. The severity of the disease was measured using Pemphigus Disease Area Index (PDAI) for pemphigus and Bullous Pemphigoid Disease Area Index (PBDAI) for bullous pemphigoid. The aim of this report is to evaluate the therapy response and the side effects of this regimen therapy. After being given six MCP, four patients showed excellent response therapy, one patient showed a good response therapy, while one patient showed a poor response therapy. MCP might be an effective treatment for severe pemphigus and BP but the side effects should be closely monitored. Further long follow up is needed to see the possibilities of relapse and the safety of this regimen therapy to be used in larger sample population.

1 INTRODUCTION

Pemphigus is a rare autoimmune bullous skin disease involving the skin and mucosa that is characterized with intraepidermal bullae formation. Pemphigus vulgaris (PV) is the most frequent type of pemphigus, accounting for about 70% of cases, while pemphigus foliaceus accounts for about 20%-30% of cases (Joly, 2011). Bullous pemphigoid is an autoimmune subepidermal blistering disease with incidence is estimated to be between 6 and 20 new cases per million people (Bernard, 2017). There were 27 cases of pemphigus vulgaris, 8 cases of pemphigus foliaceus, and 9 cases of bullous pemphigoid hospitalized in Dr. Sardjito General Hospital from January 2015 to December 2017.

The mainstay therapy of PV, PF, and BP have been systemic corticosteroids, which has reduced the mortality rate from 75% to less than 10% since their introduction in the 1950s. However, because of the chronicity of the disease, prolonged therapy is necessary, leading to the development of a wide

spectrum of corticosteroid related side effects. Thus, mortality today are caused by treatment complication of corticosteroids (Atzmony et al, 2015). Because of the side effects associated with long-term systemic corticosteroids, a lot of recent research has been directed at finding the optimal steroid-sparing agent (Daniel, 2014).

One of the drugs that can be used as a steroid-sparing agent is cyclophosphamide. There was an evidence of a steroid-sparing benefit for cyclophosphamide compared with glucocorticoid alone (Atzmony et al, 2015). In 1984, Parischa and Ramji introduced intravenous corticosteroid and cyclophosphamide pulse therapy monthly with 50 mg cyclophosphamide orally given daily that is known to have less side effects compared to corticosteroid group alone and have longer remission period (Gupta, 2015),(Saha, 2010). Because cyclophosphamide oral regimen was unavailable widely in Indonesia, we modified this regimen into intravenous methylprednisolone and cyclophosphamide pulse therapy weekly with oral corticosteroid between the

pulse given twice per week. In this report, we evaluate the therapy outcome of MCP weekly in 6 patients with severe PV, PF, and BP who have completed six pulsed therapy. The severity of the disease was measured using Pemphigus Disease Area Index (PDAI) for pemphigus and Bullous Pemphigoid Disease Area Index (PBDAI) for bullous pemphigoid (Rahbar, 2014), (Daniel, 2012), (Fuertes, 2014). The aim of this report is to evaluate the therapy response and the side effects of this regimen therapy.

2 CASE

Six patients were included in this report. It consisted of one case of PF, one case of BP, and four cases of PV. All patients had already undergone various therapies previously. The baseline characteristics of each patient are described in table 1.

All patients had undergone biopsy and direct immunofluorescent before starting MCP to ensure the diagnosis of PV, PF, and BP. An informed consent about the benefit, risk, and possible complication that might happen was explained to the patient and their family, and they were asked to sign an informed consent form. Before starting MCP, evaluation of electrocardiogram and laboratory test that consisted of complete blood test, electrolytes, blood glucose, albumin, renal and liver function test were done for these patients. Contraindications include hypersensitivity to this regimen, pregnancy and lactation, altered renal and hepar function, leucopenia

(leucocyte < 3000/ \square L), thrombocytopenia (thrombocyte < 100000/ \square L), and urine erythrocyte sediment > 10/ \square L. Methylprednisolone 250 mg intravenous injection was given in the morning. Premedication of cyclophosphamide that consisted of 10 mg diphenhydramine intravenous injection, 8 mg ondansetron intravenous injection, and 100 mg of 2-mercaptoethanesulfonate sodium (mesna) in 50 ml NaCl 0.9% were given within 15 minutes. Then 500 mg of cyclophosphamide in 250 ml NaCl 0.9% was given within 1-2 hours. After infusion of cyclophosphamide was finished, 100 mg mesna in 50 ml NaCl 0.9% was given three times with interval of three hours. Vital signs were assessed during and after cyclophosphamide infusion. Evaluation of electrocardiogram and urinalysis were done after the MCP. This MCP regimen was repeated once weekly for six consecutive weeks with methylprednisolone varying from 32 mg to 64 mg given orally, twice a week.

The severity of the disease was measured at every visit using PDAI for patients with PV/PF, and BPDAI for patient with BP. The score can be seen in table 2 below.

Side effects were found in 2 patients. One patient developed furuncles after the fourth injection of MCP and was later healed with tetracycline 500 mg, four times orally. One patient had nausea and vomiting after three injection of MCP. Because of the severe nausea and vomiting, one patient had the MCP given every two weeks to minimize the side effects. Neither of these patients developed severe hematologic deprivation nor renal and liver failure.

Table 1. Baseline Characteristics of Patients Before Treatment with MCP.

Patient	Age (years old)	Sex	Ethnic Background	BMI (Kg/m ²)	Diagnosis	Duration of Disease	Previous Treatment	Comorbidities
1	55	M	Java-nese	22.0	PF	1 year	IVMP, MTX, MP	HT
2	40	F	Java-nese	31.2	BP	6 months	IVMP	DM
3	72	F	Java-nese	27.3	Eritroder-ma e.c PV	1 year	IVMP, AZA	HT
4	62	F	Java-nese	25.3	PV	11 year	IVMP, MTX, MP	-
5	20	F	Resi-dent from Papua	22.2	PV	1 year	IVMP, IVIG, MP, Dapson, MMF	Anemia
6	52	F	Java-nese	20.2	PV	3 months	IVMP	HT, DM

Aza, azathioprine; BP, bullous pemphigoid; DM, Diabetes mellitus; HT, hypertension; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; MCP, intravenous methylprednisolone and cyclophosphamide pulse therapy; MMF, mycophenolate mofetil; MP, methylprednisolone oral; MTX, methotrexate; PF, pemphigus foliaceus; PV, pemphigus vulgaris

Table 2. PDAI and BPDAI Score

Patient	Diagnosis	PDAI/BPDAI Score						
		Before MCP	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
1	PF	86	84	64	39	20	10	7
2	BP	255	240	213	109	40	13	6
3	PV	140	126	65	29	11	7	5
4	PV	98	89	79	50	27	14	11
5	PV	107	83	48	29	11	6	3
6	PV	50	47	32	32	51	47	48

PDAI, Pemphigus Disease Area Index; BPDAI, Bullous Pemphigoid Area Index; MCP, intravenous methylprednisolone and cyclophosphamide pulse therapy



Figure 1. A 40 year old bullous pemphigoid patient. A-C: Pictures before starting MCP therapy; D-F: Pictures after given six MCP therapy.

3 DISCUSSION

Cyclophosphamide is a nitrogen mustard compound. After hepatic metabolism, it acts as an actively alkylating agent, thus causing cross-linking of DNA. While the half-life of the unmetabolized substances is only short (4-6.5 hours), its metabolites have a longer half-life. Cyclophosphamide

suppresses B and T lymphocyte responses. The lymphocyte nadir (maximum reduction) after pulse therapy is reached after 8-15 days. A return to previous levels should be reached after 28 days. The active metabolites are eliminated via the kidneys. They are bladder toxic and may cause hemorrhagic cystitis if hydration is insufficient. A fluid intake > 1.5 liters should be observed. The simultaneous

administration of 2-mercaptoethansulfonat-natrium (mesna) dose adapted is definitely to be considered for high-dose and pulse therapy. Evaluation of complete blood count, renal and liver function test, electrolytes, as well as urinalysis should be performed to closely monitor the side effects that might happened (Eming, 2015), (Shimizu, 2014).

The side effects that were happened in this report are furuncles in one patient after the fourth MCP that was healed after administration of systemic antibiotics, and nausea/vomiting in one patient after the third MCP. These side effects are common as reported before in the previous study. Patients with MCP therapy are more susceptible to infections, especially when the skin and/or mucosa are eroded. Nausea and vomiting are the most common gastrointestinal side effects that occurred in MCP patients (Gupta, 2015), (Saha, 2010). Any other side effects like hematological abnormalities (thrombocytopenia, leucopenia), electrolyte imbalance, and signs of bladder toxicities were not found in these patients receiving MCP.

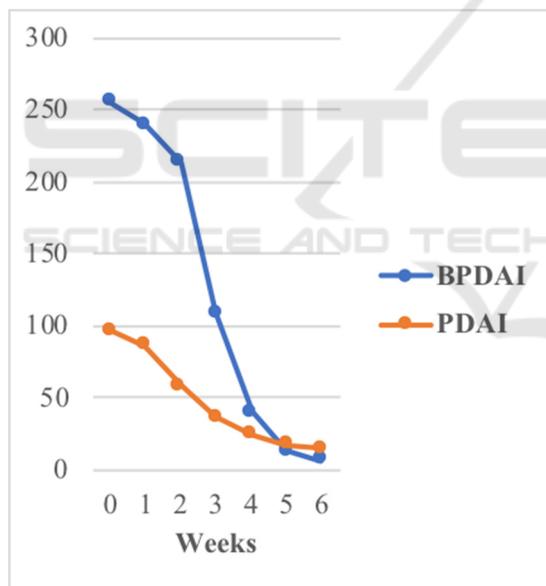


Figure 2. The Average of PDAI and BPDAI Score.

We used PDAI and BPDAI score as the disease severity measurement of this report because it had the highest validity (Rahbar, 2014), (Fuertes, 2014). The PDAI score can be classified as mild (score 0-8), moderate (score 9-24), and severe (score > 25) (Shimizu, 2014). At the beginning of this study all patients had severe disease. After being given six MCP, four patients showed excellent response therapy with PDAI/BPDAI score < 8, one patient showed a good response with PDAI score classified

as moderate, while one patient showed a poor response therapy. The patient with poor response to the therapy might be caused by uncontrolled diabetes mellitus. Although the patient had already been given subcutaneous insulin daily, the glycemic control was still poor because of unhealthy diet of this patient.

4 CONCLUSIONS

After being given six MCP, four patients showed excellent response therapy, one patient showed a good response therapy, while one patient showed a poor response therapy. MCP might be an effective treatment for severe pemphigus and BP but the side effects should be closely monitored. Further long follow up is needed to see the possibilities of relapse and the safety of this regimen therapy to be used in larger sample population.

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