Journal of the Turkish Academy of Dermatology
eISSN 1307-394X

Review DOI: 10.6003/jtad.19132r2

The Use of Adjuvant Drugs in Pemphigus Treatment: Azathioprine and Mycophenolate

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Published:
J Turk Acad Dermatol 2019; **13 (2)**: 19132r2.
This article is available from: http://www.jtad.org/2019/2/jtad19132r2.pdf
Keywords: Adjuvant, Azathioprine, Mycophenolate, Pemphigus, Steroid

Abstract

Background: Pemphigus group diseases have high mortality and morbidity. The mainstay of pemphigus treatment is systemic high dose corticosteroids. However, the long-term use of high dose corticosteroids is impossible due to their side effects. Adjuvant drugs are added either at the time of diagnosis of the disease together with systemic corticosteroids or during dose tapering of corticosteroids or at disease flare-ups. The most commonly used adjuvant drugs are Azatioprine and Mycophenolate. Although both of these drugs decrease the yearly cumulative corticosteroid dose of a pemphigus patient, the corticosteroid sparing effect of Azathioprine is stronger. Both of these drugs are immunosupressants and have several side effects; Mycophenolate's side effects are more tolerable compared to Azathioprine. Dapsone, methothrexate, cyclosporine, tetracycline derivatives and niacin are other adjuvant drugs that are used less commonly.

Introduction

Pemphigus group diseases have high morbidity and mortality. Therefore, all patients who are diagnosed with pemphigus should receive treatment even if the disease is mild. The main aim of treatment is to rapidly control the disease course. The first line of treatment is 1-1.5 mg/kg/day systemic prednisone or prednisolone [1]. Clinical response to treatment is usually observed within two weeks [2] In order to decrease the daily dose of systemic steroids, adjuvant drugs are added to the treatment regime. These agents are Rituximab, Azathioprine, Mycophenolate and Cyclophosphamide. An alternate first line treatment is the combination of systemic steroids with Rituximab. Cyclophosphamide is reserved for severe and treatment resistant cases [3].

There are two accepted methods about the addition of Azathioprine and Mycophenolate to the systemic corticosteroid treatment. In the first accepted method the adjuvant agents and systemic corticosteroid treatments are initiated simultaneously or adjuvant agents are added within a few days. In the second accepted method the adjuvant agents are added only if there is disease flare-ups during corticosteroid dose tapering or if the patient is resistant to corticosteroid mono-therapy [4, 5].

The disease is under control if no new lesions have formed in the past few weeks, Nikolsky sign is negative and all the pre-existing lesi-

ons have healed [**4**]. When the disease is under control, corticosteroid dosage is diminished initially. The dosage of adjuvant agen ts are reduced at least eight weeks after corticosteroid treatment is stopped. Azathioprine dose is reduced 50 mg/day for eight we eks. Mycophenolate Mofetil is reduced 500 mg every eight weeks and Mycophenolate Sodium is reduced 360 mg every eight weeks until the drugs are stopped [**2, 3**].

Azathioprine

Azathioprine is marketed in Turkey as Imuran tablet: 50 mg. It is the most commonly used non-steroid immunomodulatory agent in pemphigus treatment. The yearly cumulative steroid dosage of the patients receiving corticosteroids and Azathioprine is lower compared to the patients receiving corticosteroids alone. However, the disease activity is similar in both groups [**6**]. In two meta-analysis studies comparing Azathioprine and Mycophenolate, the steroid sparing effect of Azathioprine was found to be greater than the Mycophenolate Mofetil [**7, 8**].

Azathioprine is the imidazole derivate of mercaptopurine. It is integrated into the replicating DNA, stops the DNA replication and purine base synthesis. 6-Thioguanine is the metabolite of Azathioprine that is responsible for the immunosuppressive and toxic effects. Thiopurinemethyltransferase (TPMT) is the enzyme that degrades Azathioprine into its inactive metabolites. Dose adjustments of Azathioprine are done according to the TPMT levels. The risk of myelosupression is increased if TPMT levels are moderate. Severe or even lethal myelotoxic side effects can be seen if TPMT activity is low or if it is inactive [**9, 10**].

In adult pemphigus patients with high levels of TPMT, Azathioprine treatment is started at a dose of 1 mg/kg/day. The dosage is calculated according to the ideal age and height adjusted weight of the patient. Given that no side effects occur, a maintenance dose of 2.5 mg/kg/day is reached with 0.5 mg/kg/day increments within two to three weeks. In patients with moderate or low TPMT levels, the maintenance dose of the drug is adjusted according to the enzyme level within the range of 0.5-1.5 mg/kg/day. Patients with no TPMT activity should not receive Azathioprine treatment [**9**].

In renal failure patients, the dose is adjusted according to the creatinine clearance. The patient receives normal Azathioprine dose if creatinine clearance is above 50 ml/min, 75% of the normal dose if the creatinine clearance is between 10-50 ml/min and 50% of the normal dose if the creatinine clearance is below 10 ml/min [8]. Dose adjustment is not required in hepatic failure. If leukopenia or infections occur during the follow-ups, either the dose is decreased or the treatment is stopped temporarily. The treatment should be stopped permanently if hepatic sinus occlusion syndrome (veno-oclusive disease) occurs [**10**].

Azathioprine can be administered orally or as intravascular infusion. It is recommended to be taken as a single dose; however, given the gastrointestinal side effects, the patients may receive the drug after meals in divided doses. Intravascular injections should be given in 30-60 minutes [**9**].

Due to the high risk of myelosuppresion, the patients receiving Azathioprine should be monitored closely. Complete blood count, liver and renal function tests should be performed every week in the first month, every two weeks in the second and third months and every two to three months thereafter. Furthermore, an increased incidence of skin cancer has been reported in renal transplant patients. Therefore, patients receiving Azathioprine should be advised to protect themselves from the sun as well [**2**].

The side effects of the drug vary according to the dosage, time and the concurrent use of other drugs. The most common side effects are fatigue, nausea, vomiting, diarrhea, leukopenia, thrombocytopenia, hematologic malignancies, hepatotoxicity, increase of ALP, hyperbilirubinemia, infections, myalgia and fever [9]. Lymphoma has been reported in inflammatory bowel disease patients receiving Azathioprine. Less common side effects are abdominal pain, AML, alopecia, anemia, arthralgia, interstitial pneumonia, sweet syndro me, hemorrhage, venooclusive disease, hepatosplenic T cell lymphoma [**11**], hypersensitivity, hypotension, steatorrhea and rash [**9**].

Azathioprine is contraindicated in pregnancy and hypersensitivity. The risk of malignancy is increased in patients with a history of Cyclophosphamide, Chlorambucil and Melphalane use. Severe myelosuppresion can be observed if Azathioprine is used with Mercaptopurine concurrently. Blood levels of Mercaptopurine also increases in patients receivi ng Olsalazin (a TPMT inhibitor) and Allopurinol (a xanthine oxidase inhibitor). The risk of myelosuppresion increases in these cases as well and the Azathioprine dose should be reduced. The immune response to vaccinations also decreases during Azathioprine use [**11**].

Several drug interactions of Azathioprine exist. 5-ASA derivatives decrease the metabolism of Azathioprine. ACE inhibitors increase the myelosuppressive effects. The risk of non-Hodgkin lymphoma increases in patients receiving anti TNF drugs. Ribavirin increases the active metabolite of Azathioprine. Trimethoprime- Sulfametaxazole increases the risk of myelosuppresion. Azathioprine increases the immunosuppressive effects of Tofacitinib, whereas it decreases the anticoa gulant effects of Warfarin [**10**].

Azathiopurine use during pregnancy is Category D. The drug diffuses through the placenta and fetal congenital anomalies, imm unosuppression, leukopenia, pancytopenia and intrauterine growth retardation may occur. Female patients receiving Azathioprine should not conceive. However, the partners of male patients receiving Azathioprine may conceive. Azathioprine is secreted into to the human milk as 6-mercaptopurine and reaches its peak level four hours after drug ingestion. Thus, Azathioprine use is not recommended during nursing [**12**].

Mycophenolate

SThere are two forms of Mycophenolate. Mycophenolate Mofetil: Cellcept 250 mg capsule and 500 mg tablet; Mycophenolate Sodium: Myfortic 180 mg and 360 mg tablet. The main advantage of Mycophenolate treatment compared to Azathioprine treatment is its better side effect profile. Similar to Azathioprine, Mycophenolate also decreases the cumulative steroid dose received by the patient. Mycophenolate was found to be less effective in a study comparing the steroid sparing effects of Azathiopurine and Mycophenolate [**7, 8**]. Mycophenolate use is correlated with longer remission periods [**13**].

Mycophenolate is an inosine monophosphate dehydrogenase inhibitor. It prevents the proliferation of T and B-lymphocytes by terminating the de novo guanosine nucleotide synthesis (cytostatic effect) [**14**].

The dosing is as follows when added to systemic corticosteroids as an adjuvant: Mycophenolate Mofetil 2g/day (2x1gr) and Mycoph enolate Sodium 1440 mg/day (2x720 mg). 250 mg of Mycophenolate Mofetil is equal to 180 mg of Mycophenolate Sodium. However, the two should not be used interchangeably because their oral absorptions differ. The drug can be received before or after meals; bioavailability does not change with foods [**14, 15**]. If a dose is missed, it should be received as soon as it is recognized. However, two doses should not be received simultaneously. An intravascular formulation of the drug also exists; it should be given in at least two hours and bolus injections should be avoided [**16**].

The patients receiving Mycophenolate should be monitored closely as well. Given the risk of pancytopenia, a complete blood count should be performed before starting the drug, every two weeks in the first three months, every month between the third month and one year; and every two to three months thereafter. Liver and renal function tests should be performed before treatment and every month during the treatment. Monitoring intervals should be diminished in patients with liver failure because hyperbilirubinemia and hypoalbuminemia increases the concentration of Mycophenolic acid. The risk of infection, pulmonary edema and gastrointestinal hemorrhage is increased in the elderly. In case of neutropenia, the treatment should either be stopped temporarily of the dose should be decreased [**17**].

The side effects of Mycophenolate are hypotension, hypertension, peripheral edema, chest pain, tachypnea, headache, insomnia, vertigo, anxiety, paresthesia, hyperglycemia, electrolyte imbalances, increase in LDH, urinary tract infections, abdominal pain, nausea, vomiting, diarrhea, constipation, decre ase in appetite, leukopenia, leukocytosis, hyp ochromic anemia, thrombocytopenia, increase in liver function tests, ascites, back pain, fatigue, tremor, dyspnea, upper respi-

ratory tract infections, pleural effusion, cough, sinusitis, increase in renal function tests, sepsis, reactivation of HSV infections and candida infection. Enteric-coated Mycop henolate Sodium is better tolerated in patients with gastrointestinal side effects. Certain infections are reported to be reactivated with Mycophenolate use; these are JC virus progressive multifocal leukoencephalopathy, CMV infections, hepatitis B infections, hepatitis C infections and polyoma virus related nephropathy. In these cases the dose of the drug should be decreased [**15**].

Mycophenolate use is contraindicated if a hypersensitivity reaction against any of its ingredients occurs. In Kelley Seegmiller and Lesch Nyhan syndromes, hypoxhantine pho sphoribosyl transferase is deficient and Mycophenolate use is contraindicated. Myc ophenolate does not diffuse to human milk; still it is contraindicated due to the potential side effects. Live attenuated vaccinations should not be administered during Mycophenolate use. There is dose and time dependent increased risk of lymphoma and skin cancer with Mycophenolate use [**17**].

Mycophenolate use is contraindicated in pregnant patients. Beta-HCG levels should be tested before and eight to ten weeks after the drug use is initiated. Effective contraception should be performed until six weeks after the drugs use is terminated. Mycophenolate related congenital malformations occur as well. In Mycophenolate embryopathy: cleft lip and palate, external ear and ocular malformations may occur. Furthermore, Mycophenolate is related with first trimester pregnancy loss [**18**].

Mycophenolate has several drug interactions. Acyclovir, Valacyclovir, Gancyclovir and Valgancyclovir increase the plasma concentration of Mycophenolate. Anta-acids decrease Mycophenolate absorption; therefore, they should be taken at least two hours apart with Mycophenolate. Bile sequestrating agents and Cholestyramine also decrease the plasma concentration of Mycophenolate. Denosumab increases the side effects and toxic effects of Mycophenolate. Mycophenolate dec reases the serum concentration of combined (Estrogen+Progresterone) oral contraceptives, unexpected pregnancies may occur due to insufficient contraception. Therefore, additional contraceptive methods should also be used. Magnesium, Metronidazole and Penicillin derivatives decrease the plasma concentration of Mycophenolate. The immunos uppressive effect of Tofacitinib is increased with Mycophenolate use. Quinolones and proton pump inhibitors decrease the plasma concentration of Mycophenolate. The concurrent use of Mycophenolate with other immunosuppressive drugs (eg Tacrolimus, Cyclosporine and systemic corticosteroids) increases the risk of aplastic anemia [**19,20**].

Dapsone and Other Immunosuppressive Drugs

TDapsone is used less frequently compared to Azathioprine and Mycophenolate. It may especially be used in pemphigus foliaceus and IgA pemphigus patients. The treatment is initiated at low doses of 25-50 mg/day and the dose is increased to maintenance levels of 50-200 mg/day if the patient tolerates the drug. Hemolysis is an expected side effect. The risk of hemolysis increases in glucose-6 phosphate dehydrogenase (G6PDH) deficiency. Therefore, G6PDH levels should be measured before initiating therapy. Other side effects of the drug are agranulocytosis, methemoglobulinemia, hypersensivity and motor neuropathy. The patients receiving Dapsone should be monitored closely due to the risk of hemolysis and methemoglobulinemia [**21**].

Other immunosuppressive drugs used in pemphigus treatment are 10-25 mg/week Methotrexate, 2.5-5 mg/day Cyclosporine and the combination of Nicotinamide and Tetracycline derivatives [4]. Minocycline and Niascor is a commonly used combination in the treatment of bullous pemphigoid. It was reported to be effective in pemfigus vegetans as well [**22**]. Nicotinamide 3x500 mg can be combined with tetracycline 4x500 mg or doxycycline 2x100 mg or minocycline 2x100 mg [**4**].

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