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The role of mycophenolate in the treatment of antineutrophil cytoplasmic antibody-associated vasculitis

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Abstract

Mycophenolic acid, the active metabolite for mycophenolate mofetil and mycophenolic sodium, is a strong, noncompetitive, reversible inhibitor of inosine monophosphate dehydrogenase, the key enzyme in *de novo* synthesis of guanosine nucleotides leading to selective inhibition of lymphocyte proliferation. Mycophenolic acid has been evaluated as induction and remission maintenance agent in the treatment of antineutrophil cytoplasmic antibody-associated vasculitis (AAV). Since the course of disease of AAV usually requires long term immunosuppression, mycophenolate has been explored as a less toxic agent compared to cyclophosphamide and azathioprine. Mycophenolate is a potent immunosuppressive agent in the therapy of AAV, non-inferior to other available drugs with comparable side effect profile. Therefore, it could be a valuable alternative in cases of toxicity with life threatening side effects or intolerance to cyclophosphamide or azathioprine, in cases with high cumulative dose of cyclophosphamide, but also in cases with insufficient response. Several studies have shown a higher relapse rate following discontinuation of mycophenolate or in mycophenolate treated subjects that raises concerns about its usefulness in the treatment of AAV. This review describes the efficacy of mycophenolate in AAV as remission induction agent, as remission maintenance agent, and as therapeutic option in relapsing AAV disease, the relapse rate following discontinuation of mycophenolate, and the adverse events related to mycophenolate treatment.

Key words: Mycophenolic acid; Mycophenolate mofetil; Mycophenolate sodium; Antineutrophil cytoplasmic antibody-associated vasculitis; Microscopic polyangiitis; Granulomatosis with polyangiitis; induction; Remission; Relapse

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Core tip: Antineutrophil cytoplasmic antibody-associated vasculitis is characterized by a remitting - relapsing course of disease that requires long term immunosuppression.

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Mycophenolic acid has been evaluated as induction and remission maintenance agent in the treatment of antibody-associated vasculitis as a less toxic agent compared to cyclophosphamide and azathioprine. Mycophenolate has been proven a potent immunosuppressive agent and non-inferior to other available drugs with comparable side effect profile, but several studies have shown a higher relapse rate following discontinuation of mycophenolate or in mycophenolate treated subjects. In this review, the role of mycophenolate in treatment of antibody-associated vasculitis is further discussed.

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INTRODUCTION

Mycophenolic acid was initially introduced successfully as a therapeutic agent of solid organ transplantation, reducing the incidence of acute rejection in renal transplant recipients^[1]. The encouraging efficacy of mycophenolate prompted the assessment of its potency in the treatment of antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), both as induction and maintenance therapy. ANCA-AAV includes granulomatosis with polyangiitis (GPA) (formerly Wegener's granulomatosis, WG), microscopic polyangiitis (MPA), and eosinophilic GPA (formerly Churg-Strauss syndrome, CSS). AAV has a variable course of disease activity with phases of remission and relapse requiring therapeutic regimens initially for induction of remission and subsequently for maintenance of remission. Historically, the standard induction treatment plan included high doses of corticosteroids and cyclophosphamide (CYC) that resulted in complete remission rates around 70% with increased percentage of relapse after lowering or discontinuing immunosuppression^[2]. Azathioprine was usually employed as maintenance of remission agent. However, despite their efficacy, both CYC and azathioprine were accompanied with significant side effects regarding infection and malignancies that imposed a hindrance in long term or repeated therapies that are frequently necessary in AAV. Therefore, other agents less toxic but with similar efficacy were explored, such as mycophenolate acid, rituximab, deoxyspergualin, infliximab, or etanercept.

For the purposes of this review, we searched published clinical studies of mycophenolate in AAV and more specifically GPA and MPA as induction agent and maintenance treatment.

MYCOPHENOLIC ACID MECHANISM OF ACTION

Mycophenolic acid is the active metabolite for mycophenolate mofetil and mycophenolic sodium. It is a strong, non-competitive, reversible inhibitor of inosine monophosphate dehydrogenase, the key enzyme in *de novo* synthesis of guanosine nucleotides leading to selective inhibition of lymphocyte proliferation^[3]. Purine synthesis could be also achieved *via* the salvage pathway in the majority of eukaryotic cells but not in lymphocytes that are more dependent on *de novo* pathway than on the salvage pathway. Therefore, the administration of mycophenolic inhibits DNA synthesis in the S phase of cell cycle and subsequently lymphocyte proliferation. Experimental models have confirmed that mycophenolic acid reduces the production of lymphocyte-derived cytokines such as interferon-gamma and tumor necrosis factor alpha, proinflammatory cytokines produced by monocytes, along with inhibition of primary humoral responses.

Mycophenolate mofetil and mycophenolic sodium are usually orally administered, undergo rapid absorption, and metabolized to the active metabolite mycophenolic acid. Due to the enterohepatic recirculation, the inactive phenolic glucuronide of mycophenolic acid is converted back to mycophenolic acid. A minor percentage of acylglucuronide of mycophenolic acid is also formed that is an active metabolite and could be responsible for side effects like diarrhea or leucopenia. It should be further noted that monitoring plasma mycophenolic acid levels is not routinely performed^[4]. Several measurements are required over a period of 12 hours in order to calculate the

area under the curve, which is not realistic in every day practice.

In regard to drug interactions, it is important to mention that antacids and proton pump inhibitors, which are commonly used, decrease exposure to mycophenolic but without any effect on transplant rejection rates. However, it is suggested that these two drug categories should avoid co-administration with mycophenolic^[5]. Further significant drug interactions concern colestyramine, sevelamer, ciclosporin A, and medicinal products that interfere with the enterohepatic circulation, and for that reason it is suggested to administer their drugs at different times.

MYCOPHENOLIC ACID AS INDUCTION TREATMENT

Mycophenolate has been evaluated as induction treatment in patients with relapsing AAV who have been exposed to significantly high doses of CYC or had contraindication to CYC (Table 1). Joy *et al*^[6] reported their experience in a limited number of 12 patients with relapsing or grumbling AAV that required induction therapy. The majority were proteinase 3 ANCA (PR3-ANCA) positive (75%). In a 6-mo induction phase, 60% achieved remission at least for a short period of time with negative Birmingham Vasculitis Activity Score, leading to sustained remission in 30% but also to relapse in 30% while five patients failed to show any signs of positive response.

Three prospective randomized studies comparing CYC to mycophenolate have been conducted as induction of remission treatment^[7-9]. Two published clinical trials have been performed in China and a third was led by the European Vasculitis Study (EUVAS) group. Hu *et al*^[7] examined the efficacy of mycophenolate *versus* CYC as 6-mo induction therapy in 34 patients diagnosed with MPA and one patient with GPA. After excluding subjects lost during follow-up, the mycophenolate group showed superior remission rates than the CYC group. More specifically 77.8% (14/17) of the mycophenolate group and 61.5% (8/13) of the CYC group achieved remission. The other Chinese trial randomized 41 patients, all tested myeloperoxidase ANCA (MPO-ANCA) positive, with active disease to receive CYC or mycophenolate^[8]. Remission rates were higher though not statistically significant in the mycophenolate group (78.9%) than in CYC group (63.5%). A limitation of both studies is the short period of 6 mo follow-up, so no data regarding relapse rates are included in the published results.

The EUVAS group designed an international randomized study in 140 patients with newly-diagnosed AAV to be treated with mycophenolate or CYC as induction of remission^[9]. This clinical trial concluded that remission was induced in 67% (47/70) mycophenolate *versus* 61% (43/70) CYC treated subjects. Even though the primary remission induction end-point of non-inferiority of mycophenolate was achieved, the mycophenolate treated group displayed more relapses (33% *vs* 19%) during the follow-up period along with shorter relapse-free survival. Further, the authors comment that in the mycophenolate group, higher relapse rate was accounted in PR3-ANCA patients but not in MPO-ANCA patients.

MYCOPHENOLIC ACID AS MAINTENANCE TREATMENT

Mycophenolate was initially administered as a remission maintenance agent (Table 2). The first report was published in 1999 by Nowack *et al*^[10] describing the efficacy of mycophenolate in nine patients with WG and two patients with MPA as maintenance therapy after achieving remission with standard protocol with CYC, corticosteroids and plasma exchange. Remission was maintained with 2 g/d of mycophenolate and low dose of corticosteroids (less than 7.5 mg/d) during the follow-up period of 15 mo with the exception of one relapse at 14 mo. In 2004, another small cohort of 14 WG patients evaluated mycophenolate as remission maintenance agent following initial treatment with CYC and corticosteroids^[11]. Relapse rate was reported in 43% (6/14 patients) at a median time from remission to relapse of 10 mo (range 1-25 mo).

A study by Koukoulaki and Jayne^[12] in 2005 reviewed retrospectively the efficacy of mycophenolate during the maintenance phase in 29 AAV patients. A relapse rate of 48.3% (14/29 patients) was reported in a period of 12 mo with mean time to relapse of 14.1 ± 13.9 mo.

Iatrou *et al*^[13] reported their experience of mycophenolate as maintenance therapy in 22 newly diagnosed patients with AAV and renal involvement. The majority of patients were diagnosed with MPA (16 patients) followed by WG (four patients) along with one patient with renal limited vasculitis and one with CSS with renal vasculitis. Induction protocol consisted of intravenous CYC and corticosteroids that

Table 1 Mycophenolic acid for induction treatment in antineutrophil cytoplasmic antibody-associated vasculitis

Authors	Yr	Study design	No Pt	Diagnosis	ANCA	Follow-up in mo	Remission rate
Joy <i>et al</i> ^[6]	2005	Case series	12	WG: 7, MPA: 2, Renal Limited: 2; CS:1	MPO: 3, PR3: 9	12	6/10 - 60%
Koukoulaki <i>et al</i> ^[12]	2006	Case series	22	N/A	N/A	24	18/22 - 81.8%
Stassen <i>et al</i> ^[15]	2007	Cohort	32	MPA: 3; WG: 29	MPO: 3; PR3: 29	48	Complete remission: 25/32 - 78%; Partial remission: 6/32 - 19%
Hu <i>et al</i> ^[7]	2008	Randomized	35	N/A	MPO: 28; PR3: 2	6	Mycophenolate: 77.8% (14/18); CYC: 61.5% (8/13)
Silva <i>et al</i> ^[16]	2010	Cohort	17	MPA: 17	MPO: 17	18	Remission at 6 mo: 13/17 - 76%; Sustained remission at 18 mo: 12/17 - 70%
Han <i>et al</i> ^[8]	2011	Randomized	42	N/A	MPO: 42	6	Mycophenolate: 78.9% (14/18); CYC: 63.6% (8/13)
Jones <i>et al</i> ^[9]	2018	Randomized	140	MPA: 49; GPA: 91	MPO: 53; PR3: 82	18	Mycophenolate: 67% (47/70); CYC: 61% (43/70)
Chen <i>et al</i> ^[17]	2016	Cohort	34	MPA: 34	MPO: 34	86	31/34 - 91.2%

ANCA: Antineutrophil cytoplasmic antibody; AZA: Azathioprine; CYC: Cyclophosphamide; MPA: Microscopic polyangiitis; MPO: Myeloperoxidase; No: Number; N/A: Not available; PR3: Proteinase 3; Pt: Patients; WG: Wegener's granulomatosis.

were withdrawn at the end of the induction phase, followed by remission protocol that consisted of mycophenolate monotherapy for 18 mo. After the 18 mo of maintenance treatment, mycophenolate was only given in case of relapse and the mean follow-up was 42 mo (range 24-101 mo). However, until the end of the follow-up period 31.58% of the patients had relapsed, and 15.8% progressed to end stage renal disease. The extension of the study, with the addition of new cases (in total 34 patients) and a median follow-up of 97.5 mo (range 66-128), showed significantly declining efficacy of mycophenolate as a maintenance treatment in patients with AAV during long-term follow-up. During the follow-up period, 13 patients (38.2%) had relapsed (5/13 had more than one relapse: Three patients had two relapses, one patient - three relapses, and one patient four relapses), and at the end of the follow-up period 18 patients (53%) were undergoing chronic hemodialysis and 9/34 (26.4%) had died (unpublished data presented in the 19th PanHellenic Congress of Nephrology).

The International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides study was an open label randomized controlled trial in AAV, including 156 newly diagnosed patients with either WG ($n = 100$) or MPA ($n = 56$)^[14]. CYC and corticosteroids were administered for induction of remission. For maintenance of remission, patients were randomized to receive azathioprine ($n = 80$) or mycophenolate ($n = 76$). It should be noted that prednisolone dose was 15 mg/d beginning the remission regimen, tapered to 5 mg/d at 12 mo, and discontinued at 24 mo. Follow-up was extended up to 42 mo. The overall relapse rate was 55% (42/76) in the mycophenolate group compared to 37.5% (30/80) in the azathioprine group. Correspondingly major relapses were more common in the mycophenolate treated patients ($n = 18$) versus the azathioprine group ($n = 10$).

MYCOPHENOLATE FOR INDUCTION AND MAINTENANCE OF REMISSION

In addition to the evaluation of mycophenolate either as induction agent or as remission maintenance agent after induction of remission with CYC, there is a series of studies evaluating mycophenolate both as induction (Table 1) and maintenance

Table 2 Mycophenolic acid for remission maintenance treatment in antineutrophil cytoplasmic antibody-associated vasculitis

Authors	Yr	Study design	No Pt	Diagnosis	ANCA	Follow-up in mo	Relapse rate
Nowack <i>et al</i> ^[10]	1999	Cohort	11	WG: 9; MPA: 2	PR3: 9; MPO: 2		1/11 – 9% time to relapse 14 mo
Langford <i>et al</i> ^[11]	2004	Cohort	14	WG	cANCA: 13; pANCA: 1	Median 18 (range 1-50)	6/14 – 43% median time to relapse 10 mo
Koukoulaki <i>et al</i> ^[12]	2006	Case series	29	N/A	N/A	24	14/29 – 48.3%
Stassen <i>et al</i> ^[15]	2007	Cohort	32	WG: 29; MPA: 3	PR3: 29; MPO: 3	48	Median time to relapse: 16 mo; Relapse free survival 1-yr: 63%, 3-yr: 38%, 5-yr: 27%
Iatrou <i>et al</i> ^[13]	2009	Cohort	22	MPA: 16; WG: 4; RENAL LIMITED: 1; CSS: 1	MPO: 18; PR3: 4	18	6/19 – 31.58% - median time to relapse 21.5 mo (range 18-60 mo)
Silva <i>et al</i> ^[16]	2010	Cohort	13	MPA: 13	MPO: 13	18	1/13 – 7.7%
Hiemstra <i>et al</i> ^[14]	2010	Randomized	156	WG: 90; MPA: 56	MPO: 51; PR3: 90	39	MYCOPHENOLATE GROUP 42/76 – 55% (18 major, 24 minor relapses); AZA 30/80 – 37.5% (10 major, 20 minor relapses)
Draibe <i>et al</i> ^[18]	2015	Case series	20	N/A	MPO: 18	N/A	3/20 – 16% (time to relapse 18-23 mo)
Chen <i>et al</i> ^[17]	2016	Cohort	31	MPA: 31	MPO: 31	86	7/31 – 22.6% median time to relapse 43 mo (IQR 10-128 mo)

ANCA: Antineutrophil cytoplasmic antibody; AZA: Azathioprine; CYC: Cyclophosphamide; IQR: Interquartile range; MPA: Microscopic polyangiitis; MPO: Myeloperoxidase; CSS: Churg-Strauss syndrome; No: Number; N/A: Not available; PR3: Proteinase 3; Pt: Patients; WG: Wegener's granulomatosis.

treatment (Table 2).

A cohort of 32 AAV patients mostly with GPA (29/32) with active disease were treated with oral prednisolone in combination with mycophenolate for 12 mo as induction of remission and subsequently with tapered dose of mycophenolate until 24 mo^[15]. Complete or partial remission was induced in 78% (25/32) and 19% (6/32), respectively. The authors report 1-, 3-, and 5-year free survival of 63%, 38%, and 27%, accordingly correlating the rates of relapse to previous exposure to CYC.

Likewise, another cohort of 17 MPA patients reported induction of remission with mycophenolate based treatment protocol in 76% (13/17) with prolonged remission at the end of follow-up at 18 mo in 70% (12/17)^[16].

A retrospective study by Chen *et al*^[17] evaluated mycophenolate as induction and maintenance treatment in 34 MPA patients with extended follow-up up to 7 years. Chen *et al*^[17] administered mycophenolate both for induction and remission regimen. Patients who achieved remission with mycophenolate continued treatment with mycophenolate and corticosteroids for a median period of 24 mo (interquartile range 15-53 mo). Relapse rate was 22.6% (7/31), with a median time to relapse of 43 mo (interquartile range 20-128 mo).

A Spanish group reported their experience with mycophenolate as induction therapy in 29 patients and as maintenance treatment in 67 patients with AAV, the majority MPO-ANCA positive^[18]. Treatment plan consisted of 3 mo induction phase and then maintenance phase up to 24 mo while patients remained on low dose of prednisolone along with reduced dose of mycophenolate depending on disease activity. During the follow-up period six patients experienced renal relapse and two patients relapsed with cutaneous manifestations (in total 8/67, 11.9%). In terms of initial regimen, three subjects had been treated with CYC and three with mycophenolate. During the maintenance period, four patients progressed to end stage renal disease requiring renal replacement therapy.

MYCOPHENOLIC ACID IN RELAPSING OR REFRACTORY VASCULITIS

A pilot study of efficacy of mycophenolate in relapsing or resistant AAV included 10 patients with active disease evaluated with Birmingham Vasculitis Activity Score. Transient complete remission was accomplished in six patients (60%), while just three of them maintained long-lasting remission^[6].

A retrospective analysis of 22 patients with active or partially controlled AAV who received mycophenolate while on relatively low dose of prednisolone showed 81.8% (18/22) induction of remission^[12]. However, the initial response was temporary with more than 50% relapse rate (55.6%, 10/18) through a period of 24 mo.

ADVERSE EVENTS WITH MYCOPHENOLATE TREATMENT

Adverse events related to mycophenolate treatment are associated with its mechanism of action. Therefore, rapidly regenerated cells such as the gastrointestinal track are affected, along with the leucocytes that are the main site of drug's action. Certainly, as an immunosuppressant agent, mycophenolate leads to increased risk of infections. In our case-series of 34 AAV patients treated with mycophenolate in accordance with published experience, mild gastrointestinal intolerance was reported in two patients, increased serum amylase in three patients, leucopenia in two patients, and herpes zoster infections in three patients. All adverse events resolved by reducing the dose of mycophenolate mofetil.

Among the commonest adverse events related to mycophenolate treatment regarding the gastrointestinal tract are diarrhea, nausea, bloating, vomiting, abdominal pain, and rectum bleeding. Another frequent side effect is leucopenia and seldom pancytopenia. Like all immunosuppressive agents, mycophenolate increases the possibility of infections through re-activation of latent viruses, like herpes zoster or cytomegalovirus, and more commonly in transplanted population and respiratory infections. Further cognitive or psychological side effects have been reported in some studies^[6,12,16]. A small number of cases with sleeping difficulties or insomnia, poor concentration, headache, and depression have been described.

All the studies conclude that most of the adverse events are temporary and reversible with dose reduction or rarely discontinuation of mycophenolate, which is considered a well tolerated with low toxicity immunomodulating drug.

CONCLUSION

This is a mini-review to summarize published clinical studies with mycophenolate in AAV and describe the experience of our center. Mycophenolate was introduced in the therapeutics of AAV in the middle of the 1990s^[10]. Relatively few clinical studies have been published, usually as cohorts of patients, describing single-center experience. The EUVAS study group has led important clinical trials, two of which concern the efficacy of mycophenolate as induction and as remission maintenance agent in AAV and include a considerable number of patients^[9,14]. Taken into account published studies, mycophenolate is an effective treatment for induction and maintenance of remission of AAV. In 2016, the European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association recommendations for the management of AAV state that mycophenolate could be used as remission induction of non-organ threatening vasculitis and as remission maintenance agent^[19]. For both indications mycophenolate is not the first choice as supported by published clinical trials. Published experience could not provide plausible explanations for the reasons that mycophenolate, even though a potent immunosuppressive with great and superior efficacy in organ transplantation, was not superior to other treatment options in AAV. The hypothesis of inadequate dosing or the type of positivity of ANCA, PR3 or MPO, vasculitis was not proven or supported by clinical data. Mycophenolate's efficacy in AAV is not doubted. So far it has been proven non-inferior to other options like CYC or azathioprine and should not be considered obsolete. Therefore, mycophenolate could still be a valuable alternative in cases of toxicity with life threatening side effects or intolerance to CYC or azathioprine, in cases with high cumulative dose of CYC, and also in cases with insufficient response. Several studies have shown a higher relapse rate following discontinuation of mycophenolate or in mycophenolate treated subjects. The complicated course of AAV with relapsing-remitting course requires treatments with long-term efficacy without significant side effects in order to minimize exposure to immunosuppression. Among

the available options, rituximab may have potential both as induction and maintenance of remission agent^[20-22]. Despite the recognized increased cost of rituximab, its efficacy could be proven superior and ultimately cost-effective; and, therefore, its role should be further investigated in AAV.

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