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MYCOPHENOLATE MOFETIL FOR THE TREATMENT OF WARM AUTOIMMUNE HAEMOLYTIC ANAEMIA POST-RITUXIMAB THERAPY: A CASE SERIES

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ABSTRACT

Background: Warm autoimmune haemolytic anaemia (wAIHA) is an acquired haemolytic disorder most commonly treated with a combination of corticosteroids, rituximab and/or splenectomy. Third-line therapies for refractory cases include immunosuppressive agents. Mycophenolate mofetil is frequently used in these scenarios, although its use is supported by small studies and anecdotal evidence rather than large-scale data.

Case description: We describe three cases of refractory warm autoimmune haemolytic anaemia successfully treated with mycophenolate mofetil. Case 1: A persistent case of autoimmune haemolytic anaemia in a 56-year-old was ultimately managed with mycophenolate mofetil, leading to successful steroid tapering and stable haemoglobin levels without relapse. Case 2: A woman with a complex oncological history, including lymphoma and breast cancer, achieved remission with mycophenolate therapy, maintaining stability post-steroid treatment. Case 3: Mycophenolate proved effective for a 63-year-old with cirrhosis after recurrent autoimmune anaemia and deep vein thrombosis, enabling cessation of steroids and maintaining remission.

Conclusion: Management of this condition can be challenging and balancing the available treatments is crucial to reduce potential complications from long-term therapies that appear to be ineffective. Our case series demonstrates anecdotal experience on successful use of mycophenolate mofetil for complex refractory cases of wAIHA.

KEYWORDS

Anaemia, haemolytic, autoimmune, rituximab, mycophenolic acid

LEARNING POINTS

- Warm autoimmune haemolytic anaemia can be a challenging condition to manage. Refractory cases that are steroid-dependent can benefit from trialling steroid-sparing agents such as mycophenolate.
- Anti-CD20 agents such as rituximab can be very effective in refractory cases, however there is a small percentage of patients that might not be responsive to this monoclonal antibody.
- Autoimmune haemolytic anaemias can be frequently complicated by thrombotic events, and part of the backbone treatment is establishing good thromboprophylaxis.

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INTRODUCTION

Warm autoimmune haemolytic anaemia (wAIHA) is an acquired disorder where immunoglobulin G antibodies target erythrocyte surface antigens, causing premature destruction and anaemia[1-3]. The primary treatment is corticosteroids, while rituximab and splenectomy are second-line treatments with about 80% efficacy[4,5]. Refractory cases are managed with mycophenolate mofetil (MMF) and other immunosuppressive agents, though evidence for their use varies[4]. MMF's use in wAIHA is based on small studies and anecdotal evidence, showing efficacy in refractory idiopathic and secondary AIHA[6-8]. Patients with systemic lupus erythematosus/antiphospholipid syndrome and autoimmune lymphoproliferative syndrome (ALPS)-related AIHA also respond to MMF, but more data is needed[7,8]. This series presents three wAIHA cases resistant to rituximab but successfully treated with MMF, showing good medication tolerance.

CASE DESCRIPTION

Case 1. A 56-year-old Hispanic male with no significant past medical history presented to the emergency department with fatigue and jaundice. On evaluation, he was found to have severe anaemia with a haematocrit of 15% and a haemoglobin level of 5.5 g/dl. Initial laboratory workup demonstrated features consistent with autoimmune haemolytic anaemia, including a positive Coombs test and an elevated indirect bilirubin of 3.1 mg/dl. The patient was promptly initiated on high-dose steroids in December 2017, which ameliorated the haemolytic crisis. Over the following months, he underwent a slow steroid taper, concluding in June 2018. However, he experienced a relapse of haemolytic anaemia, prompting the initiation of rituximab therapy. He received a total of six doses in conjunction with continued high-dose prednisone at 1 mg/kg/day. Despite being on a gradual steroid taper, a second relapse occurred in April 2019 when the prednisone dose was tapered to 0.04 mg/kg/day. The reintroduction of a low-dose prednisone regimen at 0.15 mg/kg/day resolved this episode. A bone marrow aspirate evaluation showed a mildly hypercellular marrow with trilineage haematopoiesis and mild erythroid hyperplasia. The patient was maintained on low-dose prednisone until February 2021, when attempts to taper the steroid dose led to another relapse with a haemoglobin level of 6.5 g/dl, requiring hospitalisation and a transfusion of 1 unit of packed red blood cells (RBCs). In March 2022, he encountered yet another setback during steroid tapering and developed a fourth episode of haemolytic anaemia with the prednisone dose at 0.3 mg/kg/day. Concurrently, he was diagnosed with osteopenia as evidenced by DEXA scan results. Subsequently, a decision was made to perform a splenectomy in April 2022. Post-surgery, the patient suffered from severe post-splenectomy haemolysis, with haemoglobin levels plummeting to 2.5 g/dl. He received transfusions and high-dose prednisone at 2 mg/kg/day (120 mg/day), alongside the initiation of rituximab, completing four weekly cycles in May 2022. He had successfully tapered off steroids by 26 August 2022. In March 2023, the patient experienced a further recurrence of haemolysis and was prescribed prednisone 1 mg/kg/day. He exhibited a positive response to the slow tapering regimen and, by October 2023, commenced treatment with MMF 500 mg twice daily alongside a reduced prednisone dose of 0.66 mg/kg/day. As of March 2024, the patient has successfully discontinued prednisone with no recurrence of haemolytic anaemia and continues maintenance therapy with MMF.

Case 2. A 47-year-old Hispanic female with an extensive oncological history, including Hodgkin lymphoma diagnosed at 16 years old, was initially treated with ABVD chemotherapy with subsequent relapse at age 18, necessitating high-dose chemotherapy and an autologous stem-cell transplant. Additionally, she had triple-negative stage III breast cancer in 2013, for which she underwent a mastectomy followed by Taxol and carboplatin chemotherapy. The patient presented to the emergency department on 7 December 2022, with symptoms of fatigue, dizziness and dark urine. Laboratory tests revealed critical anaemia with haemoglobin level of 4 g/dl, necessitating a transfusion of 3 units of RBCs. Concurrently, high-dose steroids (prednisone 60 mg/day) were initiated due to evidence of haemolysis. Despite a negative initial workup for autoimmune haemolysis, an autoimmune aetiology was presumed. On 22 December 2022, she was readmitted with a recurrence of haemolytic anaemia, a newly diagnosed pulmonary embolism and deep vein thrombosis in the left lower extremity, requiring an additional 3 units of packed RBCs and initiation of anticoagulation with enoxaparin. A direct Coombs test returned positive, confirming the suspected autoimmune diagnosis, leading to the initiation of rituximab therapy with four consecutive cycles. Unfortunately, the patient did not respond to rituximab and experienced another recurrence in early January 2023, resulting in hospitalisation. Treatment with intravenous immunoglobulin (IVIG) and high-dose steroids showed a poor response, prompting the addition of MMF 500 mg twice daily. Further testing during this admission to rule out underlying conditions, including for paroxysmal nocturnal haemoglobinuria, yielded negative results. A bone marrow biopsy indicated normocellular bone marrow (60%) with erythroid predominant haematopoiesis. Over time, the patient showed improvement with a gradual steroid taper and successfully discontinued prednisone on 18 September 2023. The deep vein thrombosis treatment spanned six months, attributed to being provoked by the haemolytic crisis. She transitioned to warfarin in March 2023 and remains stable on maintenance therapy with MMF with no recurrence of the haemolytic anaemia.

Case 3. A 63-year-old Hispanic male with a medical history of hepatic cirrhosis and thrombocytopenia was admitted to the hospital in April 2023 due to fatigue and icteric sclera. Laboratory findings, including a positive Coombs test, elevated lactate dehydrogenase levels, high reticulocyte count and a haemoglobin of 7 g/dl, supporting a diagnosis of

Patient	Age (years)	Sex	Associated disease	Time from diagnosis to treatment with MMF (months)	Rx prior to MMF	Rx when MMF started	Hb (g/dl) when MMF started	Maximum eHb (g/dl)	Time to maximum Hb (weeks)	Duration of Rx (months)	Comments
1	56	M	None	70	Prednisone Splenectomy Rituximab	Prednisone (40 mg/d)	9.1	15.3	5	5 +	
2	47	F	HL	1.1	Prednisone Rituximab IVIG	Rituximab	8.8	13.2	32	14 +	
3	63	M	Liver cirrhosis	17	Prednisone Rituximab	Prednisone 40 mg/d	8.7	12.6	3	7 +	

Table 1. AIHA patient details and results.

Reference	No of patients	Age (years)	Sex	Associated disease	Previous Rx	Concomitant Rx with MMF (dose per day)	MMF dose	Hb before MMF (g/dl)	Max Hb (g/dl)	Time to max Hb (months)	Duration of Rx (months)	Outcome
Howard et al. 2002[15]	4	50 52 31 74	M M M M	ITP WM No CLL	Pred, Aza, Splene, Cyclo Pred, Cyclo Pred, Aza, Splene, Cyclo Pred, Cyclo	Pred 10 Pred 60 mg, Cyclo 150 Pred 40 mg Mehylpred, IVIG	1 g/day 1 g/day 1 g/day 1 g/day	9.1 6.5 9.6 3.8	11.2 9.8 11 11.4	4 6 9 1	15+ 6+ 9 12	Pred dose decreased Pred and cyclo dose decreased Pred dose decreased Relapse at 5/12 months which responded to splenectomy
Alba et al. 2003[16]	2	45 29	F F	SLE + APS SLE + APS	Pred, Aza, IVIG, Phenidione Cyclo, Methylpred	NI Pulsed Methylpred	1 g/day 1 then 2 g/day	8.3 7.5	14.6 12	4 6	18+ 12+	18 months without relapse 12 months without relapse
Rao et al. 2005[8]	13	14 8.9 12.1 13.7 5.2 1.4 17 11 11 2.5 0.8 10.9 2.1	M (all)	ALP (all)	G-CSF, 6-MP, decadron PRBC, IVIG, Aza, G-CSF, Pred PRBC, Pred PRBC, Pred Pred PRBC, Pred Pred, IVIG, G-CSF IVIG, G-CSF, WinRho, Aza, Pred PRBC, IVIG, Pred, Decadron PRBC, Pred PRBC, solu-medrol, IVIG PRBC, Pred, G-CSF PRBC, Pred	NI	~600 mg/m^2 (range 290-774 mg/m^2)	14.4 11.4 7.8 11.6 9.5 9.9 11 13.1 5.3 8.4 6.5 7 9.9	14.5 13.5 10.8 13.5 11.6 12.6 14.4 12.9 14.5 11.2 5.2 14.6 11.2	NI	12+ 60 11+ 57+ 18+ 49+ 9+ 11+ 14+ 12+ 3 12+ 11+	Off prednisone Off prednisone On 6 mg prednisone Off prednisone Off prednisone Off prednisone Off prednisone Off prednisone Off prednisone On 10 mg prednisone Off prednisone Off prednisone Off prednisone
Kotb et al. 2005[17]	3	26 59 62	F F F	NI	Pred Pred, Cyclo Pred	Pred 2 mg/kg Pred 2 mg/kg Pred 2 mg/kg	Initial dose 500 mg/d raised to 1–3 g/d according to weight	4.9 5.9 7.1	12.3 14.3 10.8	2 5 8	NI 49+ 13*	No relapses at 40 months No relapses at 49 months No relapses at 13 months
O'Connell et al. 2014[18]	1	4	M	Dyskeratosis congenita (TINF 2 mutation)	Haematopoietic stem cell transplant	IVIG, rituximab, pred	15 mg/kg	4.8	12	1	24+	

Abbreviations: APS, antiphospholipid antibody syndrome; AZA, azathioprine; CLL, chronic lymphocytic leukemia; Cyclo, cyclophosphamide; G-CSF, granulocyte colony stimulating factor; ITP, immune thrombocytopenic purpura; IVIG, intravenous immunoglobulin; Methylpred, methylprednisolone; Pred, prednisone; PRBC, packed red blood cells; Splene, splenectomy; Win Rho, Immunoglobulin Anti D; WM, Waldenström macroglobulinemia.

Table 2. Summary of the evidence of mycophenolate mofetil in the treatment of AIHA.

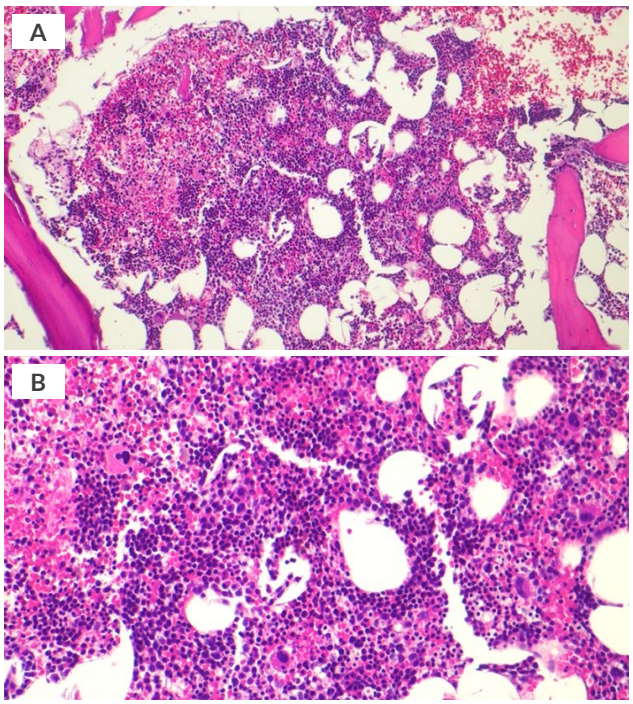

Figure 1. Bone marrow core biopsy for case 2. Figure A (10×) and B (20×) demonstrate a normocellular bone marrow (60%) with erythroid predominant haematopoiesis (myeloid to erythroid ratio of 0.6:1), without morphological dysplasia.

autoimmune haemolytic anaemia. He was treated with high-dose prednisone, starting at 1 mg/kg/day. After stabilisation and subsequent discharge, he was managed on a reduced dose of prednisone at 0.75 mg/kg/day. In May 2023, he developed deep vein thrombosis in the left lower extremity and commenced treatment with apixaban. The thrombosis was believed to be a complication of the ongoing haemolysis. By July 2023, the patient's dose of prednisone had been tapered to 0.04 mg/kg/day. However, this reduction precipitated a recurrence of haemolysis, evidenced by symptomatic anaemia with a haemoglobin level of 9.9 g/dl and a lactate dehydrogenase of 463 U/l. At this juncture, rituximab therapy was initiated, and the patient completed a course of four cycles by 4 August 2023. Prednisone was discontinued on 11 August 2023, which led to another episode of haemolysis. Consequently, on 5th September 2023, the patient was restarted on prednisone at a dose of 0.32 mg/kg/day, and MMF at 500 mg twice daily was added to his regimen. A bone marrow biopsy was also obtained at that time reporting variably cellular marrow (50–60% overall) with trilineage haematopoiesis *(Fig. 1)*. Following this intervention, he successfully tapered off prednisone by 26 October 2023. Since then, his haemoglobin levels have remained stable, indicating a positive response to the current treatment with MMF.

DISCUSSION

MMF might be an effective alternative for managing refractory wAIHA in adults, providing sustained responses as a long-term immunosuppressive treatment. The cases highlight the challenges of managing AIHA, especially in patients with comorbidities *(Table 1)*. Previous case reports and case series have reported the effectiveness of MMF in this condition *(Table 2)*.

Historically, refractory AIHA was treated with splenectomy and corticosteroids, but recently, IVIG and anti-CD20 monoclonal antibodies have been used as second-line options[9,10]. In the presented cases, patients faced challenges with steroid dependence and resistance. Cases 1 and 3 responded to initial high-dose steroid therapy but had recurrences upon discontinuation leading to chronic steroid use and complications such as osteopenia *(Fig. 2)*. One case showed steroid resistance requiring IVIG and rituximab, which also failed. Rituximab, effective in 80% of patients[11], was used with steroids but recurrences occurred when steroids were discontinued. Current guidelines suggest rituximab as second-line therapy for AIHA and first-line for cold agglutinin disease[9,11].

Thrombotic events are a severe complication of autoimmune haemolytic crises. One patient developed a pulmonary embolism and deep vein thrombosis during a haemolytic crisis. A study found that 11% of AIHA patients developed thrombotic complications, associated with intravascular haemolysis, transfusions, multiple treatments

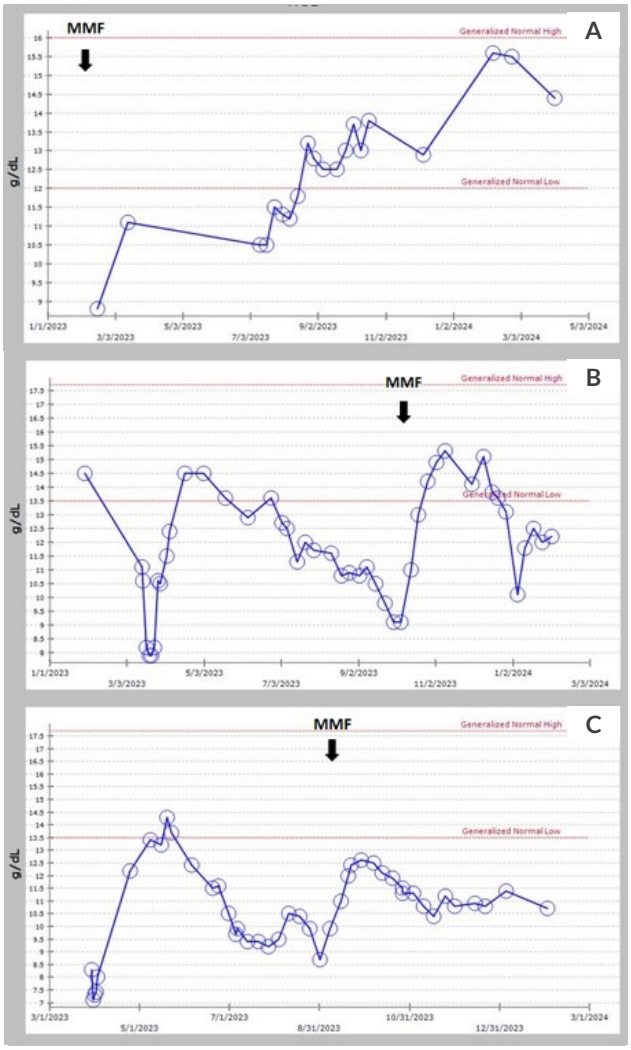

Figure 2. Trends in haemoglobin according to MMF initiation in Case 1 (A), Case 2 (B) and Case 3 (C).

and infections[12]. Primary anticoagulant prophylaxis is recommended. MMF has a favourable side effect profile compared to alternative immunosuppressive therapies such as cyclophosphamide, azathioprine or cyclosporine, which are also recommended as second- or third-line agents[13,14].

CONCLUSION

MMF can be used as an effective therapeutic alternative in cases of refractory wAIHA. Management of this condition can be challenging, and balancing the available treatments is crucial to reduce potential complications from long-term therapies, especially if these are ineffective. Our case series demonstrates anecdotal experience on successful use of MMF for complex refractory cases of wAIHA.

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