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Original Article

Autoimmune hemolytic anemia in children, 20 years experience of single center

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Abstract

Aim: Autoimmune hemolytic anemia (AIHA) is a rare disease in pediatrics, whose mortality rate was reported to be as high as 10%. AIHA can be primary or secondary to other diseases, Availability of new immunsupressive drugs like mycofenolate mofetil (MMF), has provided the opportunity to reduce long term steroid administration and mortality. In this study we aimed to represent AIHA patients of 20 years, from single centre and focus on the causes, treatment and outcomes. The secondary object was to represent outcomes of patients who received MMF.

Material and Methods: This study was designed as a retrospective study. Patients aged three months to 18 years old with hemoglobin level less than 10 g/dl and positive DAT with signs of hemolysis were included in the study.

Results: Twenty five AIHA patients (F/ M: 14/ 11) aged 6.2± 4.6 years old were followed- up for a mean period of 5.3± 4.8 years. Primary AIHA was detected in 12 (48%) patients. Immune deficiency/ autoimmune lymphoproliferative syndrome was the prominent etiological factor in secondary AIHA. The other underlying diseases were systemic lupus erythematosus, malignancy, autoimmune hepatitis and infection.

Eleven patients received MMF with a mean duration of 2.6± 1.6 years. Two of them had primary AIHA, the others had secondary disease. During the follow- up time, eight patients (75%) achieved remission with MMF. None of MMF users developed side effect. One but all patients with AIHA achieved remission. No death related to AIHA was recorde': recorded

Conclusion: Understanding the biology of the disease and making accurate diagnosis is important to avoid harmful treatment and to consider targeted therapy. After the failure of first line therapy with steroids or as a steroid- sparing agent, MMF seems to be an effective second-line maintanance immunosuppressive drug without significant side effects.

Keywords: Autoimmune hemolytic anemia; pediatrics; mycofenolate mofetil

INTRODUCTION

Autoimmune hemolytic anemia (AIHA), described as immune-mediated destruction of erythroid cell line, has an estimated incidence of 0.4 cases/ 100 000 children per year (1). AIHA can be primary or secondary to other diseases, mainly infections, lymphoproliferative disorders, autoimmune diseases and immunodeficiencies (1). The diagnosis is based on hemolytic anemia accompanied with a positive direct antiglobulin test (DAT).

Front- line treatment is based on steroid therapy, which has well known side effects in long term use, particularly on the bone and the endocrine system (1). For children with steroid dependency or refractoriness, there are many options including rituximab, cyclosporine, mycophenolate mofetil (1). Mycophenolate mofetil (MMF) is an immunosuppressive drug which reduces T and B cell proliferation by inhibiting inosine monophosphate dehydrogenase (2). It was first approved in 1995 for kidney transplantation and than it was used in several diseases including lupus nephritis (3) and nephrotic syndrome (4). In pediatric hematology area, there is limited data for use of MMF, which is particularly related to immun trombocytopenia, Evans syndrome and AIHA (1, 5- 6).

In this study we aimed to present AIHA patients in 20 years, from single centre and focus on the causes

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and treatment of AIHA, and outcomes of children. The secondary objective was to define outcomes of patients receiving MMF.

MATERIAL and METHODS

This study was designed as a retrospective study. After ethical approval by the local ethics comittee, patients admitted to our children hospital between June 1999- June 2019, aged three months to 18 years old with hemoglobin level below 10 g/ dl and positive DAT (direct antiglobulin test) with signs of hemolysis including reticulocytosis, indirect hyperbilirubinemia, increased lactate dehydrogenase (LDH) level and/ or reduced serum haptoglobin level were included in the study. Patients with hemolytic anemia other than AIHA were excluded. The data was obtained from patients' medical charts. The demographic characteristics of patients, underlying disease, treatment strategies and outcomes were recorded.

Autoimmune lymphoproliferative syndrome (ALPS) was diagnosed according to the international guidelines (7). Analysis of double negative T lymphocytes was performed with flow cytometry (BD FACSCANTO II ®). Since lymphocyte apoptosis test and mutation analysis was not available, we could not make a definitive diagnosis. Briefly, a probable diagnosis of ALPS was made for AIHA patients with chronic (>six months) non-infectious, non-malignant lymphoproliferation (lymphadenopathy and/or splenomegaly) and elevated double negative T lymphocytes (>2.5 % of CD3 positive lymphocytes) accompanying with serum elevated immunoglobuline G (IgG) levels or elevated serum vitamin B12 levels (>1500 ng/ dl) (7).

Systemic lupus erythematosus (SLE) was defined according to the international consensus criteria (8). For infection work- up, laboratory tests for Ebstein Barr Virus, Cytomegalovirus, Human Immunodeficiency Virus, Mycoplasma Pnemoniae, Parvovirus B19, Hepatitis B/C virus were performed.

Initially, megadose of methylprednisolone (30 mg/ kg/ day for seven days) and then maintenance with 2 mg/ kg, modified version of Ozsoylu protocol (9) was administered, for a period of two months and tapered over three months. In the literatüre, several terminologies have been used for response and failure to treatment (10). In our study, response to treatment was defined as increase (Hb ≥10 g/ dL) in or normalization of hemoglobin level without recent transfusion. During the follow- up period, for patients with response failure to steroid treatment (2 gr/dl drop in hemoglobin levels and findings of hemolysis in peripheral smear and blood count) or for patients with steroid dependency (decrease in hemoglobin level when steroid is tapered/ ceased), second line therapies were applied. We used rituximab (375 mg/ m2 once a week for four weeks) or cyclosporine (3- 6 mg/ kg/ day) before 2012, but after that time MMF (1200 mg/ m2) was preferred in patients with steroid refractoriness or dependency. We preferred to continue MMF for two years. However, MMF was restarted in patients who relapsed after cessation. Relapse was defined as 2 gr/dl drop in hemoglobin levels and findings of hemolysis in peripheral smear and blood count, after cessation of therapy.

Statistical analyses were performed with SPSS 18.0 for windows. The sample size consisted of all of our patients with AIHA. Data were presented as mean± SD (min-max) and frequence (%). The Shapiro- Wilk test was used to analyze normal distribution assumption of the quantitative outcomes. The frequencies were compared using the Pearson Chi-square. Value of p less than 0.05 was considered as statistically significant.

RESULTS

Twenty five patients (14 females and 11 males) were included in the study. The mean age at diagnosis was 6. 2± 4.6 years old, mean period of follow- up was 5. 3± 4.8 years (Table 1). The mean hemoglobin level at diagnosis was 5.6±1.8 g/dl, reticulocyte was 15.6±11.6 %. 11 patients had +4 positive DAT, nine had +3 DAT, four had +2 DAT and one had +1 DAT.

Table 1. Baseline Characteristics of Patients with Autoimmune Hemolytic Anemia (n=25)

	mean± 2SD	Minimum-maximum
Age at presentation (year)	6.2± 4.6	0.3- 16.0
Follow- up period (years)	5.3± 4.8	0.5- 20.0
Hemoglobin level (g/dl)	5.6± 1.8	3.3- 9.5
White blood cell count (10^3/µl)	11.9± 12.9	1.3- 66.0
Absolute neutrophil count (10^3/µl)	7.6± 10.5	0.2- 54.0
Platelet count (103/µl)	295± 184	10- 700
Reticulocyte (%)	15.6± 11.6	3- 36

Primary AIHA was detected in 12 (48%) patients and 13 (52%) had secondary disease. (Table 2). Eight of patients with secondary AIHA (61.5%) had immune deficiency: Seven had a probable diagnosis of ALPS and one had a definitive diagnosis of Wiscott Aldrich Syndrome comfirmed with mutational analysis.

Table 2. Diagnoses of Patients with Autoimmune Hemolytic Anemia (n=25)

Primary AIHA[1] n(%)	**12 (48)**
Secondary AIHA n(%)	**13 (52)**
Immune deficiency n (%)	8 (61.5)
Malignancy n (%)	2 (15.4)
Systemic lupus erythematosus n (%)	1 (7.7)
Autoimmune hepatitis n (%)	1 (7.7)
Infection n (%)	1 (7.7)
Total n(%)	13 (100)

[1]AIHA: autoimmune hemolytic anemia

Table 3. Documentation of patients with autoimmune hemolytic anemia according to treatment and outcome (n=25)

Patient	Age at presentation (years)	Diagnosis	Type of cytopenia	Second- line Treatment	Cessation of medicine	Hemolytic episodes (n)	Follow- up period (years)	Final outcome
1	5.0	ProbableALPS[1]	Anemia and thrombocytopenia	Ritux[6], Cyc[6], MMF[8]	-	>3	20.0	Refractory disease
2	0.3	Primary	Isolated anemia	Cyc	+	2	13.0	Remission
3	4.8	Primary	Isolated anemia	MMF	-	2	13.0	Remission
4	7.3	ProbableALPS	Anemia and thrombocytopenia	MMF	+	>3	9.5	Remission
5	5.5	Primary	Isolated anemia	-	+	3	1.0	Remission
6	2.2	Primary	Isolated anemia	-	+	1	3.0	Remission
7	1.5	Primary	Isolated anemia	Cyc	+	1	2.1	Remission
8	2.3	Primary	Isolated anemia	Cyc	+	2	3.0	Remission
9	2.0	Primary	Isolated anemia	-	+	1	1.0	Remission
10	7.0	Autoimmune hepatitis	Isolated anemia	-	+	1	5.0	Remission
11	1.5	Primary	Anemia and thrombocytopenia	MMF	+	3	5.0	Remission
12	16.0	SLE[2]	Isolated anemia	MMF	-	1	2.5	Remission
13	15.0	Primary	Isolated anemia	-	+	1	9.0	Remission
14	9.5	Primary	Isolated anemia	-	+	1	1.0	Remission
15	5.3	Primary	Isolated anemia	-	+	1	1.0	Remission
16	15.2	Primary	Isolated anemia	-	+	1	1.0	Remission
17	4.0	ProbableALPS	Pancytopenia	MMF	-	3	7.0	Remission
18	12.0	ProbableALPS	Isolated anemia	MMF, sirolimus	-	>3	5.0	Remission
19	9.5	AML[3]	Anemia and thrombocytopenia	-	+	1	0.5	Exitus
20	1.2	WAS[4]	Pancytopenia	MMF	+	2	4.0	Remission
21	4.5	ProbableALPS	Pancytopenia	MMF	+	3	6.0	Remission
22	6.0	ProbableALPS	Pancytopenia	MMF	+	2	6.0	Remission
23	4.5	ProbableALPS	Pancytopenia	MMF	+	2	8.0	Remission
24	9.5	ALL[5]	Pancytopenia	-	+	1	6.0	Remission
25	3.3	Leishmaniasis	Pancytopenia	-	+	1	0.6	Remission

[1]ALPS : autoimmune lymphoproliferative syndrome
[2]SLE : systemic lupus erytematosus
[3]AML : acute myeloid leukemia
[4]WAS : Wiscott Aldrich Syndrome
[5]ALL : acute lymphocytic leukemia
[6]Ritux : rituximab
[7]Cyc : cyclosporine
[8]MMF : mycophenolate mofetil

The other underlying diseases were SLE, malignancy (acute leukemia), autoimmune hepatitis and infection (leishmaniasis) (Table 2).

Fourteen patients (56%) presented with isolated erythroid-lineage disruption and the others (n=11,44%) had multilineage disorder: seven patients had pancytopenia, four had anemia with thrombocytopenia (Table 3). Isolated anemia was detected to be more common in primary AIHA (11/12), whereas multilineage cytopenia was detected to be more common in immune deficiency (6/7) this was statistically significant (p=0.025).

All patients except for one with leishmaniasis were administered steroids. Eight patients received additonal intravenous immunoglobulin and two patients received plasma exchange for life threatening anemia during first presentation.

Eleven patients received MMF with a mean period of 2. 6± 1.6 (min:1 max: 5) years (Table 4). Two patients had primary AIHA and the others (n=9) had secondary AIHA. During the follow- up time, after exclusion of three patients who underwent hematopoietic stem cell transplantation, six patients in eight (75%) achieved remission with MMF. MMF was ceased in three patients with remission and relapse was not reported in six months after cessation. No side effect was observed in any patient on MMF. Overall, patients whom received MMF (n=11) were followed- up for 2. 3± 2.5 (min: 0.5 max: 8.0) years after cessation.

Four received cyclosporine with a mean period of nine months (Table 3). Disease resolved in three of them. One patient (patient 1) who used cyclosporine was refractory; he received rituximab, cyclosporine, MMF one after other and finally he had splenectomy. During the follow- up time, except for hepatitis B, he did not have serious infections; but experienced portal vein thrombosis at 22 years old; five years after the cessation of MMF.

Twelve of patients (48%) suffered from only one hemolytic episode. The rest had more than one episode (Table 3). The mean episode time was two/ patient. During the follow- up period, none of our patients with AIHA were lost to AIHA. One patient was lost related to malignancy (acute myeloid leukemia) (Table 3).

Table 4. Documentation of autoimmune hemolytic anemia patients with mycophenolate mofetil administration (n=11)

Patient	Diagnosis	Period of MMF[4] use (years)	Cessation of MMF	Reason for cessation of MMF	Period of follow- up after cessation (years)
1	Probable ALPS[1]	1.0	yes	nonresponder	8
3	Primary	1.8	no	-	-
4	Probable ALPS	3.0	yes	HSCT[5]	2.5
11	Primary	5.0	yes	remission	0.5
12	SLE[2]	1.0	no	-	-
17	Probable ALPS	5.0	no	-	-
18	Probable ALPS	2.0	yes	nonresponder	2.0
20	WAS[3]	1.0	yes	HSCT	1.5
21	Probable ALPS	2.0	yes	remission	0.5
22	Probable ALPS	2.0	yes	HSCT	3.0
23	Probable ALPS	5.0	yes	remission	0.5

[1]ALPS: autoimmune lymphoproliferative syndrome [2]SLE: systemic lupus erytematosus [3]WAS: Wiscott Aldrich Syndrome
[4] MMF: mycophenolate mofetil [5]HSCT: hematopoietic stem cell transplantation

DISCUSSION

Immune- mediated hemolysis may be driven by several mechanisms (1). It occurs mostly due to recognization of red blood cells (RBCs) by auto- reactive immunoglobulin (Ig) G and destruction in the extra- vascular component (1). Immune- mediated destruction of thrombocytes and neutrophils are also defined (1).

Here, we present 25 pediatric AIHA patients. 48% of patients were primary AIHA. In primary AIHA (also called idiopathic AIHA), red blood cell autoantibodies are present and cause hemolytic anemia, but no evidence of an underlying systemic illness exists (11). Primary AIHA accounts for approximately 40 to 50 percent of pediatric AIHA cases; which is consistent with our findings (11).

In this study, the most common underlying disease for secondary AIHA was detected to be immune deficiency, mainly probable ALPS (44%). ALPS is an inherited disorder characterized by dysregulation of the Fas apoptotic pathway leading to abnormal survival of lymphocytes

resulting with lymphoproliferation and autoimmunity (12). Cytopenia is the most common manifestation of autoimmunity and may also appear as the first sign of the disease. (13). Since mutational analysis was not available, we could only make a probable diagnosis of ALPS in patients in the past 20 years. Immunological distinction is beyond the scope of this study. However it is important to mention that genetic heterogeneity among childhood autoimmune diseases with lymphoproliferation exists (13). Recently, mutations in various genes, including NRAS, KRAS, CARD11, FADD, and PRKCD, have been identified as causative for ALPS- like phenotypes however, identification of causative genes do need effort and further investigations (13). Some of our patients with probable diagnosis of ALPS may have an alternative diagnosis in that group. This is the main limitation of our study.

Patients with ALPS often require treatment because of cytopenias. Steroids are the first line treatment. For patients who fail steroids, MMF is the second line therapy recommended (1,14). In our cohort MMF was used in all patients with probable ALPS. In addition, it is recommended that splenectomy should be avoided in patients with ALPS. Even with appropriate precautions of immunizations and penicilin prophylaxis, there is still risk for post splenectomy sepsis (1,14,15). In our study, only one patient had splenectomy. He was diagnosed in 2002, when there was a relative lack of awareness for ALPS. Diagnosis of probable ALPS was made several years later. However, he did not experience life threatening infections. Similarly, rituximab use is not recommended in patients with ALPS, because it may cause permanent hypogamaglobulinemia (16).

Leishmaniasis and SLE were detected in two of our patients. Autoimmune manifestations of leishmaniasis are common and may resolve after treatment for leishmaniasis (17). In pediatric SLE patients, anemia is the most common hematological abnormality (18). It is reported that AIHA is much more frequent in pediatric SLE when compared with adults (18).

One patient was diagnosed to have AIHA and autoimmune hepatitis. Autoimmune hepatitis associated with AIHA is a lethal and are condition of usually early childhood after neonatal period (19). In our study the only patient was seven years old at onset. Our patients' older age at presentation combined with the relative milder clinical course may reflect the wide clinical spectrum of the disease.

In this study, two patients with AIHA are diagnosed with acute leukemia. Autoimmune hemolytic anemia (AIHA) is a potentially fatal complication of many lymphoid malignancies. Those most often associated with AIHA include chronic lymphocytic leukemia, B-cell lymphomas, and Burkitt-type acute lymphoblastic leukemia (ALL) and are clonal populations of mature B cells (20- 21).

We detected those 11 patients (44%) with AIHA presented with multi- lineage cytopenias. A wide range of patients with AIHA (13- 73%) are reported to experience multi-lineage involvement (22-24).

Here in we present the response rates of ten children who received MMF for AIHA. The response rate was 75% with MMF. Miano et al (5) reported that 13 in 16 (81%) patients with Evans Syndrome (primary and ALPS- related) had good response to MMF. In addition, MMF was also shown to be effective in ITP patients with a response rate of 58% (5). Panigrahi et al (6) reported a case series of nine patients, six with persistent or chronic ITP and three patients with persistent or chronic AIHA. All patients achieved complete response with steroids and MMF and maintained this state after steroids were discontinued. Miano (1) recommends that MMF may be the drug of choice as steroid- sparing agent and may also be preferred for ALPS patients with AIHA. It has been shown to be safe and effective in small series but data from larger groups is lacking. In patients with steroid refractoriness (without ALPS) rituximab may be chosen (1). We used MMF in both immune deficiency and primary AIHA patients with steroid dependency or refractoriness. The longest duration of MMF administration was five years, until now. We want to mention that those on remission after MMF cessation (n=3) were followed- up only for a period of six months until the end of study.

Several side effects have been reported related to MMF use, including immunosuppression, cytopenia(s), severe infections and thrombosis (25-27). Authors report that no serious side effect related to MMF was observed. One of patients, who had splenectomy, developed portal vein thrombosis five years after cessation of MMF. Authors did not find a correlation between thrombosis and MMF use in this patient mentioned. Although further studies are required to understand its efficacy and safety, we suggest that, in accordance with the current literature, MMF may be administered to children with AIHA (either primary or secondary) in a more up- front approach soon after the failure of first- line treatment.

We used cyclosporine in four and rituximab in one patient(s). Due to side effects and need for frequent monitoring for physical examination and blood level, cyclosporine alone might be an option as a steroid-sparing/ maintenance treatment only after failure of newer and more tolerable agents, such as MMF and sirolimus (1). Rituximab was preferred to splenectomy before the introduction of newer drugs (1). But the risk of perminent hypogammaglobulinemia and lower response rate in ALPS patients may be considered (1,17).

During the follow- up period, none of our pateints died related to AIHA. In the largest available study, mortality in AIHA is reported to be as high as 10% (12). We suggest that high response rate without prominent side effects may be related to the off- label use of MMF.

CONCLUSION

To sum up, it is recommended to evaluate pediatric patients with AIHA for underlying disease. Understanding the biology of the disease and making accurate diagnosis is important to avoid harmful treatment (e.g. splenectomy and rituximab use in ALPS), to ensure appropriate genetic

counselling and to consider targeted therapy. We suggest that MMF may be a promising second- line treatment option, with high response rate and minimum toxicity. Further studies are needed in larger populations for long term effectiveness and safety.

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