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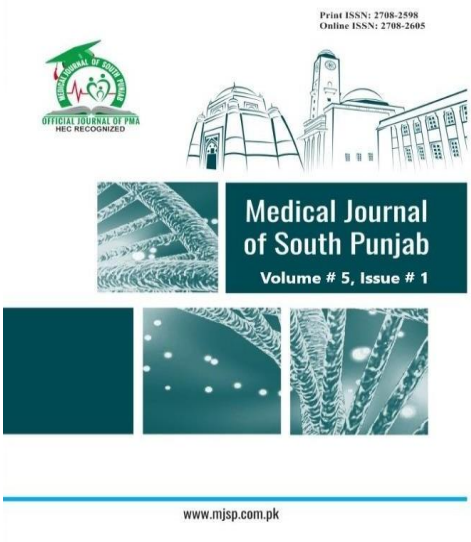

Autoimmune Hemolytic Anemia (AIHA): Response to first line therapy in patients treated at Tertiary care Centre

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Original Article

Autoimmune Hemolytic Anemia (AIHA): Response to first line therapy in patients treated at Tertiary care Centre

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ABSTRACT

Objective: *To determine the response of First line therapy in patients with AIHA.*

Methods: *Eighty individuals of various age groups with AIHA were included. Prednisolone was administered as first line treatment in maximal dose of 1-2mg/kg/day. The initial response of hemoglobin was assessed on day 14 and subsequently every two weeks until the full response was attained. Numerical variables i-e age, duration of response, hemoglobin (Hb), lactate dehydrogenase (LDH), indirect bilirubin were assessed by mean ±SD. Categorical variables i-e direct antiglobulin test (DAT), gender, response (complete response, partial response, no response), were analyzed for frequency and percentages. Data was stratified for age, gender, duration of response; Hb, LDH, Total bilirubin and DAT. Variables with p value ≤0.05 were considered statistically significant.*

Results: *The median age of the patients was 34.5 years. 38 male and 42 were female. 77 had a positive DAT, and 49 had both direct and indirect Coombs tests positive. The major symptoms reported was generalized weakness (61.3%) followed by progressive pallor (27.5%). Our study, revealed overall response rate 76.3%. An analysis was performed to assess the correlation between response to first-line therapy and various variables, including gender, co morbidities, visceromegaly, RCC ransfusion and blood counts which did not reveal any statistically significant correlation. The median duration of response to steroids was 13 months. During the study period, n=61 (76.3%) patients were alive, n=12 (15.0%) patients passed away, and n=7 (8.8%) patients lost to follow-up.*

Conclusion: *our study highlights the effectiveness of oral Prednisolone as a first-line therapy in AIHA, with a 76.3% response rate. However, non-responsiveness to steroids remains a challenge, and patient demographics do not seem to directly impact treatment outcomes.*

Keywords: *Autoimmune hemolytic anemia, Prednisolone, complete response, Partial response*

1. INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is characterized by immune mediated hemolysis resulting in the breakdown of red blood cells (RBCs). This process of RBC destruction is mediated by autoantibody and/or complement system, together with activated macrophages, T-lymphocytes and cytokines.[1, 2.]

The serological types of AIHA include warm autoimmune hemolytic anemia (wAIHA), cold agglutinin disease (CAD), mixed type AIHA (mixed AIHA) and paroxysmal cold hemoglobinuria (PCH)[3]. Worldwide estimated incidence of AIHA is 1.77 cases per 100,000 per year, of which wAIHA is the most common form and accounts for about 2/3 of cases[4]. CAD is the second most common form, accounting for approximately 15–20% of AIHA cases[5]. Mixed type accounts for less than 5% cases of AIHA[6].

AIHA clinically presents with acute onset of pallor, jaundice with splenomegaly. Laboratory findings suggestive of AIHA are; raised serum indirect bilirubin, lactate dehydrogenase (LDH), reticulocyte count, reduced hepatoglobin level, spherocytes / polychromasia in peripheral blood film examination and positive DAT using Coomb's reagent[7]. Corticosteroids are generally considered as first line therapy for autoimmune hemolytic anemia with response rate of 70-80%[8,9]. Prednisolone is the preferred corticosteroids given at a dose of 1-2mg/kg body weight orally for at-least 3 weeks until hemoglobin levels rises above 10g/dl. After stabilization of hemoglobin level and reduction in markers of hemolysis, corticosteroids are gradually tapered. Side effects of corticosteroids therapy are cumulative and most patients are symptomatic if treatment is continued at full dose of 1mg/kg for four weeks or more[10].

Jaime et al. (2019) reported an initial response in the form of complete remission in 36/46 (78%) patients[11]. Average response to corticosteroids in this study was documented in 11.5 days. A study carried out in India by Prabhu et al. (2016) reported response rate of 90% (62% complete response, 28% partial response) with oral Prednisolone at 1.5mg/kg[12]. Riumier et al. (2015) reported 43/ 53 patients with AIHA responding well who received Prednisolone at 1-2mg/kg with follow-up duration of 15 ± 3 months.[13] Naithani et al. (2006) from reported 87.5% response with oral Prednisolone[14].

Extensive literature search from international and national search engines show no such study has been carried in Pakistani patients with AIHA. This study is aimed to fill this gap and show response of our patients to first line therapy. This information will be useful in management of AIHA patients and clinicians will be able to guide patients in better manner regarding prognosis of the disease.

2. METHODOLOGY

This Cross-sectional observational study enrolled a total of 80 patients at the Armed Forces Bone Marrow Transplant Center Rawalpindi from 2013 to 2023. Both adult and pediatric Patients (all age ranges) and both genders were included. Patient with cold AIHA, alloimmune hemolytic anemia, drug-induced AIHA and secondary AIHA associated were excluded from the study. Approval from ethical review committee was taken. Written informed consent and detailed history was taken from each patient. All patients were treated with oral Prednisolone 1-2 mg/kg/day in 2-3 divided doses for 3 weeks, with tapering over another 2-6 weeks. The initial response of hemoglobin was assessed on day 14 and subsequently every two weeks until the full response was achieved. If the Hb level dropped during steroid tapering, the steroids were reverted to the preceding dose. Patients were transfused with least incompatible packed red cells with Hb <7 g/dL. Blood samples were collected on each OPD visit for Hb, LDH, retic count and peripheral film.

Direct Antiglobulin test was repeated after 3 weeks of therapy. Response to treatment was graded as per operational definitions;

Complete Response (CR): Hemoglobin level ≥12.0 g/dl in women and ≥13.0g/dl in men without recent transfusion and without features of hemolysis (normal levels of bilirubin, LDH). Partial Response (PR): Hemoglobin level ≥10 g/dl with an increase of at least 2g from baseline and elevated markers of hemolysis. No response: No improvement in Hb level and reduction in markers of hemolysis.

Data for this study was obtained from hospital records. Relevant medical records of patients diagnosed with warm autoimmune hemolytic anemia (AIHA) were accessed, and the necessary data points, including patient demographics, clinical characteristics, laboratory findings, and treatment responses, were extracted.

Subsequently, the collected data was entered and analyzed using statistical software, specifically SPSS version 25. Numerical variables, such as age, duration of response, hemoglobin (Hb) levels, Lactate dehydrogenase (LDH), and indirect bilirubin, were assessed using means and standard deviations (SD). Categorical variables, such as direct antiglobulin test (DAT) results, gender, and response categories (complete response, partial response, and no response), were analyzed in terms of frequency and percentages.

Data was further stratified based on variables like age, gender, duration of response, Hb levels, LDL, total bilirubin, and DAT results. Statistical significance was determined with a p-value set at ≤0.05. The analysis aimed to explore the relationships and correlations between these variables and the response to first-line therapy in patients with warm AIHA.

3. RESULTS

The median age of the patients was 34.5 years, ranging from 1 to 86 years. Among the patients, 38 (47.5%) were male, and 42 (52.5%) were female. Coombs test was positive in 77 (96.3%) patients, indicating immune-mediated hemolysis, while 3 (3.75%) patients had a negative Coombs test despite clinical and laboratory findings consistent with hemolytic anemia. Of the 77 patients who had positive Coombs test, 49 (61.4%) had both direct and indirect Coombs tests positive while 28 (%) had only DAT positive. Autoimmune workup showed 6 (7.5%) patients with positive ANA (Antinuclear Antibody) and 5 (6.25%) with a positive RA factor (Rheumatoid Arthritis factor). Prior to the start of therapy, 61 (76.3%) patients received RCC (Red Cell Concentrate) transfusions. The major symptoms reported by patients included generalized weakness (61.3%), progressive pallor (27.5%), shortness of breath on exertion (21.3%), easy fatigability (20.0%), jaundice (13.8%), and fever (12.5%). Splenomegaly was found in 25% patients, hepatomegaly in 3.8% while hepatosplenomegaly was observed in 17.5% of patients. Nine (11.3%) patients had lymphadenopathy.

Table 1: Demographic data

Characteristics	N (%)	
Age		
>30 Years	35 (43.8)	
>30 Years	45 (56.2)	
Comorbid		
DM	4 (23.5)	
HTN	3 (17.6)	
DM+HTN	6 (35.3)	
COPD	1 (5.9)	
CA Thyroid	1 (5.9)	
CA Breast	1 (5.9)	
CA Bronchus	1 (5.9)	
Lymphadenopathy		
Yes	9 (11.3)	
No	71 (88.7)	
Visceromegaly		
Splenomegaly	20	25
Hepatomegaly	3	3.8
Hepatosplenomegly	14	17.5

Laboratory parameters and their means with standard deviations (SD) are mentioned in Table 2.

Laboratory Parameters	Mean±SD
Hemoglobin	6.080±1.3867
WBC	8.810±3.9677
Platelets	217.1±84.912

Retics count	12.886±6.8171
Indirect Bilirubin	29.81±13.769
LDH	939.51±568.067

Patient's demographics and their clinical findings are given in table 1. Complete response documented to first line therapy was seen in 36(45%) while partial response was seen in 25 (31.3%). However over-all response was 76.3%. Details of CR, PR and NR are given below in figure 1. The median duration in CR was 15 months (3-96 months) however, 4(11.1%) patients relapsed and received second line therapy. The median duration of PR was 10 months (03-108 months) however 14(56%) patients required second line therapy.

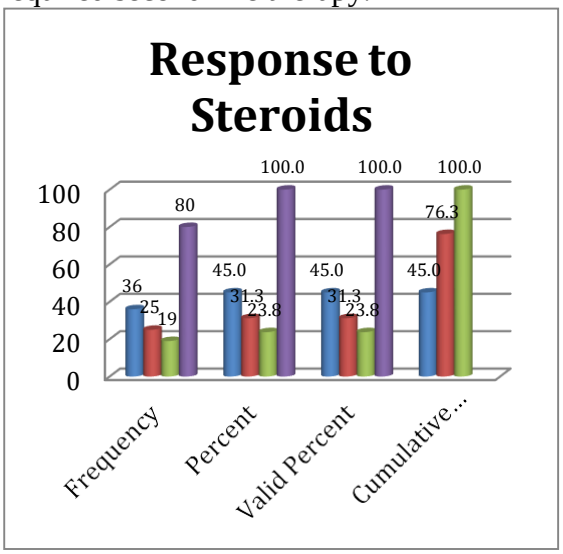

Figure 01: Frequency and Percentage of response to steroid

A correlation analysis was performed to assess the relationship between response to first-line therapy and various variables, including gender, comorbidities, visceromegaly, and RCC transfusion given in **table 03**. The analysis did not reveal any statistically significant correlations. When blood counts were stratified with the response to therapy, no statistically significant correlation was found between different variables and treatment response. During the study period, 61 (76.3%) patients were alive, 12 (15.0%) patients passed away, and 7 (8.8%) patients lost to follow-up. The disease and treatment related death was seen only in 8(10%) patients.

Table-3 Correlation of Response with different variables

Response to first line				
	Complete Response	Partial Response	No Response	P-Value
Gender				
F	16	16	10	0.323
M	20	9	9	
Comorbid				
Yes	5	6	6	0.288
No	31	19	13	
Visceromegaly				
Yes	15	11	11	0.499
No	21	14	8	
Visceromegaly Category				
No	21	14	8	0.323
Hepatomegaly	0	2	1	
Splenomegaly	9	7	4	
Hepatosplenomegaly	6	2	6	
RCC				
Yes	28	18	15	0.830
No	8	7	4	

4. DISCUSSION

Autoimmune Hemolytic Anemia (AIHA) is a complex disorder characterized by the immune system's misguided attack on the body's own red blood cells, resulting in their destruction[15]. This phenomenon involves a diverse array of immune cells and their mediators that contribute to immune-induced hemolysis[16]. AIHA presents a wide range of serological types, with warm autoimmune hemolytic anemia (wAIHA) being the most prevalent, followed by cold agglutinin disease (CAD) and mixed-type AIHA, each contributing to the variability in clinical presentation[17]. Worldwide, wAIHA accounts for nearly two-thirds of AIHA cases, further highlighting its significance[18].

Prednisolone has long been considered the primary treatment for AIHA, making corticosteroids the cornerstone of therapy[19]. The median age of the patients was 34.5 years with 38 (47.5%)

male, and 42 (52.5%) female. In contrast to our study Julien et al from France reported median age of patients 69 years with predominant female patient (55.6%)[20]. Our study, which revealed a 76.3% overall response rate to oral prednisolone, aligns with these findings. Numerous studies have consistently demonstrated the effectiveness of corticosteroids in managing AIHA. Previous research reported response rates of 78% and even 90% among individuals treated with steroids[21]. A separate study conducted in India by Prabhu et al. in 2016 reported an even higher response rate[22]. Three patient in our study had atypical hemolytic anemia with negative coombs test. In similar to our study prabhu et al from India also reported in his study two patients with atypical hemolytic anemia.

However, it remains a puzzle why some patients fail to respond to steroids or experience relapses after an initial positive response[23]. Interestingly, patient-related factors such as age, gender, or underlying medical conditions do not appear to directly correlate with treatment response[24]. Our investigation, consistent with this observation, found no statistically significant association between patient characteristics and treatment response[25]. These findings underscore the complexity of AIHA and the need for personalized treatment approaches. In our study, we observed a complete response in 36 individuals, accounting for 45% of the participants, while a partial response was documented in 25 subjects, constituting 31.3% of the cohort. Notably, in a study by Jaime and colleagues from Mexico, they reported a lower complete response rate at 16% and a partial response rate at 20%, with a median duration of response[26]. In our investigation, the median duration of the overall response was 13 months, which contrasts with Jaime et al.'s findings, where they reported a longer median duration of overall response at 22 months. This variance could be attributed to their incorporation of low-dose rituximab and steroids as part of the first-line therapy[27].

The effectiveness of prednisolone in the Pakistani population, as demonstrated in this study, mirrors global patterns, reaffirming its role as a dependable first-line therapy. However, it's crucial to address the 15% fatality rate observed in our cohort. This underscores the importance of vigilant monitoring and consideration of additional therapeutic strategies, especially when steroids prove ineffective[28].

Despite the valuable insights offered by our study, numerous challenges persist. The precise reasons behind non-responsiveness to steroids remain elusive[29]. Additionally, the risk of adverse effects associated with prolonged steroid use, exceeding four weeks at the recommended dosage, underscores the need to explore alternative or adjunctive therapies that can enhance treatment effectiveness while mitigating side effects[30].

To gain a more comprehensive understanding of AIHA, its diverse patient profiles, disease trajectories, and variable treatment responses, larger multi-center studies are warranted. The unpredictable nature of AIHA necessitates a more holistic approach to treatment and further exploration of therapeutic options beyond corticosteroids.

5. CONCLUSION

In summary, our study on Autoimmune Hemolytic Anemia (AIHA) in Pakistani patients highlights the effectiveness of oral prednisolone as a first-line therapy, with a 76.3% response rate. However, non-responsiveness to steroids remains a challenge, and patient demographics do not seem to directly impact treatment outcomes. Further research into the causes of non-responsiveness and alternative treatments is essential to improve AIHA management. Larger multi-center studies are needed to gain a more comprehensive understanding of this complex clinical entity.

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