Original Article

원발성 온난자가면역용혈빈혈의 치료에 대한 후향적 분석

문홍섭[1]* · 박치영[2]*

[1]국립목포대학교 약학대학, [2]조선대학교병원 내과
(2015년 7월 20일 접수 · 2015년 9월 1일 수정 · 2015년 9월 7일 승인)

Retrospective Clinical Analysis of Treatment for Primary Warm Autoimmune Hemolytic Anemia

Hong Seop Moon[1]* and Chiyoung Park[2]*

[1]College of Pharmacy, Mokpo National University, Jeonnam 58554, South Korea
[2]Department of Internal Medicine, Chosun University Hospital, Gwangju 61453, South Korea
(Received July 20, 2015 · Revised September 1, 2015 · Accepted September 7, 2015)

ABSTRACT

Background: Primary warm autoimmune hemolytic anemia (AIHA) is a relatively rare hematologic disorder resulting from autoantibody production against red blood cells. There has been very few studies about primary warm AIHA in South Korea because of its low incidence. We retrospectively analyzed the treatment outcome of primary warm AIHA. **Method:** We reviewed retrospectively the medical records of 9 primary warm AIHA patients from December 2002 to January 2015. We analyzed the causes and clinical characteristics of primary warm AIHA patients. We retrospectively analyzed the clinical data in electronic medical records for 9 Korean patients with AIHA patients who were diagnosed during the period from December 2002 to January 2015 at the Regional University Hospital in Korea. The study protocol was approved by the Institutional Review Board (IRB #2015−08−007, Chosun University Hospital IRB). **Results:** The mean age was 52 years (range 27~78), the mean hemoglobin level was 5.0 g/dL (range 2.5~6.4 g/dL). All patients received steroids at therapeutic dosages (corticosteroid 1 mg/Kg) as first line treatment. Eight of them showed complete response (5/8, 62.5%) and partial response (3/8, 37.5%), one patient required second−line treatment with rituximab. Two patients who responded first line treatment were relapsed at 86 weeks and 24 weeks after response, respectively. Only one patient of them was retreated with corticosteroid because of anemic symptoms. **Conclusion:** This study indicates that oral corticosteroid is an effective therapy for primary warm AIHA.

KEY WORDS: warm, autoimmune hemolytic anemia, corticosteroids, rituximab

The lifespan of red blood cells is 90-120 days and the hemolytic anemia occurs as the red blood cells are prematurely destroyed due to various reasons. Among them, an Auto Immune Hemolytic Anemia hereinafter called AIHA is a disease that causes premature destruction of red blood cells due to the autoantibodies on the red blood cells and it is one of the hemolytic anemia rarely seen clinically.[1,2] According to serological characteristics, it can be divided into 3 types; warm AIHA due to lgG warm autoantibodies, cold AIHA due to lgM cold autoantibodies and paroxysmal cold hemoglobinuria due to Donath-Landsteiner (lgG) autoantibodies. In addition, depending on the presence or absence of underlying disease, it can be classified as primary and secondary AIHA.[3]

Among them, warm AIHA accounts for 48-70% and the cold AIHA accounts for 16-32%. And the self-expression of

*Correspondence to: Hong Seop Moon, College of Pharmacy, Mokpo National University, 1666 Youngsan-ro, Muan-gun, Jeonnam-do 58554, South Korea
Tel: +82-61-450-2685, Fax: +82-61-450-2689
E-mail: hbsmoon@mokpo.ac.kr
*Co-correspondence to: Chiyoung Park, Department of Internal Medicine, Chosun University Hospital, Gwangju 61453, South Korea
Tel: +82-62-220-3279, Fax: +82-62-234-9653
E-mail: pcy@chosunn.ac.kr

lgG and lgM autoantibodies are called hybrid AIHA, and this is almost identical to the clinical features of warm AIHA and accounts for 7-8% of the total AIHA. In 50-70% of AIHA, it corresponds to the primary AIHA where the cause cannot be identified, and in the case of secondary AIHA, there are drugs, systemic lupus erythematosus, B-cell lymphomas and chronic lymphocytic, etc, as its cause.[4,5]

AIHA appears in extremely diverse ways from subclinical to fatal clinical manifestations and the start of treatment is determined according to the degree of symptoms and the selection of treatment method varies according to the type of AIHA. For warm AIHA, if primary, a steroid is used for the primary therapeutic agent, and for secondary, treatment methods can vary according to the underlying disease. In the case of cold AIHA, steroid and Spleen Hysterectomy is often ineffective, thus underlying disease is treated by avoiding the exposure to the low temperature and by maintaining a warm environment.[2,3] A steroid is used for the primary treatment of primary warm AIHA with initial reaction rate of 70-80%, domestic reports are rare and long-term observation was not made.[1,5] Therefore, the authors have tried to report the response rate and long-term elapses in the origin targeting the patients undergoing a diagnosis and treatment due to primary warm AIHA.

Methods

Study Subject

Study subjects were 9 patients having primary warm AIHA without underlying disease selected among the patients diagnosed with warm AIHA at Chosun University Hospital from December 2002 to January 2015. Analysis was made using an electronic medical record; EMR of 9 female patients diagnosed with warm AIHA, and the collection of all study materials were made after being approved by the IRB Committee (Institutional Review Board #2015-08-007, Chosun University Hospital IRB).

Among the hemolytic anemia, the diagnosis was made on the case showing positive results and lgG warm autoantibodies in the Coombs test which is essential for AIHA diagnosis and those without underlying disease before the diagnosis and during the observation. Hematologic findings and the treatment responses before and after the treatment were analyzed retrospectively.

Treatment Response Evaluation Criteria

Due to the lack of unified international response criteria, hemoglobin criteria among the treatment response of aplastic anemia were used (Table 1).

1) Complete response: When the hemoglobin is maintained

Table 1. Response criteria for AIHA are classified as follows.

Classification	
Complete response (CR)	A stable hemoglobin level of > 12 g/dL, no requirement for transfusion, and absence of clinical and laboratory signs of hemolysis
Partial response (PR)	A rise in hemoglobin levels of > 2 g/dL, no or reduced transfusion requirement, and improvement of clinical and laboratory signs of hemolysis
No response (NR)	< 30% improvement of clinical and laboratory signs of hemolysis

Table 2. Clinical characteristics and clinical course.

Case No.	Age/Sex	Hb (g/dL)	Response	Response duration (weeks)	Relapse
1	27/F	2.5	NR → 2PR → 5CR	32	YES
2	46/F	3.9	2PR	86	YES
3	72/F	6.4	4PR → 14CR	12	YES
4	46/F	6.4	3PR → 4CR	40	NO
5	46/F	6.4	1PR → 3CR	38	NO
6	63/F	5.7	4PR → 12CR	40	NO
7	78/F	5.1	1PR → 3CR	5	NO
8	66/F	3.7	2PR	4	NO
9	27/F	5.1	3PR	52	NO
Average	52.3	5.0		34.3	

Hb (Hemoglobin, g/dL); PR (Partial response); CR (Complete response); NR (No response)

at 12 g/dL or more

2) Partial response: Without requiring transfusion, when the hemoglobin has increased by more than 2 g/dL compared to before the treatment.

Results

Clinical characteristics of the patient

During the diagnosis, the average age was 52 (27~78) and they were all females. The average hemoglobin value before the treatment was 5.0 g/dL (2.5~6.4 g/dL) (Table 2).

Response on the treatment

1 mg/kg of steroid was administered for the initial treatment. In the Case 1 where there was no response for the initial treatment, rituximab (375 mg/m^2 weekly $\times$ 4) was administered.

The reaction rate was 89% as 8 out of 9 people have shown a response in the initial treatment with 3 partial response and 5 complete response. 8 people who have shown reaction had a partial response after 2.5 average week (1~4), and in the case of a complete response, a complete response was shown after 7.2 average week (3~14) after the treatment. Case 1 which have shown no response until the 2nd week had 2.5 g/dL of hemoglobin value with no increase in the hemoglobin value even after the red blood cell transfusion, thus rituximab was administered for 2 weeks due to severe symptoms of anemia. A partial response was shown after 2 weeks of administration and a complete response was shown after the 5th week. Response maintaining period for 8 people was 34 weeks average (4~86) from the point of initial response.

The recurrence rate was 25% as 2 out of 8 people who have

Fig. 1. Clinical course of primary warm autoimmune hemolytic anemia patients.

shown reaction to initial steroid treatment had recurred. Recurrence patients were 3 people and the recurrence occurred at 12th and 86th week respectively from the initial response point. With no response to the steroid, the patient who was administered with rituximab also had a recurrence after 32 weeks. Case 1 and 3 was maintained with 8 g/dL of hemoglobin without any anemia-related symptoms so the observation was made. Only the hemoglobin of Case 2 had reduced to below 6 g/dL with the occurrence of anemia symptoms, thus 0.5 mg/kg of steroid was re-administered. A partial response was shown on the 2nd week and a complete response was shown on the 8th week (Fig. 1).

Discussion

Auto Immune Hemolytic Anemia hereinafter called AIHA is a disease that causes premature destruction of red blood cells due to the autoantibodies on the red blood cells and it is one of the hemolytic anemia rarely seen clinically.[1,2] In general, according to the type of antibody, it can be divided into 3 types; warm AIHA due to lgG warm autoantibodies, cold AIHA due to lgM cold autoantibodies and paroxysmal cold hemoglobinuria due to Donath-Landsteiner (lgG) autoantibodies. Warm AIHA is most common with 48-70% followed by cold AIHA with 16-32% and the mixed AIHS having both lgG and lgM autoantibodies accounts for 7%, and the paroxysmal cold hemoglobinuria with case report level has been reported very rarely. In addition, depending on the presence or absence of underlying disease, it can be classified as primary or secondary AIHA. For the cause of secondary AIHA, autoimmune diseases such as lymphoproliferative disease and systemic lupus erythematosus are most common and approximately 50% of AIHA corresponds to secondary AIHA.[3,4]

Clinical symptoms of AIHA are very diverse according to the degree of hemolysis with a slow progress, and jaundice and anemia symptoms such as general prostration, difficulty in breathing and dizziness, and so on are shown as the main symptoms. In the inspection findings, according to the destruction of the red blood cells, indirect bilirubin, LDH and reticulocytes have increased and the haptoglobin had decreased. A Coombs test is important for diagnosing the autoimmune hemolytic anemia and non-immune hemolytic anemia. Coombs test is a method of recognizing the antibody or complement in the serum or on the surface of red blood cells, where most of AIHA is shown to be positive but rarely, a negative can be seen.
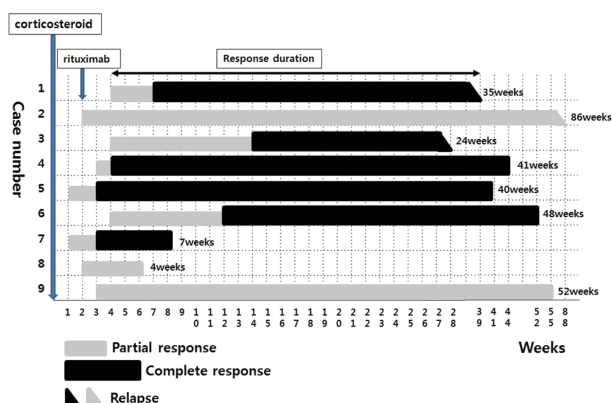
A negative can be shown when the numbers of autoantibodies attached to the surface of red blood cells are small or when the autoantibodies are lgA, or when there is a technical failure of the test.[3,6]

The start of AIHA treatment is determined according to the degree of symptoms of hemolytic anemia, and the selection of treatment method varies according to the type of AIHA. For primary warm AIHA, a steroid is used as the primary therapeutic agent and for secondary, the treatment method may vary depending on the underlying disease. In the case of cold AIHA, steroid and Spleen Hysterectomy is often ineffective, thus underlying disease is treated by avoiding the exposure to the low temperature and by maintaining a warm environment.[3,4]

Steroid inhibits the macrophages of spleen from recognizing the lgG and Fc receptor of the complement and prevents the phagocytosis of red blood cells and shows its effectiveness by inhibiting the formation of autoantibodies on the red blood cell in the body. Initial response rate is also known as 70-80%, and in general, it is started with 1~2 mg/kg of steroid to determine the response status based on the increase in hemoglobin increase and the decrease in reticulocytes.[3,4] Mostly, it shows a response within 3 weeks, and when the hemoglobin level increases to 10 g/dL, is decreased by 5-0 mg per week, and when it reaches 10 mg per day, the capacity is reduced over several months. When the side effects of steroid are severe or requiring a high dose of steroid in order to normalize hemoglobin or when the steroid is not responding, a splenectomy is required. When a splenectomy is denied or when there is no response to a splenectomy, immunosuppressants such as cyclophosphamide, azathioprine and cyclosporine can be used, or Rituximab[®] anti-CD20 monoclonal antibody which is effective for autoimmune diseases can be used.[6-9]

Recently, Roumier M,[10] et al, have shown 94% response rate to steroid among the 23 primary warm AIHA patients with a complete response of 69%, and it recurred in 45% undergoing rituximab or splenectomy and the average maintaining period was reported as 3.6 years. Among 19 patients having only the warm AIHA, the domestic Back SW, et al, has shown the response rate of 93.8% (complete response 25%, partial response 68.8%) one month after the initial treatment. In this study, 89% (complete response 37.5%, partial response 62.5%) response rate was shown after one month of initial treatment, and for the maximum response, 37.5% was a partial response and 62.5% was a complete response. The recurrence rate was 25% as 2 out of 8 people who have shown response to the

initial treatment had a recurrence at 24th and 86th week respectively. Among them, one patient who required a treatment has shown a partial response to the re-administration of steroid. Another person who did not show any response to the steroid has shown a partial response on the administration of Rituximab after the 5th week with a recurrence on the 35th week but only an observation was made because no symptoms were shown. Response maintaining period was 37.8 average weeks (4-86 weeks). Although the response rate was approximately 90% and similar to the domestic and international studies but the domestic response maintaining period was shorter than 3.6 years of other countries. Due to a small number of cases, the reasons cannot be accurately estimated, and a prospective study targeting more patient groups are thought to be required.

Conclusion

As a result of analyzing retrospective case reports on the 9 patients having primary warm autoimmune hemolytic anemia, the response rate of steroid during the treatment was 89%. This is similar to the response rate of 90% reported by other studies. Response maintaining period showing the response was 34 average weeks (4-86 weeks) from the initial response point, but, due to a small number of cases, a study targeting more patient groups is thought to be required.

Acknowledgements

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