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Research Article

Realistic efficacy of oxymetholone compared with rabbit-antithymocyte globulin for severe acquired aplastic anemia

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ABSTRACT

Although anti-thymocyte globulin with cyclosporine (rATG/CsA), bone marrow transplantation, and eltrombopag are the cornerstone treatment for severe and very severe aplastic anemia (SAA/vSAA), oxymetholone remains beneficial in ineligible patients. This study was conducted to compare the realistic effectiveness of oxymetholone with rATG/CsA in SAA/vSAA. The primary outcome was 2-year overall response rate (ORR). Factors associated with ORR were evaluated using a logistic model. The secondary outcomes were 3-, 6-, 12- and 18-month ORR and overall survival (OS). Kaplan-Meier estimates were calculated for OS and risk factors related to PFS were assessed using Cox proportional hazards models. A total of 47 eligible patients and 53 treatment periods were included. The ORR of rATG/CsA treatment was significantly higher than for oxymetholone (46.7 vs. 15.8%, p=0.025). With a median follow-up time of 20.4 months, OS among patients initially treated with rATG/CsA and oxymetholone were 78.6% and 28.5%, respectively (p=0.001). However, patients responding to oxymetholone had a longer median survival compared with patients having no response to rATG/CsA as front-line treatment (11.8 years and 2.9 years, respectively) although a statistically significant difference between the two groups was undetected (p=0.092). Severity of disease and response to treatment were significant predictors of mortality from AA. This study revealed the superiority of rATG/CsA in response and survival improvement. However, the patient's situation, needing to start oxymetholone as front-line treatment, oxymetholone, still had improved survival among the responders. Patients unresponsive to oxymetholone within 3 months should be switched throughout the treatment.

Keywords:
Hematologic disorder, Acquired aplastic anemia, Oxymetholone, Androgens, Anti-thymocyte globulin, Immunosuppressive therapy

1. INTRODUCTION

Bone marrow transplantation (BMT) is recommended as first-line treatment for BMT-eligible severe aplastic anemia (SAA) patients, whereas antithymocyte globulin with cyclosporine (ATG/CsA) is considered for patients who are ineligible for BMT or not responding to BMT[1]. Eltrombopag, which has shown satisfactory hematologic response among patients with AA[2] is a recommended alternative therapy, but remains out of reach for most of our patients due to high treatment cost. However, deciding about treatment depends on government policy, health insurance, availability of donors for hematopoietic stem cell transplantation (HSCT) and patients' conditions. Although ATG/CsA is superior to androgens in response rate and survival improvement[3], oxymetholone remains an alternative therapeutic option for some patients who cannot access treatment with ATG/CsA. Oxymetholone's probable mechanisms of action include stimulating erythropoiesis, increasing telomerase activity and extending the lifespan of $CD34^+$ stem cells[4-5]. Moreover, oxymetholone treatment causes only minor side effects, is more convenient for outpatients and has a lower cost.

Over the last decade, reimbursement was an important

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barrier to ATG treatment in Thailand. Patients with Social Security Scheme and Universal Health Care Coverage had to copay for treatment and experienced economic problems. The result of barriers has led to limited access to appropriate treatment. Today, most treatment costs for rabbit-ATG (rATG) is under the responsibility of the government[6]. This has resulted in an increasing number of patients with SAA obtaining access to suitable and affordable treatment. However, oxymetholone remains the initial treatment for those patients with exceptions such as infection complications. This clinical study aimed to compare the realistic effectiveness of oxymetholone with rATG/CsA among patients with SAA and very severe aplastic anemia (vSAA).

2. MATERIALS AND METHODS

2.1. Study design and participants

This retrospective study included patients 15 years of age or older receiving a diagnosis of idiopathic SAA or vSAA and receiving initial treatment with oxymetholone or rATG/CsA at Songklanagarind Hospital between January 2004 and December 2019. SAA was defined as having a bone marrow cellularity <25% (or 25 to 50% with <30% residual hematopoietic cells), plus at least two of the following: absolute neutrophil count (ANC) $<0.5\times10^9$/L, platelets $<20\times10^9$/L and reticulocyte count $<20\times10^9$/L [1]. If the patients had ANC $<0.2\times10^9$/L, they would be assessed as having vSAA[1]. Because treatment with androgens and ATG take at least one month to show a valuable therapeutic response[7-9], patients who died within the first month after beginning treatment were excluded. Moreover, patients receiving a diagnosis of drug-induced AA or having incomplete data of diagnosis or treatment were also excluded.

The study determined the required sample size for the comparison of two proportions, considering an overall response rate (ORR) from previous studies by Pizzuto et al.[10], which reported ORR of 10% for oxymetholone in SAA/vSAA, and Zhang et al.[11], which presented ORR of 66.7% for rATG/CsA at a significance level of 0.05 for a two-sided test. Based on these variables, 11 patients were required per group. Accounting for a 10% possible dropout rate, 13 patients were enrolled.

2.2. Treatment protocols

According to the recommended treatment guidelines[12], patients were treated with oxymetholone 2-5 mg/kg/day in the oxymetholone group or rATG 2.5-3.5 mg/kg/d intravenously on days 1 to 5, then CsA 5 mg/kg/day in the rATG/CsA group to maintain a proper CsA level with 200 to 400 µg/L. A test dose of rATG was administered to all patients before infusion to prevent anaphylaxis. Supportive treatments including transfusion therapy, prevention and treatment of infection, granulocyte macrophage colony-stimulating factor (G-CSF) and iron chelating therapy were considered if indicated. This study was approved by the Human Research Ethics Committee of Songklanagarind Hospital, Prince of Songkla University (approval number: REC.62-026-19-9).

2.3. Response to treatment

Complete response (CR) was defined as transfusion independent with all of the following conditions: hemoglobin >10 g/dL, platelets $>100\times10^9$/L, and ANC $>1\times10^9$/L at least four weeks apart[13]. The criteria for partial response (PR) was blood transfusion independent and no longer meeting the criteria for SAA or CR. Patients still dependent on blood transfusion, still fulfilling the criteria for SAA/vSAA or death without response were defined as nonresponse. Relapse was recorded whenever patients received a blood transfusion or died after response to treatment.

2.4. Outcomes and statistical analysis

We reported the primary outcome as ORR, including CR and PR, two years after initiating each medication. Intention-to-treat analysis was performed. However, ORR at 3, 6, 12 and 18 months after initiating treatment were set as secondary outcome. Moreover, OS was evaluated as well. Because of all data were gathered from the hospital database, missing baseline hemoglobin and red blood cell data were found among six patients. In these cases, we replaced the missing values using the maximum likelihood equation.

Baseline characteristics were reported as numbers with percentage and median with IQR for categorical and continuous data, respectively. The factors related to overall response was evaluated in univariable and multivariable analysis using logistic regression models and presented as odds ratio (OR) and 95% confidence intervals (95% CI). OS was analyzed using the Kaplan-Meier method and compared using the log-rank test. The timepoint of event and censor for survival analysis were defined as the start of treatment initiation until death and the start of treatment initiation until the last date of follow-up or at the study-end date, respectively. Factors associated with mortality were determined using the Cox proportional hazard model, and a *P*-value less than 0.05 was considered statistically significant.

3. RESULTS

3.1. Patient characteristics

A total of 47 patients with idiopathic severe and vSAA were recruited for this study. Thirteen of these patients were given rATG/CsA as a first-line treatment,

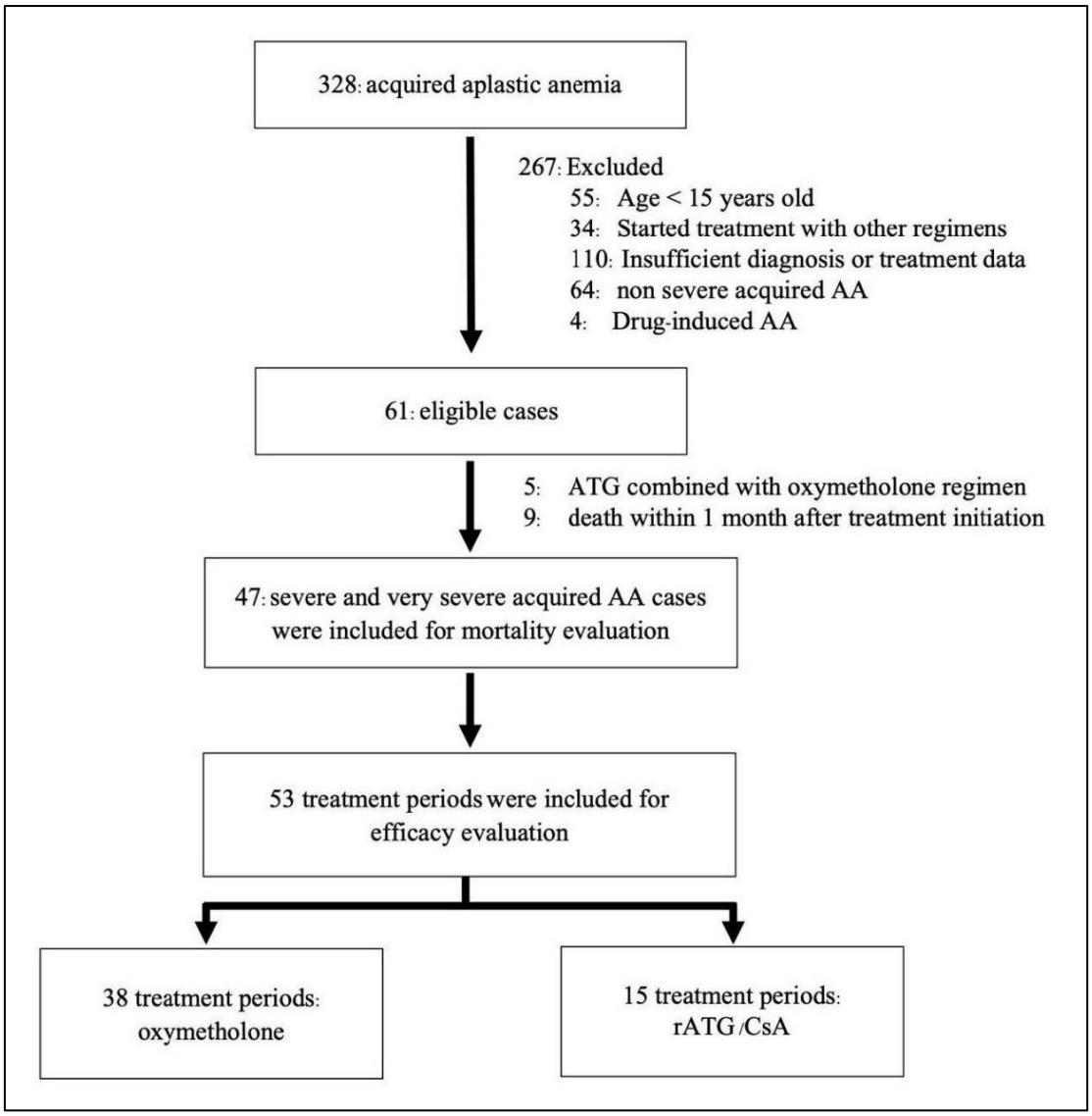

Figure 1. Flow diagram of the study participants.

Table 1. Baseline characteristics of patients.

Characteristic	Total (N=53)		Oxymetholone (N=38)		ATG + CsA (N=15)		*p* value
n (%)							
Male	25.0	(52.8)	22.0	(57.9)	6.0	(40.0)	0.178
Severity (very severe); n (%)	14.0	(26.4)	10.0	(26.3)	4.0	(26.7)	0.616
Continuous variables, median (IQR)							
Age	46.7	(36.2)	46.6	(36.6)	46.7	(36.3)	0.851
Time from symptom to diagnosis (months)	1.4	(3.1)	1.1	(1.9)	3.1	(4.9)	0.173
Time from symptom to treatment (months)	2.6	(5.8)	2.3	(4.1)	6.1	(6.0)	0.014
Time from diagnosis to treatment (months)	0.9	(1.7)	0.5	(1.2)	2.1	(4.5)	0.001
Marrow cellularity (%)	5.0	(5.0)	7.6	(5.0)	5.0	(5.0)	0.496
Baseline hemoglobin (g/dL)	7.2	(2.7)	7.2	(2.7)	7.6	(2.5)	0.388
Baseline ANC (N/μL)	316.0	(446.4)	297.5	(453.2)	455.4	(555.4)	0.435
Baseline platelet (N/μL)	7000.0	(8,000.0)	7,000.0	(7,000.0)	5,000.0	(10,000.0)	0.165
Baseline ARC (N/μL)	10,234.0	(17,225.1)	8,110.0	(17,425.6)	15,250.0	(25,663.0)	0.040
Transfusion prior treatment (unit/month)							
PRC	3.0	(5.0)	4.0	(3.0)	3.0	(7.0)	0.414
Platelet	8.0	(9.0)	8.0	(6.0)	12.0	(18.0)	0.072

IQR: interquartile range, CBC: complete blood count, ANC: absolute neutrophil count, ARC: absolute reticulocyte count, PRC: packed red cells

and 34 were given oxymetholone. However, three non-responders of the oxymetholone group were switched to rATG/CsA treatment, whereas three of the rATG/CsA group were shifted to oxymetholone due to nonresponse or experiencing adverse events with nonresponse. As a result, eligible patients received 53 treatment periods (Figure 1).

For a total of 53 treatment periods, males comprised 57.9% of the oxymetholone group and 40% of the rATG/CsA group. The median age of patients and percent of severe AA were similar between the groups, 46.6 vs. 46.7 years and 73.7 vs. 73.3%, respectively. No difference of hematologic characteristics was found between the two groups except the median of absolute reticulocyte count (ARC) which was 15,250/μL for the rATG/CsA group and 8,110/μL for the oxymetholone group, p=0.040. Baseline characteristics are summarized in Table 1.

3.2. Response

Of the 53 treatment periods, 38 patients received oxymetholone and 15 patients were included in the rATG/CsA group. However, one patient did not receive CsA because he developed febrile neutropenia with a severe multiple organ infection, and the patient passed away as a result. Ten (71.4%) of the 14 patients who received CsA achieved the appropriate CsA level during the course of treatment. Four patients were unable to reach their CsA goal, including three patients who discontinued CsA due to severe headache, seizure, and transaminitis within 10 days, 1.6 months and 2.6 months after initiation, respectively, and one patient who had a low level of CsA. However, these patients received the recommended dose of CsA during their therapy. The two-year ORR was 62.5% (20% of CR and 42.5% of PR). Two-year ORR for the rATG/CsA and oxymetholone groups were 46.7 and 15.8%, respectively. The ORR of rATG/CsA treatment was significantly higher than that for oxymetholone at 3, 6, 12 and 18 months after treatment initiation (3 months: 40.0 vs. 5.3%, p=0.004; 6 months: 40.0 vs. 13.1%, p=0.040; 12 months: 46.7 vs. 15.8%, p=0.025; 18 months: 46.7 vs. 18.4%, p=0.042). The median time to respond were 3.0 months and 8.2 months for the rATG/CsA group and oxymetholone group, respectively (p=0.027). Additionally, two patients receiving the second course of rATG remained nonresponsive to treatment. Of those who responded to treatment, disease relapse was documented among three patients of the oxymetholone group. One patient needed to receive platelet transfusion within seven months after achieving CR and two patients had progressive disease and died at 4.6 and 7.7 months after treatment response. Compared with oxymetholone, no relapse or disease progression was observed among the patients with response to rATG/CsA.

Four nonresponding patients in the initial rATG/CsA group needed to change treatment to oxymetholone. One patient became a partial responder to oxymetholone within five months after initiating treatment, whereas none of the remaining patients responded to treatment. For the initial oxymetholone group, three patients not responding to treatment had to change to rATG/CsA. However, all those patients were still non-responders after switching regimen.

3.3. Overall survival

With the median follow-up time of 20.4 months, OS was 42.6% with a median survival of 2.0 years. Independently assessed median survival was not reached in the rATG/CsA group and at one year in the oxymetholone group (Figure 2A). The one- and two-year OS was 40.5% and 28.5%, respectively, among patients initially treated with oxymetholone. For those who started treatment with rATG/CsA, the one- and two-year OS were the same, 78.6%.

Among responders, no significant difference was found in the median survival between patients initially treated with rATG/CsA and those treated with oxymetholone (p=0.224). Moreover, patients with response to oxymetholone had a longer median survival compared with patients not responding to rATG/CsA as front-line treatment (11.8 years vs. 2.9 years, respectively), although a significant difference between the two groups was undetected (p=0.092) (Figure 2B).

Twenty-seven (57.5%) deaths were reported, 3 in the rATG/CsA initiation group and 24 in the oxymetholone initiation group. The majority of patients (15) died from infections, five deaths resulted from bleeding complications, three from non-AA related death and four were unknown.

3.4. Factors associated with response at two-year follow-up and mortality

Univariable analysis showed that baseline ANC ≥500/μL and treatment with rATG/CsA was associated with two-year ORR. However, only ANC ≥500/μL (OR= 3.89, 95% CI: 1.017-14.913, p-value=0.047) exhibited a statistically significant association with two-year ORR in multivariable analysis, whereas treatment with rATG/CsA showed a higher response trend than oxymetholone treatment (OR=3.91, 95% CI: 0.988-15.443, p-value=0.052) (Table 2).

In the survival analysis, an age of 60 years or older, ANC <200/μL, initial treatment with oxymetholone, and lack of response to treatment were identified as influencing factors in the univariable analysis, whereas vSAA showed a higher mortality trend. The variables with p-value <0.2 in univariable analysis were included in the multivariable analysis, except severity, which was reflected by ANC. Two variables, initial treatment with oxymetholone and lack of response to treatment, remained significant predictors for mortality (Table 3).

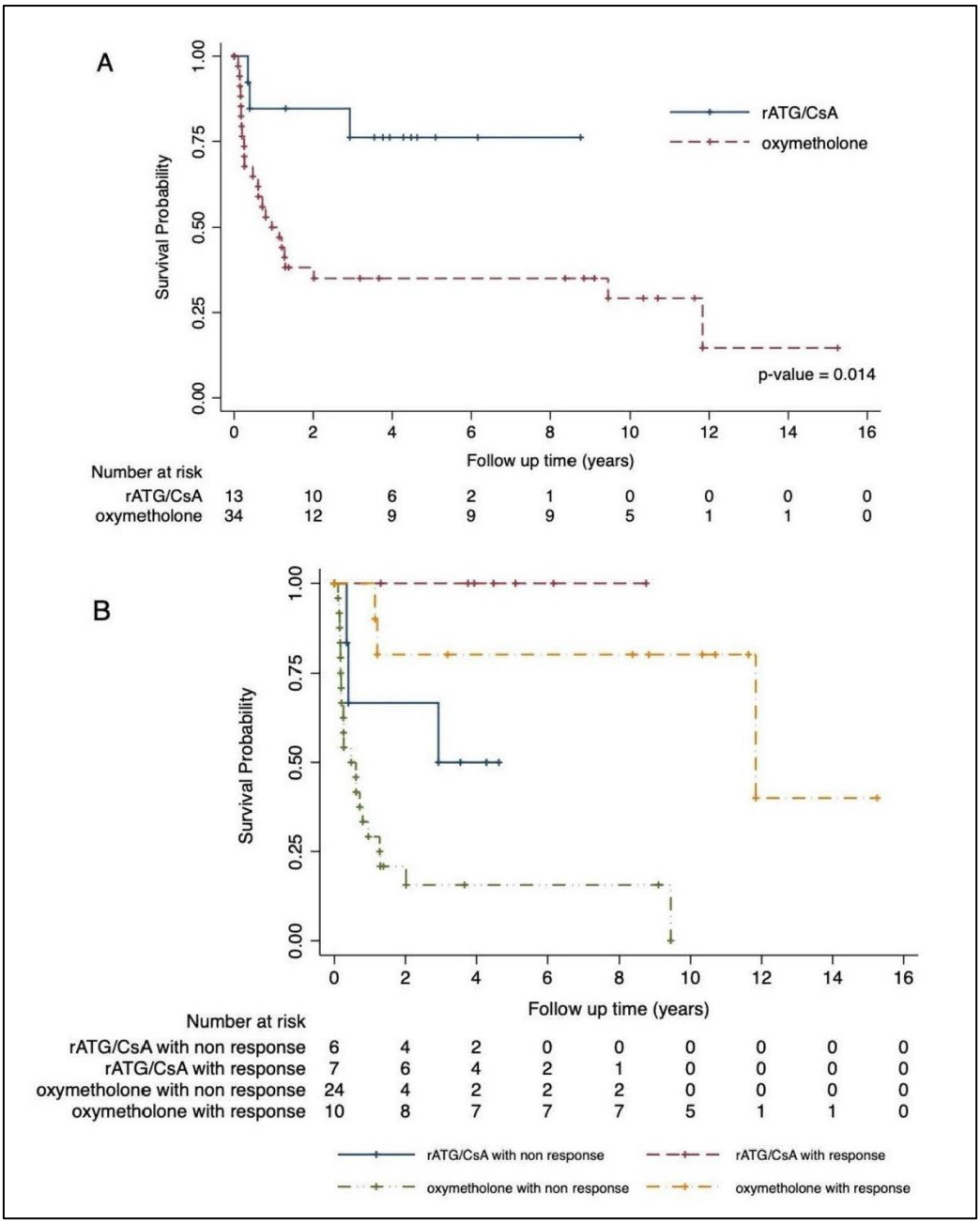

Figure 2. Kaplan-Meier plots of overall survival for patients with SAA/vSAA, stratified by treatment (A) and by treatment and response (B).

Table 2. Factors associated with 2-year overall response in SAA/vSAA.

Factors	Univariable analysis			Multivariable analysis		
	Crude OR	95% CI	*p* value	Adjusted OR	95% CI	*p* value
Sex: female	1.17	0.344-3.961	0.805			
Age: <60 years	0.55	0.129-2.303	0.409			
Severity: severe	0.69	0.162-2.973	0.623			
Interval between diagnosis and treatment: >1 month	1.05	0.310-3.570	0.934			
Baseline Hb: ≥6.5 g/dL	0.90	0.250-3.237	0.872			
Baseline platelet: ≥10000 /μL	1.50	0.490-5.238	0.525			
Baseline ANC: ≥500 /μL	3.87	1.076-13.900	0.038	3.89	1.017-14.913	0.047
Baseline ARC: ≥30000 /μL	1.50	0.320-7.030	0.607			
Baseline PRC transfusion: <2 units/month	0.83	0.241-2.878	0.773			
Baseline platelet transfusion: ≥6 units/month	1.05	0.310-3.570	0.934			
Treatment: rATG + CsA	3.87	1.051-14.282	0.042	3.91	0.988-15.443	0.052

Hb: hemoglobin, ANC: absolute neutrophil counts, ARC: absolute reticulocyte counts, PRC: packed red cells

Table 3. Prognostic factors associated with mortality among patients with SAA/vSAA.

Factor	Univariate analysis			Multivariate analysis		
	Crude HR	95% CI	*p* value	Adjusted HR	95% CI	*p* value
Sex: female	1.06	0.488-2.319	0.876			
Age: ≥60 years	2.31	1.059-5.021	0.035	2.20	0.949-5.111	0.066
Severity: very severe	2.00	0.908-4.404	0.085			
Baseline Hb: ≥6.5 g/dL	1.27	0.551-2.927	0.574			
Baseline platelet: ≥10000 /µL	1.10	0.504-2.399	0.811			
Baseline ANC: <200 /µL	2.66	1.218-5.796	0.014	2.21	0.948-5.169	0.066
Baseline PRC transfusion: <2 units/month	1.58	0.739-3.363	0.240			
Baseline platelet transfusion: <6 units/month	1.47	0.669-3.215	0.339			
Treatment: oxymetholone	4.05	1.209-13.592	0.023	3.94	1.066-14.612	0.040
Response to treatment: nonresponse	13.91	3.220-60.053	<0.001	10.87	2.482-47.631	0.002

Hb: hemoglobin, ANC: absolute neutrophil counts, PRC: pack red cell

Table 4. Adverse events following oxymetholone or rATG/CsA treatment.

Adverse events	oxymetholone (N=38), n(%)	rATG ± CsA (N=15), n(%)
Infections	21 (55.3)	12 (80.0)
Febrile neutropenia	11 (29.0)	12 (80.0)
Hepatic complications	16 (42.1)	6 (40.0)
Bleeding complications	5 (13.2)	3 (20.0)
Serum sickness	0	3 (20.0)
Allergic reactions	0	2 (13.3)
Virilizations	2 (5.3)	0
Others	3 (7.9)*	5 (33.3)**

***** palpitation: 1 case, acute MI secondary to MI: 1 case; severe headache: 1 case
****** severe headache: 2 cases; cyclosporine induced creatinine rising: 1 case; thrombophlebitis: 1 case, cyclosporine induced seizure: 1 case

3.5. Safety

Thirty-eight patients developed adverse events with 101 adverse events being reported (58 events for oxymetholone and 43 events for rATG/CsA). The adverse events are shown in Table 4. Infections were the most common adverse events in both groups. Eighty percent of patients receiving rATG/CsA developed febrile neutropenia compared with 29% of patients treated with oxymetholone. Although premedication and test dose for anaphylaxis prophylaxis was performed, serum sickness and allergic reactions were found at 20 and 13.3%, respectively. The proportion of patients experiencing hepatotoxicity was similar in oxymetholone (42.1%) and rATG/CsA (40%). Most patients experiencing oxymetholone induced hepatotoxicity could continue treatment using the same dose. Only about one third of those patients needed to decrease the dose of oxymetholone due to hepatotoxicity, whereas 4 of 6 patients in the rATG/CsA group had to discontinue CsA.

4. DISCUSSION

ATG/CsA is an immunosuppressive therapy showing a good response rate and an increased survival rate among patients who ineligible for bone marrow transplantation[14-16]. ATG has been shown to be superior to androgens in improving hematologic response and OS[3]. However, over a decade ago, some patients could not reach to rATG due to financial problems. Today, rATG is included in the Thai National List of Essential Medicine (NLEM), so the majority of patients can receive rATG as first-line treatment for SAA/vSAA. However, oxymetholone is an appropriate treatment for patients with serious infection.

In the study, we evaluated the realistic efficacy of oxymetholone compared with rATG/CsA. As expected, rATG/CsA had a higher response rate with ORR of 46.7% at two-year follow-up, whereas only 15.8% in the oxymetholone group achieved overall response. The response rate was similar to another study reporting ORR of androgens was 10%[10]. The ORR of rATG/CsA at 6 months and 18 months of treatment was similar to related studies, reporting an ORR of 45 and 50.9%, respectively[17-18]. However, ORR of rATG/CsA at two-year follow up was lower than the Asian multicenter retrospective study reporting ORR of 73.9%[19]. The response of rATG/CsA increased by approximately 20% after the second course [17,20]. Nevertheless, our patients who were unresponsive to the first course of rATG/CsA did not show any response after the second course of rATG/CsA was given. The

varied response rate could be caused by the difference of response criteria definition. However, it exhibited a minor impact on clinically meaningful findings[21].

The median response time of rATG/CsA ranged from 3.0 to 4.9 months[7,9,13] and the median response time for oxymetholone ranged from 3.0 to14.8 months[22-23]. In our study, the median response time was similar to what had been previously reported. The median response time of the rATG/ CsA group and the oxymetholone group was 3 months and 8.2 months, respectively.

The interval between diagnosis and treatment, as well as the period between symptom and treatment, affects response and survival outcomes regardless of the therapeutic option chosen[24]. A shorter interval between diagnosis and treatment was related to better response and survival[25-27]. However, due to the treatment of serious infections prior rATG initiation and the need for hospitalization, several of our patients received delayed rATG treatment and had significantly longer symptom-treatment and diagnosis-treatment interval than the oxymetholone group, which might have influenced the outcomes. Nevertheless, after adjusting for these intervals, rATG/ CsA regimen remained significantly associated with a better response (OR=0.18, *p*-value=0.025 95%CI: 0.040-0.807). Additionally, if rATG could be started earlier, ORR might be higher. Moreover, the related study showed a significantly higher response rate with ATG/CsA compared with ATG alone[28]. In the study, three patients received rATG alone due to adverse effects of CsA. However, two responded to the treatment with rATG alone and relapse did not occur.

Wash-out period is another factor that should be concerned. Without wash-our period, the outcome could be misinterpreting because of the previously treatment effects. However, this is a retrospective study which revealed real-world treatment. A wash-out period with only supportive treatments in SAA/vSAA who have failed to response to treatment or developed complications was not practicable. Moreover, according to prior studies' finding, the median response times for rATG/CsA and oxymetholone 3.0 to 4.9 months[7,9,13] and 3.0 to 14.8 months[22-23], respectively. Likewise, all patients who needed to change treatment in this study did not respond to the treatment within three months of its initiation. As a result, the wash-out period had no effect on the study's outcomes.

ANC >500/μL and ATG/CsA treatment were identified as predictive factors for treatment response in AA[13,29]. Similarly, this association was found in this study. However, a significant association between rATG/CsA and response found in this study was only in the univariable analysis, while a significant lower response rate in the anabolic steroids group compared with ATG/CsA was presented in the related study (OR=0.57, 95% CI: 0.33-0.98, *p*=0.039) [30]. According to another study, a baseline absolute reticulocyte count above 30,000/μL was a factor affecting response to treatment[29]. However, we could not find this association in our study. These findings might have resulted from the limited sample size which reduced the power of study.

OS has been reported as about 11% for patients with SAA/vSAA receiving androgens[10], whereas two-year OS in SAA/vSAA with rATG/CsA was reported ranging from 54.8 to 93% and 5-year OS was 64%[9,13,19,29-30]. The difference in survival rate depended on follow-up time and severity. In our study, two-year OS was 71.4% for patients with SAA treated with rATG/CsA compared with 23.8% for patients treated with oxymetholone. Unsurprisingly, the median survival in the oxymetholone group was shorter than that in the rATG/CsA group. However, patients responding to treatment had longer survival times in both groups. As shown in this study, patients responding to oxymetholone had longer survival times than those not responding to rATG/CsA (11.8 years vs. 2.9 years, respectively). Median survival among patients not responding to oxymetholone was 3.6 months. Accordingly, switching therapy to ATG/CsA is recommended for patients not responding to oxymetholone after a three-month follow-up.

Infection complications are the major threat for patients with AA[9,13,31], although the incidence of infection-related death significantly decreased[32]. The majority of our patients died from infections (55.6%), followed by hemorrhagic complications (18.5), unspecified conditions related to AA (14.8%) and unrelated-causes to AA (11.1%). About one third of the mortality data in this study was collected from a civil registration database. Therefore, data on the definite cause of death may be lacking. However, infections and bleeding complications remain the two main causes of mortality as others have reported.

The risk of death for SAA/vSAA increased with increasing age, as has been presented[13,18,29,30,33]. In our study, age over 60 years was detected as a factor affecting mortality rate, although a significant difference between <60 years and ≥60 years of age was not found after adjusting for variables. ANC is one factor associated with mortality. ANC <500 /mm^3 is a significant risk for infection and related to mortality in AA. ANC <100/mm^3 and 100 to 500/mm^3 were identified as significant prognostic factors for death[29]. Moreover, the neutrophil count reflects the severity of disease. Very severe disease related to ANC <200/mm^3 was one factor influencing mortality [13,19,30,34-35]. Although patients with ANC <200/mm^3 showed only a trend toward higher mortality compared with that of patients with ANC ≥200/mm^3 in multivariable analysis, the association of ANC <200/mm^3 was found using univariable analysis.

This study was limited by its retrospective design. We collected historical data between 2004 and 2019. Because of the retrospective design, missing data due to inadequate registration quality or loss of follow-up can result in information bias. To minimize this effect, the

patients with missing data for diagnosis or severity of disease were excluded. Furthermore, data imputation was performed. We used the maximum likelihood equation to replace missing values in baseline hemoglobin and red blood cell data. However, it did not result in severity misclassification. For loss of follow-up cases, we evaluated the ORR using the most recent information available. However, mortality data from a civil registration database was additionally obtained. Patients who died after the loss of follow-up would be recorded as nonresponse. Moreover, we evaluated ORR using the number of patients remaining in each period. Both investigation revealed the comparable results (Supplementary Material: Table S1). These results could still reflect the realistic efficacy of oxymetholone and rATG/CsA in real-life practice. The small sample size constituted another limitation. Because aplastic anemia is a rare disease and this study has been initiated in single center, the number of patients in our study might be limited. Although this included number had sufficient power to indicate the difference in ORR, it was underpowered to detect a significant association between certain predictive factors and response or mortality outcomes. To identify the prognostic factors associated with response and mortality, a multicenter study with larger sample size is required in the further study.

5. CONCLUSION

In conclusion, combined ATG and CsA remains the treatment of choice for patients with BMT-ineligible SAA/vSAA. However, patients with response to oxymetholone could survive longer than those not responding to rATG/CsA treatment. Thus, in case of limitation in first-line therapy and for patients needing to start oxymetholone as front-line treatment, close monitoring should be performed. Switching therapy to other treatments immediately is recommended when patients could not achieve a response within three months after initiating treatment.

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Conflicts of Interest
All authors declare that they have no conflict of interest.

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Ethics approval
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Conceptualization, P.S., T.P. W.S., T.D., and P.T.; method, P.S., T.P., W.S., T.D. and P.T.; formal analysis, T.P. and P.S.; data curation, T.P., P.S. and W.S.; writing-original draft preparation, T.P. and P.S.; writing-review and editing, P.S. and T.P. All authors have read and agreed to the published version of the manuscript.

Informed Consent Statement
Patient consent was waived due to the retrospective design by the Research Ethics Committee at the Faculty of Medicine, Prince of Songkla University.

Data Availability Statement
No additional data was generated in the study.

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