Original Article

A systematic review and meta-analysis of the safety and efficacy of anti-thymocyte globulin combined with eltrombopag in the treatment of severe aplastic anemia

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Background: When it comes to the treatment of aplastic anemia fever, *the Guidelines for Aplastic Anemia* regards Anti-thymocyte globulin (ATG) combined with eltrombopag as the standard immunosuppressive treatment plan, and ATG is the main mode to treat severe aplastic anemia. A large number of prospective studies and clinical trials have confirmed the clinical application value of eltrombopag in aplastic anemia. Although ATG combined with eltrombopag brings satisfactory treatment results, the safety of long-term use is still unclear. Therefore, more clinical trial studies are needed to verify its safety.

Methods: Literature in the Chinese and English medical databases was searched using the following search terms: "Antithymocyte globulin", "severed aplastic anemia" and "eltrombopag". Patients in the experimental group were administered ATG combined with eltrombopag and patients in the control group received ATG treatment alone. Rev Man5.3 software was used for meta-analysis.

Results: A total of 16 references were included in this meta-analysis. Heterogeneity tests examining total effective rate demonstrated that Chi^2 =4.48, df =15, I^2=0%<50%, and P=1.00>0.01. The effective rate of the experimental group was higher than that of the control group, with odds ratio (OR) =1.90 and 95% confidence interval (CI) 1.35 to 2.68 (Z=3.70, P=0.0002). The heterogeneity test results of the survival rate within 2 years were Chi^2 =3.09, df =7, I^2=0%<50%, and P=0.88>0.01. The survival rate of the experimental group was higher than that of the control group, with OR =2.54, and 95% CI: 1.58 to 4.09 (Z=3.84, P=0.0001). The heterogeneity test results of the mortality rate were Chi^2 =3.49, df =6, I^2=0%<50%, and P=0.75>0.01. The mortality rate of the experimental group was lower than that of the control group, with OR =0.48 and 95% CI: 0.33 to 0.70 (Z=3.84, P=0.0001). The heterogeneity test results of the occurrence of side effects were Chi^2 =0.12, df =3, I^2=0%<50%, P=0.99>0.01. The incidence of side effects in the experimental group was lower than that in the control group, with OR =0.74, 95% CI: 0.48 to 1.17 (Z=1.29, P=0.20).

Discussion: This meta-analysis demonstrated that the combination of ATG with eltrombopag in the treatment of SAA is safer and more effective than ATG alone.

Keywords: Anti-thymocyte globulin (ATG); eltrombopag; severe aplastic anemia (SAA); safety

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Introduction

Aplastic anemia (AA) refers to bone marrow failure syndrome due to the combined action of chemical, biological, and other factors. The main clinical manifestations are anemia, repeated infections, decreased bone marrow nuclear cell division, and reduced pancytopenia count (1). The incidence of AA can be as high as 75% in China (2). According to the disease condition, AA can be divided into severe aplastic anemia (SAA) and mild aplastic anemia (MAA) (3). SAA has an acute onset with a mortality rate of 90%. Patients with SAA usually require regular blood transfusions which often lead to severe bleeding or infections. Since SAA is largely due to damage of the bone marrow stem cells and the hematopoietic internal environment, immunosuppressive agents have been used in the treatment of acute AA (4).

Anti-thymocyte globulin (ATG) therapy uses T lymphocytes in the human body as antigens to immunize animals such as rabbits, horses, and pigs. These immunized animals then produce the corresponding specific antibodies against the donor T lymphocytes (5). These specific immunoglobulins against T lymphocytes are harvested and used to remove abnormal T lymphocytes in patients with AA, via cell apoptosis. Thus, normal hematopoietic function is restored (6).

In the 1970s, Yang *et al.* (7) proposed that ATG exerts remarkable therapeutic effects in patients with SAA and in recent years, ATG has become the main mode of treatment for SAA. In fact, studies have reported that ATG has an effective rate of 55% in treating SAA. The main side effects reported were bleeding and serum sickness. Eltrombopag is a drug that can enhance the regulation of T cells and B cells, increase the secretion of transforming growth factor (TGF)-β, and reduce the release of tumor necrosis factor (TNF)-α (8). Interestingly, the application of ATG combined with eltrombopag increased the effective rate of SAA to about 70%. Lengline *et al.* (9) found that 15% of patients recovered completely, whereas those of a high recurrence rate accounted for 33%.

Although the combined administration of ATG with eltrombopag has significantly improved the prognosis of patients, the mortality rate from associated bleeding and infections is still 30% (10). To further explore the safety and efficacy of these two drugs in the treatment of SAA, the Cochrane system was adopted to scientifically evaluate randomized controlled trials (RCTs) published in the literature. This will provide a theoretical basis for the clinical application of ATG and eltrombopag in the treatment of SAA.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-21-1049).

Methods

Literature retrieve

PubMed, Medline, Cochrane Library, Chinese Biomedical Literature Database, CNKI (China National Knowledge Infrastructure) database, WANFANG database, VIP database, and Google Scholar were searched from the establishment of the database to December 20, 2020. The Boolean logic retrieval method was used to retrieve relevant references. In the Chinese databases, a combination of the following search terms was used: “anti-thymocyte globulin”, “severe aplastic anemia”, and “eltrombopag”. In the English databases, “anti-thymocyte globulin”, “severe aplastic anemia”, and “eltrombopag” were used as the search terms. The quality of the literature was evaluated according to the Rev Man 5.3 software provided by the Cochrane system.

Each database adopted a joint search strategy of free words and subject words. After confirmation, the references were tracked using the search engine, and the latest research progress was obtained by contacting experts and researchers in the field.

Literature inclusion and exclusion criteria

The literature was selected according to the following inclusion criteria: (I) studies related to the treatment of SAA using ATG combined with eltrombopag; (II) RCTs; (III) pathological control analysis showed a reliability index of 95% confidence interval (CI); (IV) articles were in the Chinese or English language; and (V) the diagnosis of SAA met the standards of the World Health Organization.

The following studies were excluded: (I) literature not relevant to this study; (II) duplicate publications; (III) review articles, literature abstracts, case reports, and animal experiments; (IV) literature with incomplete data; and (V) literature in languages other than Chinese or English.

Two senior experts independently screened the abstracts and full text articles. In the case of disagreements, a consensus conclusion was obtained through discussion, or a third expert was invited to arbitrate.

Evaluation index

The evaluation indexes included total effective rate (complete reaction and partial reaction were both defined as effective reaction), final mortality rate, survival rate within 2 years, side effects, and recurrence rate.

Data extraction

Two experts independently collated the data using a standardized Excel table. Three preliminary experiments were performed before extraction. Any inconsistencies were resolved through discussion or arbitration by a third expert. The following data were collated: (I) the title of the research; (II) the first author; (III) the name of the publication; (IV) year of publication; (V) the basic characteristics of the patient including age, gender, treatment plan, and drug dosage; (VI) the grouping methods and statistical methods applied; and (VII) the source, sample size, and outcome indexes of the cases.

Bias risk assessment and quality evaluation

Two researchers conducted a risk assessment of bias simultaneously. Any inconsistencies were resolved via discussion or arbitration by a third expert. In this study, the Cochrane Collaboration for "bias risk assessment" was used for RCTs. The assessments of "low risk bias", "unclear", and "high risk bias" were made according to the five aspects of random allocation method, blind method, allocation concealment, complete data, and research results.

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the literature according to three aspects, namely, patient selection, comparability of the study, and outcome. The score ranged from 0 to 9. References with a score of 1 or less were considered low quality (high risk bias); references with a score of 2–5 were considered medium quality (unclear); and references with a score of 6–9 were considered high-quality literature (low risk bias).

Statistical analysis

StataSE12.0 software was used for statistical analyses. Odd ratios (ORs) and 95% confidence intervals (CI) were used to evaluate the blood response rate, mortality rate, survival rate, and side effects of ATG combined with eltrombopag in the treatment of SAA. The Rev Man5.3 software was used to assess the bias risk of the included references. The effect was expressed using a 95% CI. When P>0.1 and I^2<50%, the fixed effects model was used for meta-analysis. When P<0.1 and I^2>50%, the random effects model was used for meta-analysis.

Results

Basic information of included references

Initially, a total of 1,753 references were identified, and 1,717 were excluded after reading the abstract and the title. A further 20 studies were excluded after reading the full text article. References were excluded due to duplicate research data [985], data which did not include case-control analyses [324], patients who did not undergo anesthesia surgery for liver cancer [394], and failure to extract relevant information [18] (*Figure 1*). Finally, 16 studies were included in this meta-analysis.

Figure 2 shows the quality classification results. There were 8 references with a score of 6–9 and above, 5 articles with a score of 2–5, and 3 studies with a score of 2 and below.

Of the 16 references that met the inclusion criteria, 12 were retrospective analyses and 4 were RCTs, with a total of 1,264 patients. All 16 studies had an ATG control group with sample sizes ranging from 28 to 54. These studies were analyzed for the number of cases, intervention measures, and observation indexes. The general characteristics of the research subjects are shown in *Table 1*.

The risk bias assessment

Figures 3 and *4* show the risk bias assessment using Review Manager 5.3 software. Of the 16 RCTs involved in this study, 3 (11,12,13) had the correct random allocation method, and only 2 (14,15) had allocation concealment. One (16) reference adopted the blinding method, which was not used in the other studies. However, the measurement indexes were laboratory indexes determined by computer and hence, it can be considered that all references adopted the blinding method.

The total effective rate

The total effective rate in the RCTs was analyzed. There were a total of 1,264 cases, with 638 patients in the experimental group, and 626 patients in the control group. The heterogeneity test results with the fixed effects

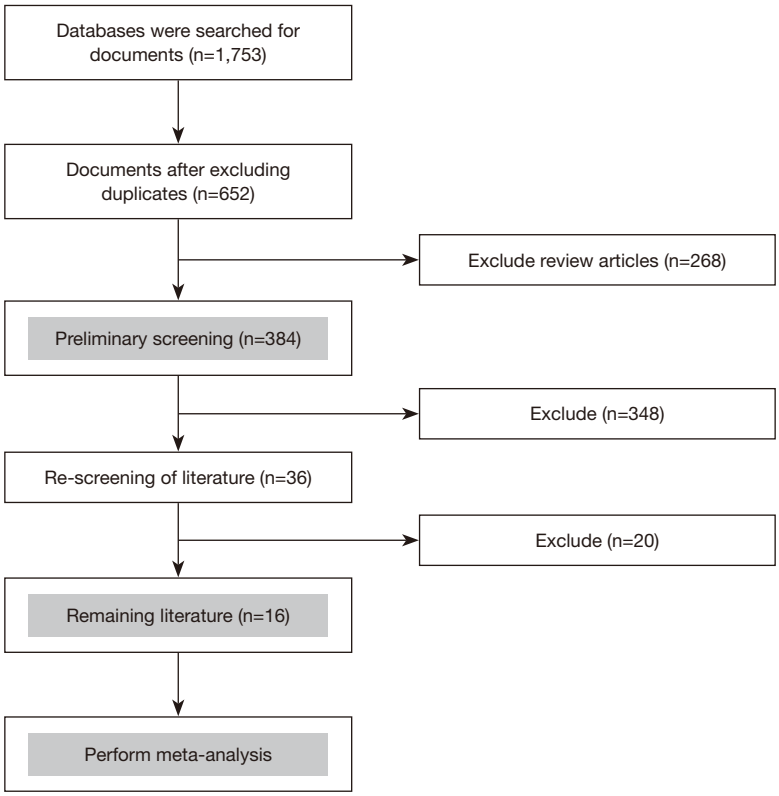

Figure 1 A flow chart depicting the literature search process.

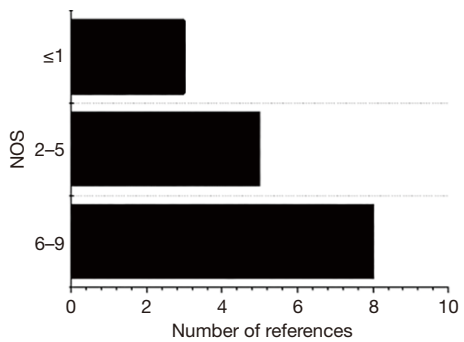

Figure 2 Literature quality classification results using the Newcastle-Ottawa Scale (NOS).

model revealed that Chi^2 =4.48, df =15, I^2=0%<50%, and P=1.00>0.01. The horizontal line and the invalid vertical line crossed at 95% CI: in all the studies. Meta-analysis showed that the effective rate of ATG combined with eltrombopag was higher than that of ATG alone (OR =1.90, 95% CI: 1.35 to 2.68), and the difference was notable (Z=3.70, P=0.0002; *Figure 5*).

The Rev Man 5.3 was used to obtain the funnel chart for the total effective rate (*Figure 6*). The circles in some studies were basically symmetrical to the midline, suggesting that the research accuracy was high and there was no publication bias.

The survival rate

There were 8 RCTs which analyzed the 2-year survival rate. There was a total of 642 cases, with 324 patients in the experimental group, and 318 patients in the control group. The heterogeneity test using the fixed effects model demonstrated that Chi^2 =3.09, df =7, I^2=0%<50%, and P=0.88>0.01. The horizontal line and the invalid vertical line crossed at 95% CI: for all studies. Meta-analysis showed that the survival rate of patients in the ATG combined with eltrombopag group was higher than that of patients in the ATG alone group (OR =2.54 and 95% CI: 1.58 to 4.09), and the difference was significant (Z=3.84, P=0.0001; *Figure 7*).

The Rev Man5.3 was used to obtain a funnel chart of the survival rate (*Figure 8*). The circles in some studies were basically symmetrical to the midline, suggesting that the research accuracy was high and there was no publication bias.

Table 1 General characteristics of the research subjects

Author	Year of publication	Number of cases		Intervention		Observation index
		Experimental group	Control group	Experimental group	Control group	
Scheinberg P	2011	48	48	ATG + Eltrombopag	ATG	Total effective rate (3–6 months), survival rate, mortality, side effects
Bacigalupo A	2019	46	44	ATG + Eltrombopag	ATG	Total effective rate, survival rate, infection (incidence rate, related death)
Tichelli A	2020	32	34	ATG + Eltrombopag	ATG	Total effective rate, adverse reaction over 1 year, survival rate over 2 years
Rogers ZR	2019	26	26	ATG + Eltrombopag	ATG	Total effective rate, mortality rate, basic cure rate
Hayakawa J	2017	52	50	ATG + Eltrombopag	ATG	Total effective rate, basic cure rate, recurrence rate
Yang N	2017	28	28	ATG + Eltrombopag	ATG	Total effective rate, survival rate, recurrence rate
Lengline E	2018	34	32	ATG + Eltrombopag	ATG	Total effective rate, recurrence rate
Sasaki N	2019	42	40	ATG + Eltrombopag	ATG	Total effectiveness, mortality rate, side effects
Li F	2020	48	48	ATG + Eltrombopag	ATG	Total effective rate, basic cure rate, recurrence rate
Sharma R	2012	36	38	ATG + Eltrombopag	ATG	Total effective rate, mortality rate, recurrence rate
Bevans MF	2004	40	40	ATG + Eltrombopag	ATG	Total effective rate, average onset time
Frickhofen N	2000	26	26	ATG + Eltrombopag	ATG	Total effective rate, mortality rate, basic cure rate
Chandra J	2008	54	52	ATG + Eltrombopag	ATG	Total effective rate, average onset time, side effects
Lum SH	2016	52	50	ATG + Eltrombopag	ATG	Total effective rate, survival rate over 1 year
Jeong DC	2014	36	32	ATG + Eltrombopag	ATG	Total effective rate, mortality, T cell subpopulation distribution changes before and after treatment
Tang X	2012	38	38	ATG + Eltrombopag	ATG	Total effective rate, recurrence rate, side effects

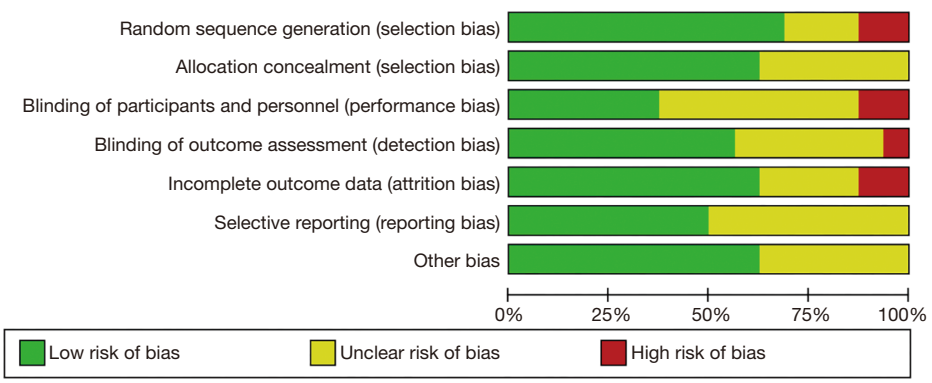

Figure 3 The bias risk evaluation results of the included literature.

The mortality rate

There were 7 RCTs analyzing the final mortality rate, including a total of 514 cases, with 260 patients in the experimental group and 254 patients in the control group. The heterogeneity test using the fixed effects model showed that Chi^2 =3.49, df =6, I^2=0%<5 0%, and P=0.75>0.01. In most studies, the horizontal line and the left side of the invalid vertical line crossed at 95% CI, and some were on the left side of the invalid vertical line. Meta-analysis demonstrated that the mortality rate of patients in the ATG combined with eltrombopag group was lower than that of patients in the ATG alone group (OR =0.48 and 95% CI: 0.33 to 0.70), and the difference was significant (Z=3.84, P=0.0001; *Figure 9*).

The Rev Man5.3 was used to obtain a mortality funnel chart (*Figure 10*). The circles in some studies were basically symmetrical to the midline, suggesting that the research accuracy was high and there was no publication bias.

Side effects of treatment

A total of four RCTs analyzed the side effects of treatment. There were a total of 360 cases, with 182 patients in the experimental group, and 178 patients in the control group. The heterogeneity test using the fixed effects model demonstrated that Chi^2 =0.12, df =3, I^2=0%<50%, and P=0.99>0.01. The horizontal line and the left side of the invalid vertical line crossed at the 95% CI for all studies. Meta-analysis results showed that the incidence of side effects in patient treated with ATG combined with eltrombopag was lower than that in patients treated with ATG alone (OR =0.74, 95% CI: 0.48 to 1.17, Z=1.29, P=0.20; *Figure 11*).

The Rev Man5.3 was used to obtain the funnel chart for side effects (*Figure 12*). The circles in some studies were basically symmetrical to the midline, suggesting that the research accuracy was high and there was no publication bias.

The recurrence rate

There were six RCTs analyzing the rate of SAA recurrence. There were 470 cases in total, with 236 patients in the experimental group and 234 patients in the control group. The heterogeneity test using the fixed effects model showed that Chi^2 =1.01, df =5, I^2=0%<50%, and P=0.96>0.01. In most studies, the horizontal line and the invalid vertical line crossed at the 95% CI. The meta-analysis showed that compared with the ATG group, the recurrence rate of patients treated with ATG combined with eltrombopag group was slightly lower (OR =0.95 and 95% CI: 0.66 to 1.37), however, the difference was not statistically significant

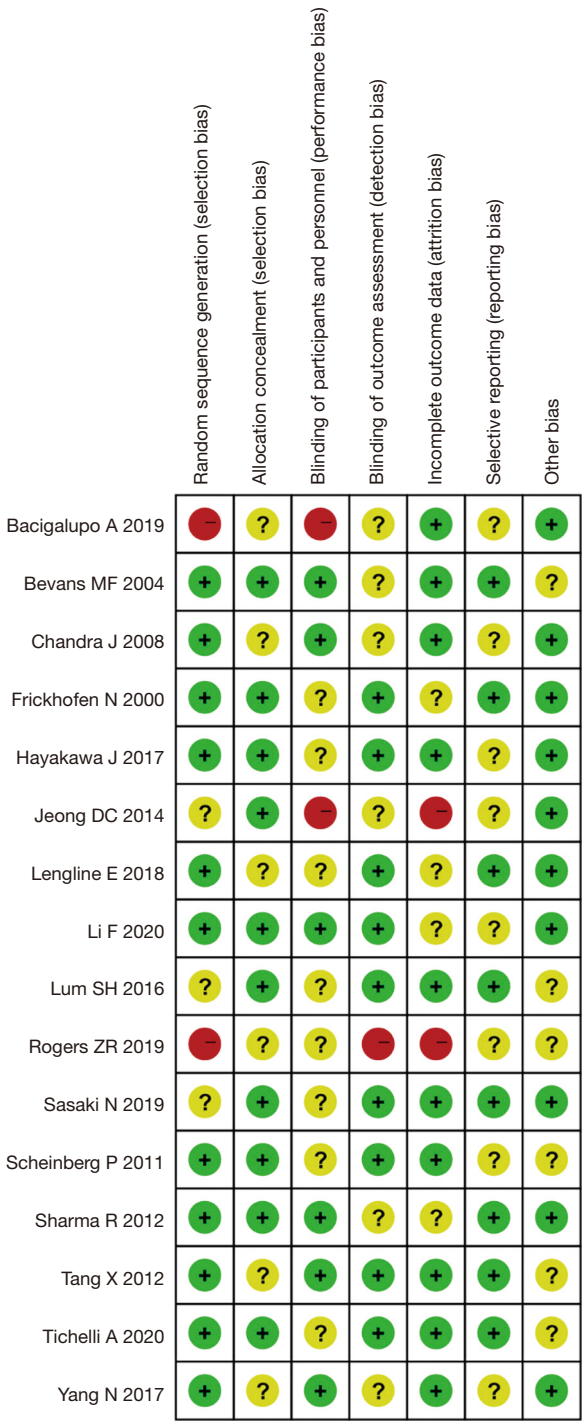

Figure 4 The multiple risk bias evaluation results of the included literature.

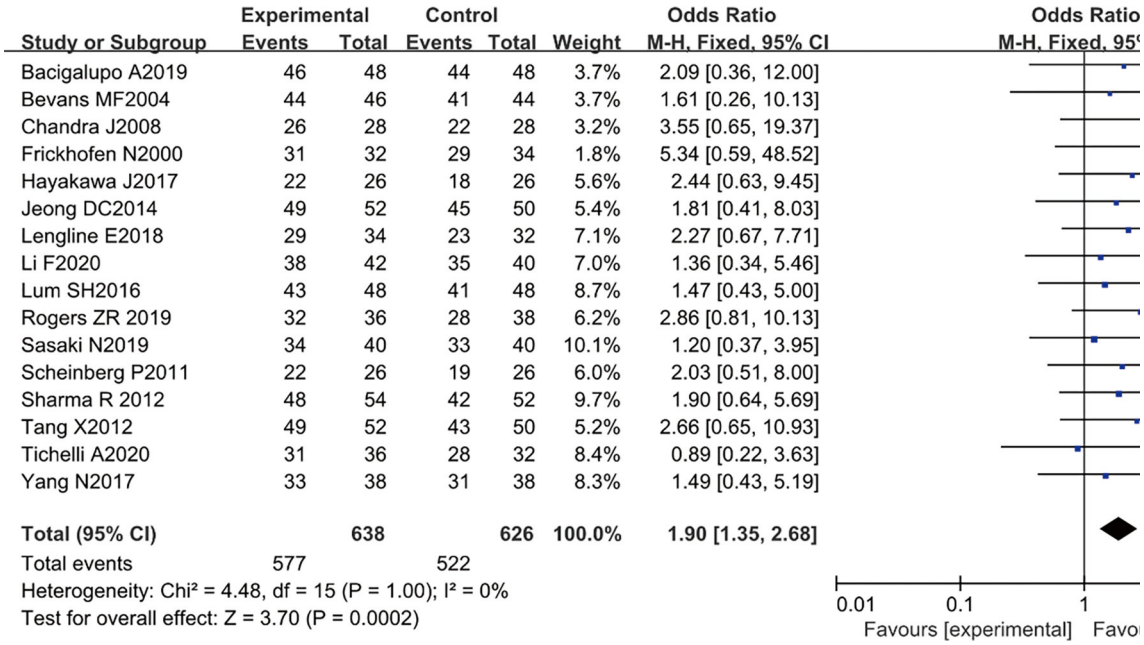

Figure 5 A forest plot showing the total effective rate between patients administered anti-thymocyte globulin (ATG) combined with eltrombopag and patients given ATG alone.

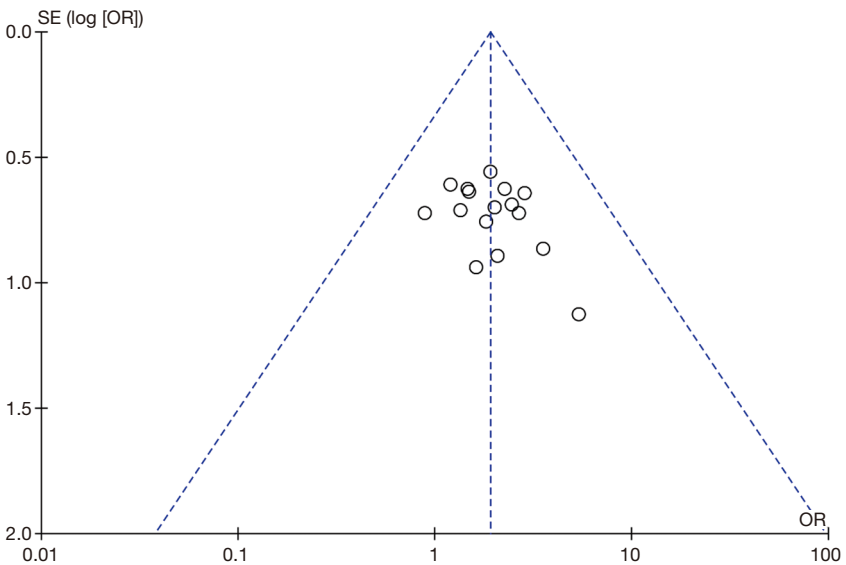

Figure 6 A funnel chart showing the total effective rate between patients administered anti-thymocyte globulin (ATG) combined with eltrombopag and patients given ATG alone.

(Z=0.29, P=0.77; *Figure 13*).

The Rev Man5.3 was used to obtain a funnel chart of the recurrence rate (*Figure 14*). It was evident that the circles in some studies were not symmetrical along the midline, suggesting that the research accuracy was low and the publication may be biased.

Discussion

ATG is a biologically active protein obtained by injecting

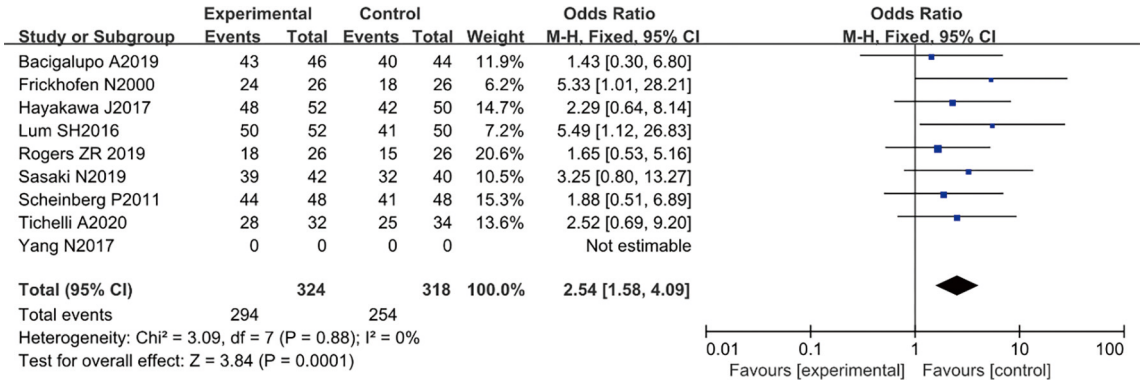

Figure 7 A comparison of the survival rates between patients administered anti-thymocyte globulin (ATG) combined with eltrombopag and patients given ATG alone.

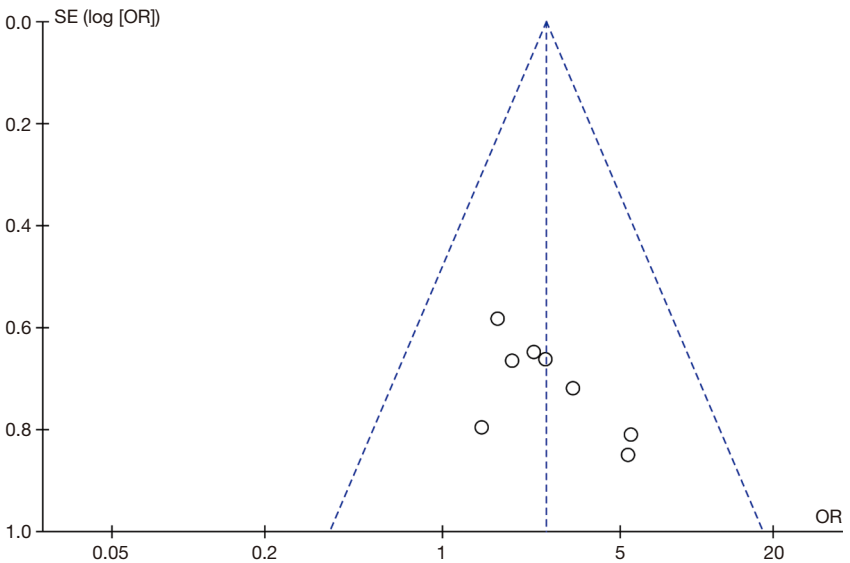

Figure 8 A funnel chart showing the survival rate between patients administered anti-thymocyte globulin (ATG) combined with eltrombopag and patients given ATG alone.

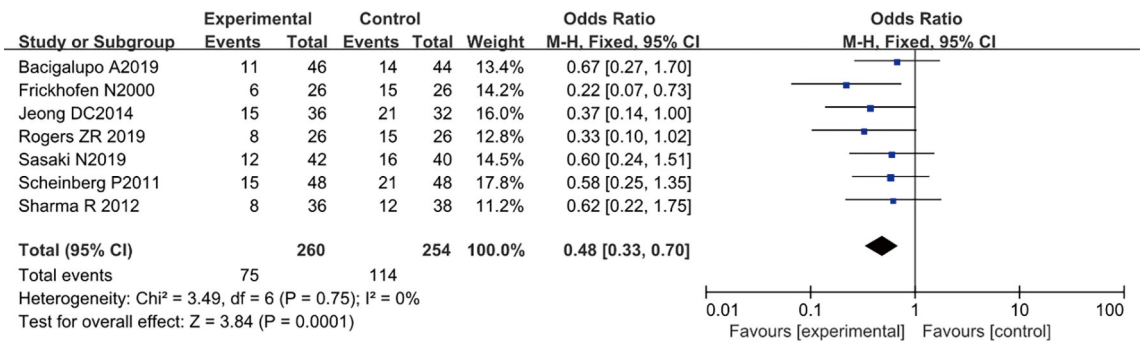

Figure 9 A forest plot showing the mortality rate between patients administered anti-thymocyte globulin (ATG) combined with eltrombopag and patients given ATG alone.

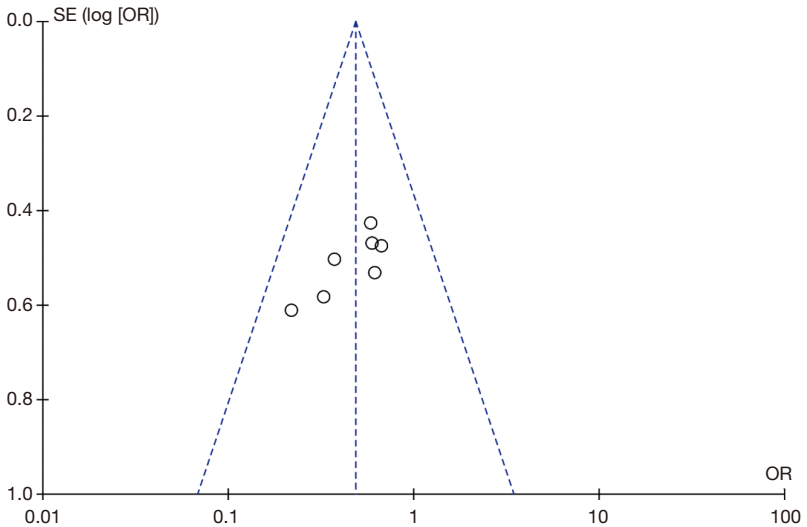

Figure 10 A funnel chart showing the mortality rate between patients administered anti-thymocyte globulin (ATG) combined with eltrombopag and patients given ATG alone.

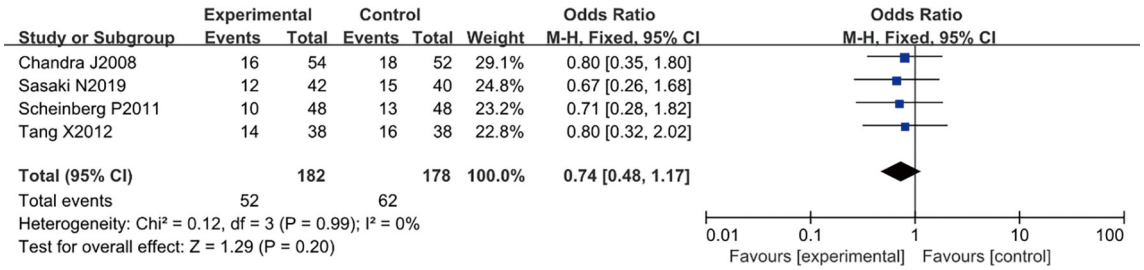

Figure 11 A forest plot showing the side effects between patients administered anti-thymocyte globulin (ATG) combined with eltrombopag and patients given ATG alone.

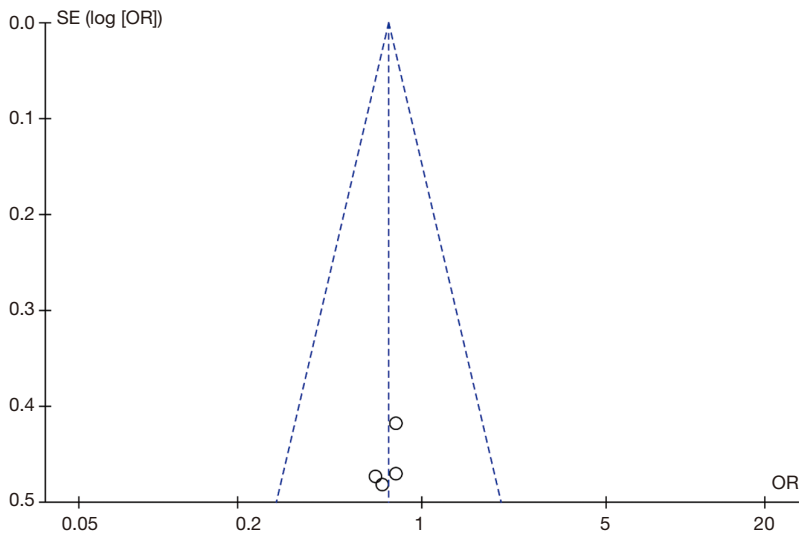

Figure 12 A funnel chart showing the side effects patients administered anti-thymocyte globulin (ATG) combined with eltrombopag and patients given ATG alone.

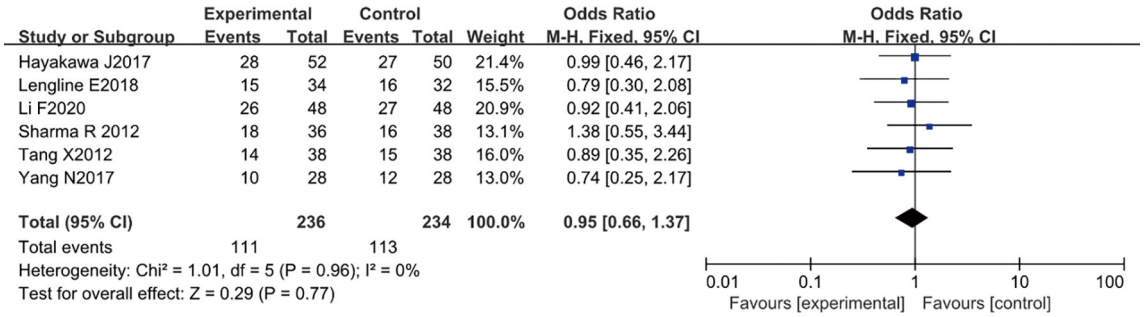

Figure 13 A forest plot showing the recurrence rate between patients administered anti-thymocyte globulin (ATG) combined with eltrombopag and patients given ATG alone.

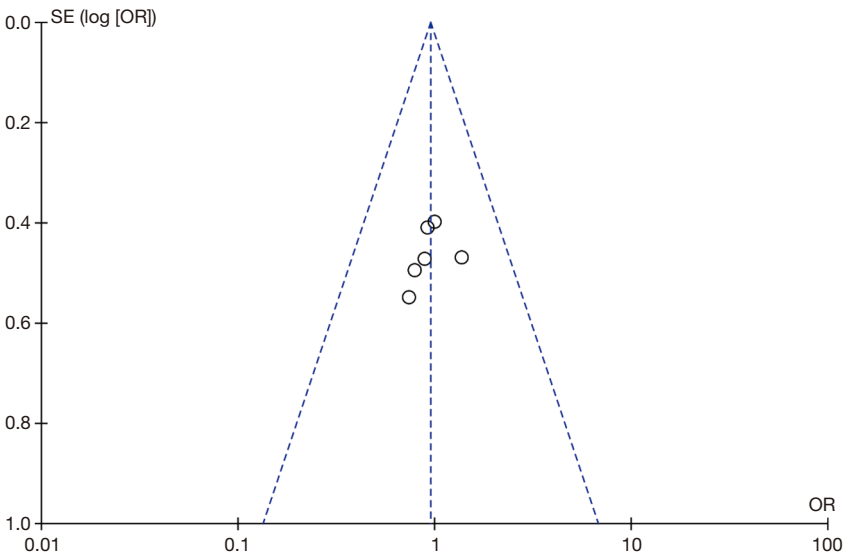

Figure 14 A funnel chart showing the recurrence rate between patients administered anti-thymocyte globulin (ATG) combined with eltrombopag and patients given ATG alone.

human thymocytes into animals such as rabbits and horses. The animals produce specific antibodies against the human thymocytes (17). These resultant anti-thymocyte antibodies can then be used for immunosuppressive therapy in patients with SAA. Lengline *et al.* (18) suggested that the effect of combined immunosuppressive therapy was more extensive than that of single-drug therapy, and that synergy could be easily achieved.

A total of 16 publications were selected from Chinese and English medical databases. The quality classification results of the meta-analysis showed that 8 references scored 6–9 or above, 5 references scored 2–5, and 3 references scored 2 points and below. Among the 16 RCTs, 3 had a correct random allocation method, with only 2 adopting allocation concealment.

In this study, patients treated with ATG combined with eltrombopag were compared to patients administered ATG alone. The total effective rate, survival rate, mortality, side effects, and recurrence rate were examined. Meta-analysis results showed that patients administered ATG combined with eltrombopag had higher effective rate, greater survival rate, lower mortality, and lower incidence of side effects. While the recurrence rate of patients in the ATG combined with eltrombopag group was slightly lower than that of patients in the ATG alone group, this was not statistically significant and may be caused by publication bias.

There are some limitations to this study. Several of the references included were of low quality and had high

heterogeneity, and the sample size was small. Hence, further verification using larger numbers of clinical RCTs is warranted.

Conclusions

In this meta-analysis, 16 studies were included using the Boolean logic search method, with combined ATG and eltrombopag therapy as the experimental group and ATG therapy alone as the control group. The investigation confirmed that the application of ATG combined with eltrombopag in the treatment of SAA was safer and more effective than ATG alone. The results of this study provide a reliable theoretical basis for the clinical treatment of SAA.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/apm-21-1049

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-21-1049). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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