ORIGINAL ARTICLE

# Safety and Effectiveness of Cyclosporine and Eltrombopag in Acquired Aplastic Anemia: Experience from a Tertiary Care Center in Eastern India

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Visual Abstract


## Abstract

**Introduction:** Acquired aplastic anemia (AAA) is an immune-mediated bone marrow failure syndrome traditionally treated with antithymocyte globulin (ATG)–based immunosuppressive therapy. However, many patients—particularly older adults and those with significant comorbidities—are unable to tolerate ATG. The combination of cyclosporine (CSA) and eltrombopag (EPAG) without ATG has emerged as a potential alternative, though real-world data from India remain limited.

**Materials and methods:** This single-center, retrospective observational study included consecutive adult patients ($n$ = 40; ≥18 years) with severe or very severe AAA treated with CSA and EPAG without ATG between January 2020 and December 2025, study ends December 2025. Patients had contraindications to ATG due to age and/or comorbidities. Hematologic responses were assessed at 3–6 months. Overall response rate (ORR) was defined as complete plus partial response. Safety was evaluated using CTCAE v5.0 criteria.

**Results:** The median age was 56.5 years, with 72.5% having severe and 27.5% very severe AAA. At 6 months, complete response was observed in 17.5% and partial response in 45%, yielding an ORR of 62.5%. Notable improvements were observed in hemoglobin, absolute neutrophil count, and platelet count (all $p < 0.001$). Younger age (≤60 years), fewer comorbidities (≤1), higher baseline blood counts, and severe (vs very severe) disease were significantly associated with response. Treatment was well tolerated; hepatic adverse events were mild (grade ≤2), transient, and did not necessitate treatment discontinuation.

**Conclusion:** Cyclosporine combined with eltrombopag is a relatively safe and effective ATG-free therapeutic option for selected patients with acquired aplastic anemia, particularly older individuals and those with comorbidities. This regimen offers meaningful hematologic recovery with acceptable toxicity and represents a pragmatic alternative in real-world and resource-limited settings.


**Keywords:** Acquired aplastic anemia, Comorbidities, Cyclosporine, Eltrombopag, Overall response rate.

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## Introduction

Acquired aplastic anemia (AAA) is a rare, heterogeneous disorder characterized by pancytopenia and a hypocellular bone marrow without abnormal infiltration or fibrosis, resulting from immune-mediated destruction of hematopoietic stem and progenitor cells. Diagnosis requires at least two of the following: hemoglobin <100 gm/L, platelets <50 × $10^9$/L, or neutrophils <1.5 × $10^9$/L.[1] Severe aplastic anemia (SAA) is defined by bone marrow cellularity below 25% (or 25–50% with less than 30% hematopoietic cells) and at least two of the following: neutrophils <0.5×$10^9$/L, platelets <20×$10^9$/L, or reticulocytes <60×$10^9$/L. Very severe AA (VSAA) meets the same criteria as SAA but with neutrophils <0.2×$10^9$/L. Nonsevere AA (NSAA) includes cases that do not meet the thresholds for SAA or VSAA.[2] The incidence of AA varies widely worldwide and across India, with limited epidemiological data from Asia. Reported incidence in Asia is two to three times higher than in Western countries, reaching up to 8.8 per million per year. While Western studies show a bimodal age distribution (15–25 years and ≥60 years), Indian studies report a younger median age at presentation, ranging from 25 to 36.5 years. The disease shows a biphasic age distribution (10–25 years and over 60) and occurs more frequently in East Asia than in Europe (2–3 cases per million annually).[3] Cyclosporine (CSA) suppresses T-cell–mediated immune injury and improves hematopoiesis, though responses are variable and relapses frequent.[4] Antithymocyte globulin (ATG) combined with CSA is recommended as the first-line treatment for patients with NSAA who are transfusion-dependent, have recurrent infections or bleeding, or whose daily functioning is notably affected. For those with SAA/VSAA without a matched sibling donor (MSD), the preferred initial therapy includes ATG, CSA, and eltrombopag (EPAG). This combination is also advised for patients with an MSD who are over 40 years old. In individuals aged 40 to 50, hematopoietic stem cell transplantation (HSCT) from an MSD may still be considered, depending on their general health, functional status, and the expertise of the transplant center.[5] In routine clinical practice, treating AAA in patients with significant comorbidities—such as advanced age, diabetes, hypertension, cardiovascular disease, infections, or organ dysfunction—poses substantial challenges due to poor tolerance to intensive immunosuppressive therapy (IST). Many such patients are unable to receive ATG because of concerns regarding infusion-related reactions, infectious complications, prolonged hospitalization, and overall treatment-related morbidity. In these settings, a less intensive immunosuppressive approach combining CSA with EPAG, without ATG, may offer a safer and more feasible therapeutic alternative, particularly in low-resource environments or when ATG is contraindicated. EPAG's oral administration, favorable safety profile, and capacity to stimulate hematopoiesis make it especially suitable for vulnerable patient populations. Emerging real-world evidence supports the use of CSA with EPAG in patients with multiple comorbidities, although prospective data remain limited.[6] The present study evaluates the safety and effectiveness of this combination in such high-risk patients to help inform pragmatic treatment strategies.

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## Materials and Methods

### Study Design and Patients

This was a single-center, retrospective observational study evaluating the safety and effectiveness of CSA combined with EPAG in patients with AAA. Consecutive patients ($n$ = 40) aged ≥18 years treated between January 2020 and December 2025, study ends December 2025 were included. The diagnosis of AAA was confirmed by bone marrow biopsy demonstrating hypocellularity without malignant infiltration or fibrosis.

### Inclusion and Exclusion Criteria

Patients were eligible for inclusion if they had a diagnosis of AAA classified as SAA or VSAA, were aged ≥18 years, and were treated with CSA and EPAG without ATG due to the presence of contraindications to ATG. Eligible patients had at least one significant comorbidity, including poorly controlled diabetes mellitus, hypertension, chronic infection such as tuberculosis, organ dysfunction (pulmonary, hepatic, or renal), or cardiovascular disease. Comorbidities were defined based on documented physician diagnosis and active medical treatment at the time of initiation of immunosuppressive therapy.

Patients were excluded if they had inherited bone marrow failure syndromes, had undergone prior hematopoietic stem cell transplantation, or had no contraindication to ATG and were eligible for standard ATG-based immunosuppressive therapy.

### Treatment Protocol

Cyclosporine was administered orally at an initial dose of 5 mg/kg/day in two divided doses, with dose adjustments to maintain therapeutic trough levels between 150 and 250 ng/mL.[4] Eltrombopag was initiated at 50–75 mg/day based on baseline liver function and was titrated according to platelet response and tolerability.[6] In patients with hepatic dysfunction, reduced starting doses were used in accordance with prescribing guidelines. Transfusion support was given as per institutional guidelines.

### Data Collection and Parameters Analyzed

Baseline demographic and clinical data, including age, sex, and comorbidities, were recorded. Hemoglobin concentration (Hb), absolute neutrophil count (ANC), and platelet count were assessed at baseline, 3 months, and 6 months after initiation of therapy. Treatment-related adverse events—including hepatotoxicity, renal dysfunction, thromboembolic events, gastrointestinal symptoms, and skin hyperpigmentation—were documented and graded according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0).[7]

### Outcome Definitions and Response Assessment

Treatment response at the end of 6 months was categorized as:[5]

- *Complete response (CR)*: Hemoglobin >10 gm/dL, ANC >1.5 × $10^9$/L, and platelet count >150 × $10^9$/L without transfusion support.
- *Partial response (PR)*: Transfusion independence with improvement in at least one hematopoietic lineage.
- *No response (NR)*: Persistent transfusion dependence and cytopenias.
- Overall response rate (ORR) was defined as the sum of CR and PR.

### Ethical Considerations

The study was approved by the Institutional Ethics Committee (Nilratan Sircar Medical College and Hospital), India (IEC approval No. IEC/NMC/6673), and conducted in accordance with the Declaration of Helsinki. Patient confidentiality was maintained throughout the study.

### Statistical Analysis

SPSS 20.0 statistical software (SPSS Inc., Chicago, IL) was used for statistical analysis to draw appropriate conclusions. Qualitative data (Categorical variables) were presented in numbers and percentages (%). Data distribution was assessed and found to be nonparametric. Continuous variables were expressed as median with interquartile range (IQR) and compared using the Wilcoxon signed-rank test for paired observations. Categorical variables were expressed as frequencies and percentages. Associations between baseline variables—including age, sex, baseline blood counts, and comorbidities—and treatment response were analyzed using the Chi-square test or Fisher's exact test, as appropriate. A two-sided $p$-value <0.05 was considered statistically significant.

## Observationand Results

### Baseline Characteristics and Outcome

The median age of the patients was 56.5 years (interquartile range/IQR 54.0–64.0). Males comprised 57.5% ($n$ = 23) and females 42.5% ($n$ = 17) of the cohort. None or single comorbidity was present in 72.5% ($n$ = 29) of patients, while over a quarter (27.5%) of the patients presented with more than one significant comorbidity, most commonly a combination of type 2 diabetes and hypertension. On severity assessment, 72.5% ($n$ = 29) had SAA and 27.5% ($n$ = 11) had VSAA. At baseline, the median hemoglobin level was 7.0 gm/dL (IQR 5.7–8.0). The median absolute neutrophil count was 0.9 × $10^9$/L (IQR 0.6–1.1), and the median platelet count was 15 × $10^9$/L (IQR 5–19). Regarding safety, hyperbilirubinemia occurred in 27.5% ($n$ = 11) of patients, and elevation of aspartate aminotransferase and alanine aminotransferase was observed in 22.5% ($n$ = 9). All hepatic adverse events were grade ≤2 according to CTCAE v5.0, were transient in nature, and did not require dose reduction or discontinuation of CSA or EPAG.

At 6 months, complete response was achieved in 17.5% ($n$ = 7) of patients, partial response in 45% ($n$ = 18), while 37.5% ($n$ = 15) had no response. Table 1 summarizes the baseline characteristics and outcome.

### Hematological Kinetics Over Time

To assess the primary efficacy of the treatment, blood counts were tracked at three critical time points: baseline, 3 months, and 6 months. Given the paired nature of the data and the non-normal distribution of blood counts in bone marrow failure states, the Wilcoxon signed-rank test was utilized to determine statistical significance. All hematologic parameters showed significant improvement over the 6-month period (Table 2). Median hemoglobin increased from 7.0 gm/dL at baseline to 9.1 gm/dL at 6 months ($p$ < 0.001). ANC rose from 0.9 to 1.95 × $10^9$/L ($p$ < 0.001), and platelet count improved from 15 to 54 × $10^9$/L ($p$ < 0.001). Significant changes were observed at both 3 and 6 months compared to baseline, with additional incremental gains between 3 and 6 months.

### Quantitative Baseline Predictors of Response

To further delineate the differences between responders and non-responders, baseline continuous variables were compared using the Mann–Whitney $U$ test. This analysis identifies the specific hematologic thresholds that distinguish the two groups at the outset of therapy. Responders were significantly younger than non-responders (median 56 vs 66 years, $p$ < 0.001). Responders had significantly higher baseline hemoglobin, ANC, and platelet counts compared to nonresponders (Hb: 7.4 vs 5.8 gm/dL; ANC: 1.0 vs 0.4 × $10^9$/L; Plt: 17 vs 6 × $10^9$/L; all $p$ < 0.001). Younger age was also significantly associated with response (Table 3).

**Table 1:** Descriptive statistics of the study cohort (*N* = 40)

| *Characteristic* | *Value* |
|---|---|
| Age (Years): median (interquartile range) | 56.5 (54.0–64.0) |
| *Sex* | |
| Male, *n* (%) | 23 (57.5%) |
| Female, *n* (%) | 17 (42.5%) |
| Comorbidities | |
| None or single comorbidity, *n* (%) | 29 (72.5%) |
| More than one comorbidity (>1), *n* (%) | 11 (27.5%) |
| Type 2 diabetes mellitus | 16 (40%) |
| Hypertension | 15 (37.5%) |
| Ischemic heart disease | 2 (5%) |
| Chronic obstructive lung disease | 4 (10%) |
| Severity | |
| Severe aplastic anemia | 29 (72.5%) |
| Very severe aplastic anemia | 11 (27.5%) |
| Baseline blood counts (median, interquartile range) | |
| Hemoglobin (gm/dL) | 7.0 (5.7–8.0) |
| Absolute Neutrophil Count (/$10^9$/L) | 0.9 (0.6–1.1) |
| Platelets (/$10^9$/L) | 15 (5–19) |
| Side effects | |
| Hyperbilirubinemia, n (%) | 11 (27.5%) |
| Elevated AST/ALT, n (%) | 9 (22.5%) |
| Clinical response at 6 months | |
| Complete response, *n* (%) | 7 (17.5%) |
| Partial response, *n* (%) | 18 (45%) |
| No response, *n* (%) | 15 (37.5%) |

### Categorical Predictors of Response

Understanding which patients are likely to benefit from a CsA–eltrombopag regimen is essential for personalized treatment planning. A subgroup analysis using Fisher's exact test was performed to evaluate the association between baseline categorical variables and objective response at 6 months (Table 4). Response rates were significantly higher in patients aged ≤60 years compared with those >60 years (84.0% vs 26.7%, $p < 0.001$). Similarly, patients with ≤1 comorbidity demonstrated markedly superior responses compared with those having multiple comorbidities (75.9% vs 27.3%, $p < 0.001$). Disease severity also influenced outcome, with patients with severe aplastic anemia (SAA) showing significantly better responses than those with very severe aplastic anemia (VSAA) (79.3% vs 18.2%, $p < 0.001$). Although response rates were numerically higher in females compared with males (64.7% vs 60.9%), this difference did not reach statistical significance ($p = 0.31$).

## Discussion

In this geriatric cohort of severe aplastic anemia (SAA), frontline treatment with cyclosporine (CsA) combined with

**Table 2:** Hematologic response over 6 months in patients of aplastic anemia

| *Parameter* | *B median (IQR)* | *3 m median (IQR)* | *6 m median (IQR)* | *B vs 3 m (p-value)* | *B vs 6 m (p-value)* | *3 m vs 6 m (p-value)* |
|---|---|---|---|---|---|---|
| Hb (gm/dL) | 7.0 (5.7–8.0) | 8.2 (7.0–9.0) | 9.1 (8.2–11.8) | <0.001 | < 0.001 | <0.001 |
| ANC (×$10^9$/L) | 0.9 (0.6–1.1) | 1.6 (0.8–1.9) | 1.95 (1.5–2.3) | <0.001 | < 0.001 | 0.004 |
| Plt (×$10^9$/L) | 15 (5–19) | 33 (10–64) | 54 (15–87) | <0.001 | < 0.001 | 0.002 |

Hb: hemoglobin; ANC: absolute neutrophil count; Plt: platelet count; B: baseline; 3m: 3 months; 6m: 6 months

**Table 3:** Comparison of baseline hematologic parameters and age between responders and non-responders

| *Variable* | *Responders (n = 29) median (IQR)* | *Nonresponders (n = 11) median (IQR)* | *z-score* | *p-value* |
|---|---|---|---|---|
| Age (years) | 56 (54–60) | 64 (60–70) | −3.10 | 0.002 |
| Baseline hemoglobin (gm/dL) | 7.4 (6.5–8.5) | 5.8 (5.0–6.5) | −3.85 | <0.001 |
| Baseline absolute neutrophil count (×$10^9$/L) | 1.0 (0.7–1.4) | 0.4 (0.2–0.6) | −4.20 | <0.001 |
| Baseline platelet count (×$10^9$/L) | 17 (10–30) | 6 (3–10) | −4.35 | <0.001 |

**Table 4:** Subgroup analysis showing the effect of age, sex, comorbidities, and disease severity on treatment response in patients with acquired aplastic anemia

| *Variable* | *Subgroup* | *Responders (n)* | *Nonresponders (n)* | *Response rate* | *p-value* |
|---|---|---|---|---|---|
| Age | > 60 Years | 4 | 11 | 26.7% | <0.001 |
| | ≤ 60 Years | 21 | 4 | 84 % | |
| Sex | Male | 14 | 9 | 60.9% | 0.31 |
| | Female | 11 | 6 | 64.7% | |
| Comorbidity | ≤ 1 | 22 | 7 | 75.9% | <0.001 |
| | > 1 | 3 | 8 | 27.3% | |
| Severity | SAA | 23 | 6 | 79.3% | <0.001 |
| | VSAA | 2 | 9 | 18.2% | |

**Table 5:** Comparison of the present study with other studies published in literature

| | *Study population* | *Study type/focus* | *Response* |
|---|---|---|---|
| Present study | 40 adults (≥18 years) patients with treatment-naive SAA, VSAA | Retrospective cohort (older adults) | ORR 62.5% (CR 17.5%, PR 45%) at 6 months |
| Scheinberg et al.[8] | 54 adults (≥18 years) patients with treatment-naive SAA | Phase II, single-arm (CsA + EPAG) | Overall hematological response rate by 6 months of treatment was 46% |
| Chen et al.[9] | AAA patients receiving front-line ATG combined with CSA and EPAG (group A, 51 patients) or CSA plus EPAG alone (group B, 38 patients) | Retrospective, real-world multicenter analysis | The 6-month ORR/CR was 73.3%/24.4% and 60.6%/27.3% in groups A and B ($p > 0.1$). For SAA patients, the 6-month ORR was 74.1% vs 50% and 6-month CR was 25.9% vs 20% in Groups A and B ($p > 0.1$) |

AAA, acquired aplastic anemia; SAA, severe aplastic anemia; VSAA, very severe aplastic anemia; CSA, cyclosporine A; EPAG, eltrombopag; ATG, antithymocyte globulin; ORR, overall response rate; ORR, overall response rate; CR, complete response

eltrombopag (EPAG) resulted in a high overall response rate (ORR) of 72.5% at 6 months, with clinically meaningful trilineage hematologic recovery. Median hemoglobin increased from 7.0 to 9.0 gm/dL, absolute neutrophil count (ANC) from 0.9 to 1.95 × $10^9$/L, and platelet count from 15 to 54 × $10^9$/L, translating into reduced transfusion dependence and lower risks of infection and bleeding. Continued improvement between 3 and 6 months highlights the gradual kinetics of hematologic recovery in SAA and supports persistence with therapy even in the absence of early robust responses, consistent with prior eltrombopag-based frontline studies.[8,9] These findings align with the SOAR trial by Scheinberg et al.,[8] a multicenter phase II study of frontline CsA plus EPAG in treatment-naïve adult SAA, which reported a 46% ORR at 6 months. Despite enrolling a younger, fitter population, SOAR confirmed biological activity and acceptable safety of this ATG-free regimen, with hepatic toxicity being the most common adverse event. The higher response observed in our real-world cohort likely reflects differences in patient selection, disease severity, dosing strategies, and treatment persistence. Additional support comes from the multicenter Chinese study by Chen et al.,[9] which compared ATG + CsA + EPAG with CsA + EPAG alone as frontline therapy. Although response rates were numerically higher with triple therapy, differences were not statistically significant, including in SAA patients. Notably, CsA + EPAG was associated with fewer adverse events and no treatment-related mortality, underscoring its favorable tolerability. Collectively, these findings suggest that CsA plus EPAG offers comparable efficacy with reduced toxicity in selected patients, particularly older individuals and those unsuitable for ATG-based therapy.

In the landmark study by Peffault de Latour et al.,[6] the addition of EPAG to ATG and CSA resulted in higher response rates; however, such regimens may not be feasible in older patients or those with multiple comorbidities. In this context, our findings support the growing evidence that EPAG combined with CSA alone can offer meaningful hematologic improvement in carefully selected patients. Importantly, our study specifically focuses on a clinically challenging subgroup—patients with contraindications to ATG—who are often underrepresented in clinical trials. The median age of 56.5 years and the high burden of metabolic and cardiovascular comorbidities reflect real-world practice in India and other low- and middle-income countries. In such settings, avoidance of ATG may reduce treatment-related morbidity without completely compromising efficacy.

Baseline hematopoietic reserve emerged as a dominant determinant of response. Responders were younger (median 56 vs 64 years) and had significantly higher baseline ANC and platelet counts, reinforcing prior observations that preserved marrow activity predicts responsiveness to IST augmented with EPAG.[10] Age >60 years, multiple comorbidities, and VSAA were associated with inferior outcomes, highlighting the importance of early intervention before irreversible marrow exhaustion occurs. These findings are consistent with the large international analysis by Fattizzo et al.,[11] involving 1,113 patients with aplastic anemia, which demonstrated significantly lower response rates and higher mortality in elderly patients irrespective of treatment modality, with age and disease severity emerging as the strongest independent predictors of adverse outcomes—even in the TPO-receptor agonist era.

Comparison of the present study with other studies published in the literature is outlined in Table 5.

This study has several limitations inherent to its retrospective, single-center design, including potential selection bias and incomplete capture of confounding variables. The relatively small sample size limits statistical power and precludes robust subgroup analyses. Absence of a contemporaneous control group receiving ATG-based immunosuppression restricts direct comparative conclusions. Follow-up was limited to 6 months, preventing assessment of long-term outcomes such as relapse, clonal evolution, and overall survival. Additionally, treatment decisions and dosing adjustments were individualized, introducing heterogeneity.

## Conclusion

Cyclosporine combined with eltrombopag is an effective and well-tolerated treatment option for selected patients with acquired aplastic anemia who are unsuitable for ATG-based immunosuppression. This regimen provides meaningful hematologic recovery with acceptable toxicity, particularly in older patients and those with comorbidities. Further prospective and multicentric studies are needed to validate these findings and define long-term outcomes.

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