Use of Cyclosporine A and danazol in treatment of aplastic anemia: A real-world data from a teaching hospital in South India

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INTRODUCTION

Aplastic anemia (AA) is a rare disease syndrome characterized by pancytopenia resulting from hypocellular bone marrow.¹ The global incidence of this disease is 1.4–14 cases/million populations.² Annually, in western countries, the incidence of this disease is estimated to be 1.5–2.3/million.³,⁴ However, in Asia, the incidence of AA is much higher compared to western population. Incidence of this disease is approximately 6.8/million among Indians. There is a high association of this disease with low socioeconomic status.²

The standard curative treatment, especially for severe AA (SAA), includes allogenic hematopoietic stem cell transplantation (HSCT) and immunosuppressive therapy (IST). HSCT with bone marrow harvested stem cells and cyclophosphamide-ATG as conditioning regimen has 10-year survival rate of 90% in younger population and 74% in adults.⁵ However, outcome of HSCT is not so good in India. In one of the study, overall 5-year survival was found to be 64.8%.⁶

IST with anti-thymocyte globulin (ATG) and cyclosporine A (CsA) is recommended for patients who are not eligible for HSCT. The success rate of ATG alone is 40–50%; however, addition of CsA increases response up to 80%.⁷ However, survival rate with IST is far less in Indian studies. In one of the large study, it was observed that, with IST, overall response rate was 58%.⁶
Aims and objectives
Bone marrow failure has different epidemiological and etiological factors in developing countries. Standard of care, that is, stem cell transplantation or IST is not possible in developing countries due to lack of resources and due to logistic reasons. Hence, in many of the centers, CsA is given along with anabolic steroids such as danazol as an alternative option. Eltrombopag is added to this combination if the patient affords this treatment. However, there are limited data published in the literature from India, which highlights the utility of cyclosporine and anabolic steroids. Hence, this study was conducted to know the effect of these medications in patients with AA. As some of the patients also received Eltrombopag, those patients were also included in this observational study.

MATERIALS AND METHODS
An observational retrospective study of AA patients treated with anabolic steroid (danazol), CsA, and eltrombopag was conducted by collecting data from 2017 to 2020. The study was pre-approved by the Institutional Ethics Committee for the final permission. Data of AA patients were collected from the digital medical records data of our Hospital. The study included patients with AA of any severity who were treated with cyclosporine and danazol. Exclusion criteria included patients who underwent stem cell transplantation or IST. Patients with secondary causes such as drug induced AA were also excluded from the study. Those who did not follow-up for minimum of 6 months were also excluded from the study. Patients were categorized into very severe, severe and non-severe as per standard guidelines. Patients of AA were treated with CsA 50–100 mg BD, and danazol 100–200 mg BD for over 6 months. Eltrombopag 150 mg OD was given to patients who could afford it. Renal function and liver functions were monitored, and doses of these medicines were adjusted accordingly. Patients were transfused packed RBCs and platelets as and when required. Transfusion independence was measured which was defined as unsupported hemoglobin of 8 gm/dL and platelet count of >20,000/cmm.

Statistical analysis
Jamovi2 statistical software was used for data analysis and to find out significance of the data.

RESULTS
Data of 109 patients with bone marrow hypoplasia were collected from the hospital medical records. Among them, nine patients were initially excluded as they had secondary bone marrow hypoplasia (drug induced). Five patients were treated with IST or stem cell transplant (Table 1).

OUT OF the remaining 95 patient fulfilling inclusion criteria, 69 (73%) patients were lost to follow-up (Figure 1). Among the remaining 26 patients, 4 (15%) had very severe, 17 (65%) had severe, and 5 (19%) had non-severe disease. Out of 26 patients, 18 (69%) patients responded to the treatment (transfusion independent) and 8 (31%) patients did not show any improvement (Figure 2). Out of 18 patients who had responded 2 had very severe AA, 12 had severe AA, and 4 had non-severe AA. Eleven out of 18 (61.1%) females responded, whereas seven out of eight males (87.5%) responded to the treatment. In the study population, four patients were given Eltrombopag along with cyclosporine and danazol. Out of these four patients, three patients became transfusion independent.

DISCUSSION
There are limited publications from developing world with respect to treatment of AA. There is only one study from India, which discusses about use of Cyclosporine and Danazol. In that study, authors found that overall response rate with CsA and Danazol was 45.6%. There are few studies, where CsA or Danazol were used alone as upfront therapy due to lack of resources. In one such study from Nepal, which involved 368 patients, overall response rate to CsA was 18%, while it was 8% with Danazol. In another study from Mexico, danazol was used as first-line therapy for AA. Five-year overall survival in patients receiving Danazol was 41%. In a study by Chujo et al., total of 16 patients, who were refractory to IST, were given Danazol. Three female patients out of four showed response compared to two out of 12 male patients. In our study, 11 out of 18 females and seven out of eight males responded to CsA and Danazol. Nationwide data from Thailand showed that overall response rate to CsA was 54.8%, whereas as that for anabolic steroids was 37.6%. A study from China showed that addition of levamisole to CsA-Danazol combination has 6 months response rate of 24.3 and 52.9% for VSA and SAA, respectively. In our study, overall response rate was 69%. Compared to published literature, the use of CsA with danazol has been found to be more effective in our study. However, during routine interactions, 16 out of 26 patients revealed that they also consumed alternative medicines (Amrutaballi, i.e., Tenospora Cordifolia) along with the prescribed medicines. This exposure needs to be properly evaluated in future studies to understand the role of such alternative medicines, individually or in combination with existing treatments options of AA.

Eltrombopag is a small molecule thrombomimetic agent which has been studied as additional agent in patient receiving standard IST. This is tolerated by most of the patients. In our study population, four patients were given...
Eltrombopag along with cyclosporine and danazol. Out of these four patients, three patients became transfusion independent. In a study by Gao et al., they observed that, in total of 12 patients, overall response rate was 42%.\textsuperscript{10}

In the present study, it was also observed that 73% patients were lost to follow-up (Figure 1). High incidence of AA in India is linked to lower socioeconomic status.\textsuperscript{2} This could be a reason for lack of regular follow-up of AA patients in India, which is clearly seen in our study. Historically, CsA and Danazol have very poor response rates. In most of the centers, these medicines are given with no other options of treatment and with no hope of any response. Often patient and relatives are counseled accordingly. After finding no recovery with therapy for 2–3 months patients usually stop coming to hematologist, thinking this therapy is not working. Similarly, in absence of standard of care, hematologists also are not keen on knowing the status of such patients, which results in loss to follow-up. Hence, our study highlights the importance of long-term follow-up, to recognize the therapeutic effect of CsA and danazol.

**Limitations of study**

Due to financial constraints, CsA levels could not be monitored in study subjects. This is the major limitation of the present study. Due to large proportion of patients lost to follow-up, actual sample size was very small.

**Table 1: Metadata of patients along with treatment and response**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Occupation</th>
<th>Severity*</th>
<th>Treatment**</th>
<th>Response</th>
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<tbody>
<tr>
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<td>M</td>
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</tr>
<tr>
<td>2</td>
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<td>Labor</td>
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</tr>
<tr>
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<td>Employee</td>
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<tr>
<td>4</td>
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<td>Labor</td>
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</tr>
<tr>
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</tr>
<tr>
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<tr>
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<tr>
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<td>9</td>
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<tr>
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<td>CsA, Dz</td>
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</tr>
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<td>CsA, Dz</td>
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<td>Employee</td>
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<td>Employee</td>
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<td>CsA, Dz+Elp</td>
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</tbody>
</table>

*VS: Very severe, S: Severe, NS: Non-severe. **CsA: Cyclosporine, Dz: Danazol, Elp: Elthrombopag

**Figure 1:** Graph showing total numbers of patents actually recruited for this but data of 95 patients were excluded due to not fulfilling inclusion criteria. LTFU: Loss to follow-up

**Figure 2:** Graphical illustration of patient response to the treatment in gender wise

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CONCLUSION

Treatment with CsA and Danazol may represent a promising therapy for patients with AA, especially in resource limited settings. This study also highlights the importance of long-term follow-up in AA patients being treated with CsA and Danazol. Further, large-scale collaborative studies are necessary to evaluate such approaches in management of AA.

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REFERENCES


Authors Contribution:

GK, RKM, DG, GB, PKJ- Concept and design of the study; prepared first draft of manuscript; GK, RKM, DG, GB, AS, NM, PKJ- Reviewed the literature and manuscript preparation; GK, RKM, DG, AS, NM, PKJ- Concept, coordination, statistical analysis and interpretation, preparation of manuscript and revision of the manuscript.

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