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# POSTER ABSTRACTS

## 508.BONE MARROW FAILURE: ACQUIRED

### Early Initiation of Oral Therapy with Cyclosporine and Eltrombopag for Treatment Naïve Severe Aplastic Anemia: Interim Results of a Phase II Trial

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Introduction:
Severe aplastic anemia (SAA), a life-threatening bone marrow failure disease, is treated with allogeneic bone marrow transplantation or immunosuppression (IST). Pancytopenia meeting "Camitta" criteria and an empty bone marrow (<30% cellularity) establish the diagnosis of SAA. However, neither diagnosis nor therapeutic interventions are straightforward, resulting in delays of therapy. SAA must be differentiated from hematologic malignancy, and constitutional forms should be excluded by functional or genetic testing. Administration of IST usually occurs at a tertiary care center, and in younger patients' evaluation for BMT is first required. Ongoing immune mediated destruction of stem cells further depletes marrow reserve and increases regenerative stress with such delays. In this phase II study, we tested the feasibility and safety of early initiation of cyclosporine (CSA) to block T cells and eltrombopag (EPAG) to stimulate hematopoiesis followed by standard of care therapies to expedite treatment (NCT04304820).
Methods:
Twenty-six patients with treatment-naive SAA were enrolled since 2020. Patients were 3 years or older and median age was 35 years. Exclusion criteria included a diagnosis or high clinical suspicion for inherited disease or evidence of myeloid neoplasm. To ensure rapid initiation of therapy, enrollment was not dependent on pending specialized tests (telomere length, chromosomal breakage, cytogenetics, or genomics). Lower dose CSA (2mg/kg) and full dose EPAG were initiated after confirming eligibility. Upon completion of evaluation and confirmation of acquired SAA diagnosis, all subjects received standard IST (horse ATG, CSA, and EPAG; Figure 1A). Primary feasibility endpoint assessed a composite measure of misdiagnosis, noncompliance, and treatment-related serious adverse events (TRSAE) during oral therapy. Secondary endpoints were efficacy at 6 months, relapse, clonal evolution, and overall survival. Results were compared to a historical cohort of 139 patients treated with hATG, CSA, and EPAG initiated the same day (NCT01623167).
Results:
All patients completed the protocol-defined treatment period, with median time on oral therapy of 17 days (range 0 - 86 days). All subjects ultimately were confirmed to have acquired SAA (no misdiagnoses), all tolerated oral treatment well without any TRSAE, and patients were compliant with local and study-site follow-up. Thus, there were zero events for the primary feasibility endpoint. A single SAE during oral treatment occurred in subject #1, enrolled at the height of the COVID pandemic and was severely ill with persistently positive COVID-19 PCR and recurrent ileitis requiring hospitalization care; his time to standard IST was the longest (86 days). There was significant increase in absolute neutrophil count (ANC; median $0.315 \times 10^{3}$/mL vs 0.570, p=0.041) in a brief interval of oral therapy prior to receiving hATG. There was also a trend towards improvement in absolute reticulocyte count ($29 \times 10^{3}$/mL vs. 35.8) and a decrease in absolute lymphocyte count ($1.5 \times 10^{3}$/mL vs. 1.3; Figure 1B).
Compared to historical cohort, less patients (19% vs 52%) had very SAA (ANC <200 K/uL); age, sex, race, and pre-treatment blood counts were similar in two cohorts. Hematologic response occurred in 68% at 6 months with 45% complete responses, rates similar to the historical cohort (80% and 40%, respectively). Time to platelet and red blood cell transfusion independence

was 43 and 51 days, respectively. Only age (18-40 years) was predictive for 6 month response. With median follow-up of 396 days, the cumulative incidence of relapse at 2 years was 17%, lower than in the historical cohort (27%). Clonal evolution to secondary myeloid malignancy was not increased compared to historical cohort; one subject had myelodysplastic syndrome with excess blasts 1 with deletion 20q, and two had transient trisomy 8 without dysplasia. Overall survival was 96.2%; no deaths occurred during study treatment period of oral medications only.

Conclusion:

Early initiation of CSA and EPAG is a feasible and safe approach to rapidly treat patients with SAA as a bridge to standard therapies and it may lead to improved blood counts, in turn, decreasing early infectious complications. Hematologic response was comparable to our historic cohort. Rates of long-term complications need to be confirmed in a larger cohort with ongoing study enrollment.

**Disclosures** No relevant conflicts of interest to declare.

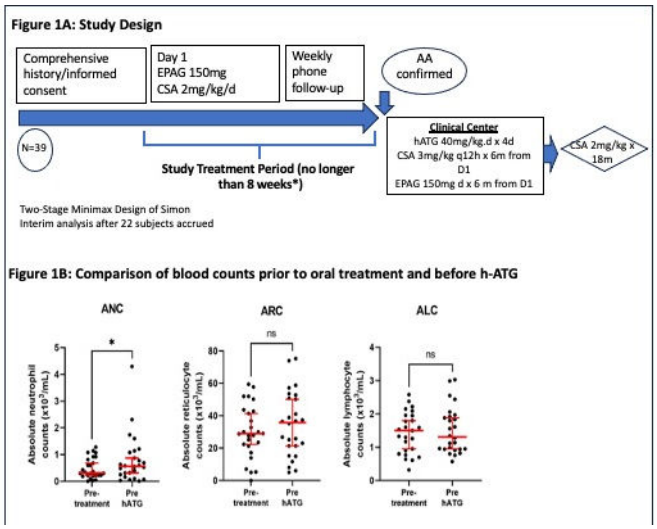


**Figure 1**

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