ORIGINAL ARTICLE

RESPONSE TO IMMUNOSUPPRESSIVE THERAPY IN PATIENTS OF ACQUIRED APLASTIC ANAEMIA: A SINGLE CENTER EXPERIENCE FROM A DEVELOPING COUNTRY

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Background: Aplastic Anaemia (AA) is characterized by pancytopenia and hypocellular marrow. Immunosuppressive therapy (IST) SHOWS impressive haematological response; however, risk of relapse and clonal evolution persists. The objective of the study is to assess response to IST in patients with aplastic anaemia. **Methods:** A retrospective single centre study at AFBMTC / NIBMT for patients of acquired AA was conducted from January 2005 to December 2019.Inclusion criteria included diagnosed cases of acquired AA receiving IST for at least 12 weeks and age >2 years. IST included cyclosporine (CsA) alone, CsA + androgens, CsA + rabbit anti thymocyte globulin (rATG), CsA + horse anti thymocyte globulin (hATG). Primary outcome measure was response to IST; secondary outcome measure was overall survival (OS). **Results:** A total of 513 patients received IST. Median age was 23 years (range 2-97 years). In study cohort, 155 (30.2%) patients responded to the IST, 63 (12.3%) achieved complete response (CR) while 92 (17.9%) achieved partial response (PR). The ORR of CsA in NSAA, SAA and VSAA was 52.6%, 28.10% and 10% respectively; whereas ORR of CsA + rATG in NSAA, SAA and VSAA was 50%, 35.1% and 22.5% respectively. OS was 38% at a median follow up of 36 months. There was a significant difference in the survival distributions of different treatment modalities (p=0.016). Median survival time 60 months (CsA), 9 months (CsA+ androgens) and 39 months (CsA+ rATG/hATG.) **Conclusion**: In resource constrained settings, single agent CsA remains a reasonable alternative with modest activity and acceptable side effect profile.

Keywords: Aplastic anaemia; Immunosuppressive therapy; Cyclosporine.

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INTRODUCTION

Aplastic anaemia is an immune mediated disorder resulting in pancytopenia and hypocellular bone marrow.[1] Incidence of aplastic anaemia is higher in Asian countries than Western counterparts.[2] Bone marrow transplantation is the standard of care in severe and very severe aplastic anaemia, however for those with no histo-compatible donor or non-severe disease, immunosuppression remains the favoured treatment option.[3] Combined use of horse Anti thymocyte antibody (ATG) and cyclosporine (CSA) provides an overall response rate of 60–80% and shows better response rate than CsA alone.[4]

The responses are higher in the younger age group.[5]Among the antithymocyte globin, horse ATG (h ATG) has consistently fared better than rabbit ATG (r ATG) in terms of response as well as safety.[3,6,7] Several attempts to improve responses have been made but with little success; including addition of high and moderate dose cyclophosphamide to standard IST. The addition of cyclophosphamide led to increased morbidity, mortality and clonal evolution without added survival benefit or improvement in quality of life(QoL).[8] Addition of eltromobopag to CSA and hATG led to improved responses and better survival than standard immunosuppression[9] and this regimen has the promise to become the new standard of care in acquired aplastic anaemia not eligible for transplantation.[10] Despite obvious efficacy and good safety profile of eltromobopag, cost remains a concern .Similarly cost and availability of horse ATG remains a hurdle to its use in developing countries. In such cases, combination of rATG with CSA[11] or CSA alone remain reasonable alternatives[12].

Compared to ATG alone, CSA is less expensive and has a better safety profile; making it a reasonable monotherapy option in resource constrained settings. Alemtuzumab, anti CD52 antibody has also been used in relapsed refractory settings albeit with poor outcomes. In developing countries; financial constraints coupled with limited drug availability are major limitations to optimal patient management.[14] Thus choice of IST needs to be individualized keeping in view infection risk, drug availability, cost and probability of response.

MATERIAL AND METHODS

This study was conducted at Armed Forces Bone Marrow transplant Centre/National Institute of Bone Marrow Transplant after approval by the hospital ethical committee. Medical records of all patients of aplastic anaemia treated at our centre with immunosuppressive therapy from 2005-2019 in either inpatient or outpatient setting were reviewed retrospectively. Outcomes were assessed in terms of response to treatment at 3, 6 and 12 months and overall survival. Patients with newly diagnosed aplastic anaemia and treated with IST for a minimum duration of 12 weeks from 2005-2019 were included in the study. Exclusion criteria included patient not completing 12 weeks of treatment owing to either death, poor compliance, loss to follow up, pregnancy, patients less than 2 years of age, a diagnosis of inherited bone marrow failure, classical paroxysmal nocturnal haemoglobinuria, myelodysplastic syndrome and aplastic anaemia post allogenic stem cell transplant. Aplastic anaemia was defined as pancytopenia(at least 2 of the following criteria; haemoglobin <10 g/dl, absolute neutrophil count(ANC) less than $1.5x10^9$/l or platelet count less than $50x10^9$/L) with hypocellular marrow in absence of bone marrow fibrosis , infiltrate and other disease .Severe Aplastic Anaemia (SAA) was defined as at least 2 of the following; reticulocyte count less than $60x10^9$/l , ANC less than $0.5x10^9$/l, platelet count less than $20x10^9$/l. Very Severe Aplastic Anaemia (VSAA) was defined the same as SAA except ANC of less than 0.2 10^9/l. Non Severe Aplastic Anaemia (NSAA) was defined as aplastic anaemia not meeting criteria of SAA/VSAA. Treatment choices were as per physician discretion, patient's disease severity, functional and socioeconomic status. Patients received five broad categories of IST therapies namely Cyclosporine (CSA) alone, CSA plus rATG, CSA plus hATG, CSA plus mycophenolate Moeftil (CSA+MMF) and CSA plus anabolic steroids. Cyclosporine was given orally at a starting dose of 5 mg/kg/day in two divided doses and dose modified as per serum trough levels and tolerance. Target drug trough levels were 150–200 ng/ml. Since the cost of frequent measurement of serum trough levels was challenging particularly in the less affording population, we relied on serum creatinine levels and side effect profile to tailor dose adjustments in this subset of patients. Dose of rATG was 3.75 mg/kg x 5 days. Response assessment was done as per British Committee for Standard Haematology (BCSH) response criteria.[3] Response was assessed at 3, 6 and 12 months. Response was defined as complete response (CR) if there was normalization of counts and transfusion independence, partial response (PR) if the patient did show improvement in counts and transfusion dependency but not full recovery and no response if the cell counts and transfusion requirement remain unchanged. Overall response rate (ORR) included both complete and partial response. CSA was discontinued at 6 months in non-responders. It was continued for 2 years in those who achieved CR and then slowly tapered. If cytopenia were observed during tapering, CSA was reinstituted at a previous higher dose and continued indefinitely. CSA was continued indefinitely in those who achieved PR or those who relapsed on drug taper and responded to drug reinstitution. CSA was stopped at any point in time if unacceptable side effects developed e.g, severe renal or hepatic toxicity, posterior reversible encephalopathy or thrombotic microangiopathy. Patients were monitored at regular intervals based on disease severity with complete blood count, renal function tests, liver function tests, complications and adverse effects, infectious episodes, transfusion requirements and additional treatments. For other treatment groups, treatment was continued for CSA+MMF and CSA+ anabolic steroid group in the same manner as CSA alone group. While in CSA+ rATG and CSA + hATG group, rATG and hATG were given as per schedule and CSA was administered as descried above. We calculated the response rate by using above defined criteria. We used univariate and multivariate Cox regression analysis to determine significance of different variables and their effect on response. Cox regressions were used to estimate hazard ratios among given subgroup stratifications. We considered *p*-value of <0.05 to be statistically significant. We used SPSS (IBM corps, Armonk, N.Y., USA) version 23.0 to complete our statistical analysis.

RESULTS

Five hundred and thirteen patients were included in the study of which 72.5 % (n=372) were males and 27.5 % (n=141) females. Severity distribution was 54.4% (n=279) SAA, 22.8 % (n=117) each of VSAA and NSAA. Median age of presentation was 23 years (2–97 years). Solvent and pesticide exposure was seen in 4.9% (n=25) and 8.8% (n=45) respectively while 22.2% (n=114) population were farmers.

Patients were divided into five categories based on age. Due to financial constraints PNH screening was performed using flow cytometry for CD55, 59 on RBCs in 52.3% (n=273) patients and PNH clone was detectable in 2.5% of evaluable (n=7) patients. This low frequency of PNH clone detection is likely due to testing on RBC only and lack of FLAER testing. Cytogenetic analysis was performed in 46.3% (n=238) patients. Only 0.2% (n=1) of total population had any anomaly on cytogenetic analysis (trisomy 8). Base line characteristics of study population are summarized in table-1. Patients were divided into five main treatment categories. Out of 513 patients, 69.2% (n=355) received CSA alone while 14.81% (n=76) received CSA and rATG. Lack of HLA compatible donor, unavailability of finances were reason for treatment with IST rather than HSCT. Treatment

modalities used and response in various disease categories are summarized in table 2. Overall response to IST in different subgroups as per disease severity are tabulated (Table-3).

Overall response rate to IST was 30.2% (n=115), of which 12.3% (n=63) achieved CR and 17.9% (n=92) achieved PR. Overall survival (OS) in the NSAA subgroup 62% (n=72) Treatment response across all treatment modalities in this subgroup was 50.4% (n=59) while 36.8% (n=43) did not respond. Disease response was highest in the CSA+hATG group (ORR 100%, CR 25%, PR 75%), however the patient number in this arm was very low (n=4) and results cannot be generalized. CSA +rATG (n=8) group had PR in 50% patients (n=4) while rest did not respond. Patients with NSAA had better response rate across all treatment modalities as compared to SAA/VSAA groups (50.4% vs 28.7% and 13.4%) (p=0.013).

Treatment response in the SAA/VSAA subgroup was 28.7% (n=80) and 13.7% (n=16) respectively. Response to CSA alone was 28.10% (n=54) in SAA and 10% (n=7) in VSAA group. CSA+ hATG gave 43.7% (n=7) response in SAA and 33.3% (n=6) in VSAA group. CSA +r ATG showed 35.1% (n=13) response in SAA and 22.5% (n=7) in VSAA group. Overall response rate to IST in this high-risk population was disappointing and overall survival in the SAA group was 43% (n=112) while in the VSAA group was only 18% (n=21). There was no difference in response to IST across different age groups (Table-4). Patients with SAA had best response to CSA alone in 41–60 age group at 29.2 % (n=12) VSAA subgroup had disappointingly poor responses across all age and treatment modality groups. Most common adverse effects recorded in our study population were febrile neutropenia in 48.2%, azotaemia 27.5%, gum hypertrophy in 18.9%, hypertension in 16.5%. Clonal evolution to MDS, AML and PNH was seen in 8, 7 and 9 patients respectively.

Table-1: Summary of baseline characteristics

Parameters	Values
Total number of subjects (N)	513
Age in years; median (range)	23 (2-97)
0–14 years	114 (22.2%)
15–24 years	160 (31.2%)
25–40 years	124 (24.2%)
41–60 years	82 (16%)
>60 years	33 (6.4%)
Gender	
Male	372 (72.5%)
Female	141 (27.5%)
Baseline laboratory parameters	
Hb median (range)	7.6 (1.3-15.40)
Reticulocyte count median (range)	0.2 (0.0-8.0)
ANC median (range	0.5 (0.01-7.19)
Platelet count median (range)	9.0 (0.0-185.0)

Table-2: **There is a statistically significant association between the treatment modality used and the overall response rate (p=0.013). The treatment modalities CSA+androgen and CSA+MMF were merged together to satisfy the conditions necessary to run Pearson's Chi square test/ chi square test of independence**

Treatment modality	Disease Severity	Response outcome n (%)					ORR
		Complete Response	Partial Response	No Response	Not evaluable	Spont. Recovery	
CSA (n= 355)	NSAA (n= 93)	22 (23.6%)	27 (29%)	32 (34.4%)	12 (12.9%)	0	52.60%
	SAA (n= 192)	20 (10.4%)	34 (17.7%)	114 (59.3%)	22 (11.4%)	2 (1.0%)	28.10%
	VSAA (n= 70)	4 (5.7%)	3 (4.2%)	49 (70%)	14 (20%)	0	10%
CSA + androgen (n= 54)	NSAA (n= 11)	0	2 (18.1%)	7 (63.6%)	2 (18.1%)	0	18.10%
	SAA (n= 33)	2 (6%)	4 (12.1%)	25 (75.7%)	2 (6%)	0	18.10%
	VSAA (n= 10)	0	0	10 (100%)	0	0	0%
CSA + rATG (n= 76)	NSAA (n= 8)	0	4 (50%)	3 (37.5%)	1 (12.5%)	0	50%
	SAA (n= 37)	4 (10.8%)	9 (24.3%)	20 (54%)	4 (10.8%)	0	35.10%
	VSAA (n= 31)	4 (12.9%)	3 (9.6%)	23 (74.1%)	1 (3.2%)	0	22.50%
CSA + hATG (n= 26)	NSAA (n= 4)	1 (25%)	3 (75%)	0	0	0	100%
	SAA (n= 16)	4 (25%)	3 (18.7%)	9 (56.2%)	0	0	43.70%
	VSAA (n= 6)	2 (33.3%)	0	4 (66.6%)	0	0	33.30%
CSA + MMF (n= 2)	NSAA (n=1)	0	0	1 (100%)	0	0	0%
	SAA (n=1)	0	0	1 (100%)	0	0	0%
	VSAA (n=0)	0	0	0	0	0	0%

Table-3: Responses to treatment based on disease severity

Response to all treatments n (%)		Response outcome according to disease severity n (%)		
		NSAA	SAA	VSAA
		n=117	n=279	n=117
Responded				
CR+PR	115 (30.2%)	59 (50.4%)	80 (28.7%)	16 (13.7%)
Not responded (NR)	298 (58.1%)	43 (36.8%)	169 (60.6%)	86 (73.5%)
Not evaluable	58 (11.3%)	15 (12.8%)	28 (10%)	15 (12.8%)
Spontaneous recovery	2 (0.4%)	0	2 (0.4%)	0

Table-4: Response to IST modalities as per age

Age Group in years	Disease severity	Treatment Modality									
		CSA	RR	CSA+Androgen	RR	CSA+ATG	RR	CSA+ALG	RR	CSA+MMF	RR
0-14 n=114	NSAA n=12	8	4 (50%)	2	0	1	0	1	1 (100%)	0	0
	SAA n=67	43	10 (23.2%)	8	1 (12.5%)	11	5(45.4%)	5	3 (60%)	0	0
	VSAA n=35	19	1 (5.2%)	4	0	9	4(44.4%)	3	1 (33.3%)	0	0
15-24 n=160	NSAA n=34	24	13 (54.1%)	5	1 (20%)	3	2(66.6%)	2	2 (100%)	0	0
	SAA n=87	58	16 (27.5%)	10	3 (30%)	14	3(21.4%)	5	2 (40%)	0	0
	VSAA n=39	20	3 (15%)	3	0	14	2 (14.2%)	1	1 (100%)	0	0
25-40 n=124	NSAA n=47	41	19 (46.3%)	1	1 (100%)	4	2 (50%)	1	1 (100%)	0	0
	SAA n=57	38	14 (36.8%)	9	1 (11.1%)	5	2 (40%)	5	2 (40%)	0	0
	VSAA n=20	14	1 (7.1%)	1	0	5	1 (20%)	0	0	0	0
41-60 n=82	NSAA n=15	12	9 (75%)	2	0	0	0	0	0	1	0
	SAA n=53	41	12 (29.2%)	4	1 (25%)	7	3(42.8%)	1	0	0	0
	VSAA n=14	11	1 (9.0%)	0	0	2	0	1	0	0	0
>60 n=33	NSAA n=9	8	4 (50%)	1	0	0	0	0	0	0	0
	SAA n=15	12	2 (16.6%)	2	0	0	0	0	0	1	0
	VSAA n=9	6	1 (16.6%)	2	0	0	0	1	0	0	0

DISCUSSION

This is one of the largest single center studies of 513 AA patients treated with IST alone in a tertiary care center in northern Pakistan. Managing aplastic anaemia patients in resource constraint settings like Pakistan has its inherent peculiarities like non availability of hATG, financial burden associated with use of TPO agonists and undergoing HSCT, lack of quality transfusion services and non-availability of MUD registry. Since there is a paucity of data pertaining to IST responses in aplastic anaemia patients in Pakistan, this study adds to our current knowledge of treatment options and response in this population subset.

The overall response rate in our study was 30.2%, of which 12.3%was complete remission (CR) and 17.9% partial remission (PR). For 11.3% of patient responses were not evaluable either due to loss of patient follow up or incomplete documentation on follow up visits. Of the responders, vast majority belonged to the NSAA group (50.4%). The response rate in our study correlated with disease severity (p<0.001) as demonstrated by other international studies.[13,14] The response rate to combined IST is 50–78%[1] in Western literature and 40–70% in Indian subcontinent[15,16]. The inferior response rate in our study is likely due to use of single agent CSA in majority of patients (69.2%) and NSAA population being only 22.8%.CSA alone gave an ORR of 52.6% in the NSAA population. CSA combined with rATG was used in 14.81% patients and ORR was 35.1% in the SAA which is comparable to the response rate in international studies.[17] Although higher responses have been reported with CsA+hATG±eltrombopag as compared to CsA+rATG, cost and availability of horse ATG and eltrombopag is a challenge in the resource constrained settings of the low-income countries. In our study, NSAA responses to CsA alone and CsA+rATG were similar; albeit lesser number of patients in CsA+rATG group which is a confounder; CSA alone seems a reasonable option given its low cost, ease of administration and reasonable response rate. Also, there was no significant difference elucidated in the response rate in terms of age in our patient population unlike other studies which report a greater, deeper and earlier response rate in the paediatric population. This difference could be due to etiological differences as compared to western patients, and also poor compliance to oral medications in this patient subgroup, although studies assessing compliance to oral medications in this age group are lacking. The higher observed incidence of aplastic anaemia in eastern population is likely linked to increased marital consanguinity, higher incidence of viral hepatitis, prevalent use of herbal and alternative medicine, role of HLA susceptibility and protective loci, aldehyde dehydrogenase enzyme and lack of genetic testing facility to adequately distinguish bone marrow failure syndromes from immune aplastic anaemia.[13] In our study, disease severity alone was an independent predictor of inferior survival. CSA along with MMF and androgens were also associated with inferior survival.

The large sample size and comparison of various single agent and combined IST modalities could be used to guide treatment and compare responses in the population of North Pakistan. This study serves to substantiate the effectiveness of CSA alone in resource constrained settings where availability of horse ATG is an issue and administration of rabbit ATG is riddled with concerns regarding questionable efficacy and possible consequence of increased infectious morbidity and mortality given the higher immunosuppressive potential of rabbit versus horse ATG. Owing to financial constraints, TPO analogues are not likely to replace conventional IST soon despite having shown promising results even in local population. Although the efficacy of CSA alone is modest, its adverse profile is acceptable and cost, although considerable

for a third world country like Pakistan, is still acceptable.

CONCLUSION

Although combined immunosuppression remains the preferred immunosuppression for aplastic anaemia, however in resource constrained settings, cyclosporine alone remains a reasonable alternative with modest activity and acceptable side effect profile. This study provides evidence for efficacy and safety of cyclosporine monotherapy in our population

Ethical Approval

All procedures performed in this study were in accordance with the ethical standards of the İnstitutional Research Committee and 1964 Helsinki Declaration and its later amendments. This study was approved by Armed Forces Bone Marrow Transplant Centre Medical Ethics Committee.

Patient's Consent

Informed consents were taken from all participants of this study.

Conflict of Interest

All authors claim no conflict of interest.

AUTHORS' CONTRIBUTION

MK: Contribution to the design, concept, data acquisition, analysis and paper writing. RI: Drafting the work, critically revising. QUN: Drafting the work, analysis and paper writing. SKM, TG, NS, MAK: Contribution to the study design and discussion writing. TF: Data analysis. GS/TAK: result analysis and final approved of the draft

REFERENCES

1. Young NS. Aplastic Anaemia. N Engl J Med 2018;379(17):1643–56. Ref no 1&13 are same
2. Ahmed P, Chaudhry QUN, Satti TM, Mahmood SK, Ghafoor T, Shahbaz N, *et al*. Epidemiology of aplastic anaemia: a study of 1324 cases. Hematology 2020;25(1):48–54.
3. Killick SB, Bown N, Cavenagh J, Dokal I, Foukaneli T, Hill A, *et al*. Guidelines for the diagnosis and management of adult aplastic anaemia. Br J Haematol 2016;172(2):187–207.
4. Vaht K, Göransson M, Carlson K, Isaksson C, Lenhoff S, Sandstedt A, *et al*. Incidence and outcome of acquired aplastic anaemia: real-world data from patients diagnosed in Sweden from 2000-2011. Haematologica 2017;102(10):1683–90.
5. Rogers ZR, Nakano TA, Olson TS, Bertuch AA, Wang W, Gillio A, *et al*. Immunosuppressive therapy for pediatric aplastic anaemia: a North American Pediatric Aplastic Anaemia Consortium study. Haematologica 2019;104(10):1974–83.
6. Georges GE, Storb R. Hematopoietic stem cell transplantation for acquired aplastic anaemia. Curr Opin Hematol 2016;23(6):495–500.
7. Alashkar F, Oelmüller M, Herich-Terhürne D, Turki AT, Schmitz C, Vance C, *et al*. Immunosuppressive therapy (IST) in adult patients with acquired aplastic anaemia (AA): A single-center experience over the past 15 years. Eur J Haematol 2019;103(1):18–25.
8. Scheinberg P, Townsley D, Dumitriu B, Scheinberg P, Weinstein B, Daphtary M, *et al*. Moderate-dose cyclophosphamide for severe aplastic anaemia has significant toxicity and does not prevent relapse and clonal evolution. Blood 2014;124(18):2820–3.
9. Peffault de Latour R, Kulasekararaj A, Iacobelli S, Terwel SR, Cook R, Griffin M, *et al*. Eltrombopag Added to Immunosuppression in Severe Aplastic Anaemia. N Engl J Med 2022;386(1):11–23.
10. Townsley DM, Scheinberg P, Winkler T, Desmond R, Dumitriu B, Rios O, *et al*. Eltrombopag added to standard immunosuppression for aplastic anaemia. N Engl J Med 2017;376(16):1540–50.
11. Chuncharunee S, Wong R, Rojnuckarin P, Chang CS, Chang KM, Lu MY, *et al*. Efficacy of rabbit antithymocyte globulin as first-line treatment of severe aplastic anaemia: an Asian multicenter retrospective study. Int J Hematol 2016;104(4):454–61.
12. Mandal PK, Baul S, Dolai TK, De R, Chakrabarti P. Outcome of Cyclosporine Monotherapy in Patients of Aplastic Anaemia: Experience of a Tertiary Care Hospital in Eastern India. Indian J Hematol Blood Transfus 2017;33(1):144–7.
13. Iftikhar R, Ahmad P, de Latour R, Dufour C, Risitano A, Chaudhri N, *et al*. Special issues related to the diagnosis and management of acquired aplastic anaemia in countries with restricted resources, a report on behalf of the Eastern Mediterranean blood and marrow transplantation (EMBMT) group and severe aplastic anaemia working party of the European Society for blood and marrow transplantation (SAAWP of EBMT). Bone Marrow Transplant 2021;56(10):2518–32.
14. Boddu P, Garcia-Manero G, Ravandi F, Borthakur G, Jabbour E, DiNardo C, *et al*. Clinical outcomes in adult patients with aplastic anaemia: A single institution experience. Am J Hematol 2017;92(12):1295–302.
15. Agarwal MB, Jijina F, Shah S, Malhotra P, Damodar S, Ross C. Safety and efficacy of indigenous equine antithymocyte globulin along with cyclosporine in subjects with acquired aplastic anaemia. Indian J Hematol Blood Transfus 2015;31(2):174–9.
16. Shah S, Jain P, Shah K, Patel K, Parikh S, Patel A, *et al*. Immunosuppressive therapy for aplastic anaemia: a single-center experience from western India. Ann Hematol 2019;98(1):41–6.
17. Bacigalupo A, Oneto R, Schrezenmeier H, Hochsmann B, Dufour C, Kojima S, *et al*. First line treatment of aplastic anaemia with thymoglobuline in Europe and Asia: Outcome of 955 patients treated 2001-2012. Am J Hematol 2018;93(5):643–8.

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