Clinical Profile of Hepatitis Associated Aplastic Anemia (HAAA) in Six Children

Hepatitis associated aplastic anemia (HAAA) is a rare condition, characterized by onset of pancytopenia, usually occurring within a period of six months from developing acute hepatitis (an elevation of alanine transaminase (ALT) more than five times the upper limit of normal), with or without acute liver failure [1]. The trigger is thought to be an autoimmune mechanism with viral induced proliferation of activated cytotoxic T-lymphocytes, mediated by tumor necrosis factor alpha (TNF-α) and inter-feron-gamma (IFN-γ) [1-3]. We report six children with this condition who were managed by us (**Table I**).

The median age of the patients was 5.5 years (range 2-9 years). The median duration to onset of pancytopenia, from the onset of acute hepatitis / acute liver failure (ALF) was 7 weeks (range 0-15 weeks). One each tested positive for anti-nuclear antibodies (ANA, titre 1:160) and anti-mitochondrial antibodies (AMA, titre 1:80), as part of extended autoimmune workup. Routine viral markers including all hepatotropic viruses (Hepa-titis A, B, C, D, E) as well as extended viral markers (including parvovirus B19) were negative in all six patients. Case 1 recovered from hepatitis with supportive care, but failed Immunosuppressive Therapy (IST) for aplastic anemia (AA) and received a haploidentical hematopoietic stem cell transplant (HSCT). Case 2 developed ALF but responded to supportive care, and was started only on eltrombopag for AA, which supported count recovery. Case 3 underwent a liver transplant for ALF, and subsequently received immunosuppre-ssive therapy (IST) for aplastic anemia (AA), failing which he underwent a matched sibling donor (MSD) HSCT. Case 4 was started on steroids and azathioprine for autoimmune hepatitis (AIH). While on treatment, he developed severe AA, and eltrombopag was added while he underwent workup for a planned HSCT. However, counts recovered without needing further treatment. Case 5 underwent a liver transplant for ALF, while counts recovered spontaneously. Case 6 presented with hepatitis and AA together, was diagnosed with AIH and started on steroids, azathioprine and eltrombopag. He responded well with resolution of both hepatitis and AA.

Three of these children are being continued on immuno-suppression, which includes one of the patients who has under-gone HSCT recently. After a median follow-up (from onset of hepatitis) of 27 months (range 6-72 months), all patients are alive with normal liver/graft functions and trilineage hematopoiesis.

A non-exhaustive review of previously reported literature is detailed in **Web Table I**. The incidence of HAAA amongst all cases of AA differs geographically ranging from 2-5% in the West to 15-20% in the Far-East where hepatitis is more common. The severity of hepatitis can be mild and self-limiting, to fulminant requiring liver

Table I Clinical Profile of Patients With Hepatitis Associated Aplastic Anemia

No.	*Serostatus (viral markers/ autoimmune)*	*Age (y) / sex*	*ALF*	*LT*	*Onset to pancyto-penia from hepatitis/ALF*	*Degree of aplastic anemia*	*Bone marrow cellu-larity*	*Spon-taneous recovery of marrow*	*Immuno-suppressive therapy*	*BMT*	*Others*	*Follow-up (mo)*
1	ANA positive (1:160)	9/M	No	No	4 wks	VSAA	<5%	No	ATG, CsA: (failed)	Yes (haplo)	Eltrombopag	30
2	Seronegative	4/M	Yes	No	8 wks	NSAA	50-60%	Yes	No	No	Eltrombopag	6
3	Seronegative	5/M	Yes	Yes	15 wks	VSAA	10-15%	No	ATG, CsA (failed) Post BMT: Tacrolimus	Yes (MSD)	Eltrombopag	12
4	Seronegative	7/M	No	No	12 wks	SAA	5-10%	No	Steroids, azathioprine	No	Eltrombopag	24
5	Seronegative	2/F	Yes	Yes	4 wks	SAA	10-15%	Yes	No	No		72
6	AMA positive (1:80)	6/M	No	No	Simultaneous	NSAA	50-60%	No	Steroids, IVIg, azathioprine	No	Eltrombopag	18

AA: Aplastic anemia, ALF: Acute liver failure, ANA: Anti-nuclear antibody, AMA: Anti mitochondrial antibody, ATG: Anti-thymocyte globulin, BMT: Bone marrow transplant, CsA: Cyclosporine A, MSD: Matched sibling donor, Haplo: Haploidentical, IVIg: Intravenous immune globulin, NSAA: Non-severe aplastic anemia, SAA: Severe aplastic anemia, VSAA: Very severe aplastic anemia.

transplantation, as seen in our cases [4]. The duration to onset of AA in our cases was similar to other reports [5,6], and the range has been reported to vary from a few days up to even a year [7]. Although, all of our patients tested sero-negative for hepatotropic viruses, non-A non-B hepatitis (NANBH) is thought to be the causative factor of nearly 80% of HAAA.

HAAA is managed similar to non-hepatitis aplastic anemia, with IST and HSCT as established primary treatment modalities [1,2,4,7,8]. Four of our patients received immunosuppression, with two treated for AIH with steroids and azathioprine, which is standard first line of treatment for AIH [9]. These immunosuppressants presumably contributed to recovery from subsequent HAAA as well, further supporting the basis of an underlying immune etiology. Eltrombopag, a thrombopoietin receptor agonist has shown promising results in adults either in isolation or in combination with IST as it is effective in stimulating trilineage hematopoiesis, even after discontinuation of the drug [10]. We used it in five of our patients.

Children developing hepatitis should be monitored closely with regular blood counts during the first year to identify possible development of pancytopenia, to initiate early therapy. A multidisciplinary approach involving the pediatric hepatologists and hematologists is vital to optimize care for such patients.

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Note: Additional material available at *www.indianpediatrics.net*

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