

cultivates social responsibility to the trainees, which is necessary for the progress of the society. We strongly believe that first aid training shall be included as part of basic education as a compulsory module, that can be taught by trained school teachers.

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Safety: A Primary Concern in Thalidomide Use in Thalassemia

I read with interest the article by Chandra, et al. [1] published in the journal recently. Authors have presented their data on the efficacy and safety of thalidomide in adolescents with transfusion dependent thalassemia (TDT). It is an excellent effort and much awaited publication keeping in view the quantum of thalassemia in India, the high cost of bone marrow transplant (BMT), and the scarce data on use of thalidomide in TDT. However, I would like to highlight a few issues in the study.

The primary concern with use of thalidomide in TDT remains safety rather than efficacy. A study period of six months is too short for a disease requiring long-term therapy with thalidomide. During a study of any new drug for a disease, the criteria for stoppage of trial are pre-defined for ensuring safety [2]. In their study, 8/37 developed infection with one death (due to unrelated causes), and 10/37 developed neutropenia (one severe grade-III neutropenia) and one grade-IV renal injury. Such a high incidence of neutropenia is unexplained by co-administration of deferiprone alone [3]. Considering the small sample size, continuing the trial despite severe adverse reactions may warrant more details.

The very low baseline mean hemoglobin F (HbF) and the steep rise in the study [1] is not supported by the literature. Mean baseline HbF levels were 2.95% and have risen to 49.2% after six months of thalidomide therapy. The baseline levels are generally higher (10-60%) in adolescents in the studies of HbF inducers in thalassemia [4]. Also in clinical studies, on an average, a 20% rise is seen in responders of HbF-inducer agents in thalassemia [5].

The baseline mean packed cell received in the study cohort was 75 mL/kg in last 6 months, which seems quite modest for adolescent children with thalassemia (12-18 years) as their requirement is high due to growth and pubertal spurt. Even the sample size calculation in the study was based on assumption of 220 mL/kg/year. Therefore, was there a selection bias as the cases were randomly enrolled?

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Presuming the mean hemoglobin (Hb) depicted in comparative table II are mean pre-transfusion Hb (not mentioned in methodology); mean Hb at baseline was 9.45 g/dL and at end of study was 8.89 g/dL. Were study children under-transfused during study period of 6 months? Also, mean thalidomide dose in baseline table I is 2.05 mg/kg/day, which is well below the mean daily dose of thalidomide in three response groups as depicted in Table III.

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REPLY

We are thankful to the reader for appreciating the need for developing drugs for thalassemia. The learned reader has reiterated the same safety issues which we had already mentioned in the last paragraph of our paper, including the need for larger studies addressing safety of thalidomide [1]. We restricted the study for 6 months on account of financial reasons.

As regards adverse effects (AEs), reader's attention is drawn to a recent study on another fetal haemoglobin (HbF) inducer—luspaterecept. In this study, 96% patients had one or more AE with 29% having AE grade 3 or more, 15% having serious AE with

several having infections. Even patients in placebo group had several infections [2]. High incidence of neutropenia is an important finding and it was rightly documented. The reader has quoted our previous work, which looked at deferiprone safety in young children. This study had children on deferiprone monotherapy [3].

The very low baseline mean HbF were on account of the fact that the patients were on regular transfusion at 2-3 weeks interval, with mean pre-transfusion Hb of 9-10.5 g/dL, which is expected to keep patients' erythropoiesis under check. The study by Ren, et al. [4] was in patients with thalassemia intermedia, where higher baseline HbF are noted as these patients are not regularly transfused [4]. A good pre-transfusion Hb is also the reason for lower requirement of packed cell. Hb during the study is slightly lower than baseline Hb but the difference is statistically not significant. The dose of thalidomide in Table I is the starting dose.

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