Hydroxycarbamide for very young children with sickle cell anaemia: no effect on the primary outcomes of spleen or kidney function, but evidence for decreased pain and dactylitis, with minimal toxicity

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Context
Sickle cell anaemia (SCA) is a disorder of haemoglobin polymerisation that results in vaso-occlusion and haemolytic anaemia, culminating in organ injury and early mortality. Elevated fetal haemoglobin has been associated with a less severe phenotype leading to an interest in hydroxycarbamide (also known as hydroxyurea) use. The MSH study demonstrated that hydroxycarbamide in adults with severe sickle cell disease reduced painful events, hospitalisations, acute chest syndrome and the number of blood transfusions. The HUG–KIDS study, a phase I/II study, demonstrated safety and haematologic responses to hydroxyurea in children aged 5–15 years of age. The HUSOFT study was conducted in infants and very young children for 2 years with similar end points and favourable results. Two adult trials document the benefits of hydroxyurea in reducing mortality in SCA. The BABY HUG study was designed to answer whether hydroxyurea given to infants with SCA for 2 years slows or delays organ damage.

Methods
To this end, a randomised, double-blind placebo-controlled clinical trial was conducted. Haemoglobin SS or Sβ0 patients, aged between 9 and 18 months, were enrolled without selection for clinical severity. Primary end points were splenic function as assessed by 99Tc spleen scans and renal function by 99mTc-DTPA scan. The treatment and placebo groups were well matched at entry for multiple potentially confounding variables. Of note, rate of splenic sequestration before study enrollment was lower in the hydroxyurea group, raising the concern that this imbalance could bias results towards the null hypothesis and not identify an increased rate of sequestration related to hydroxyurea use. Masked readings were done of splenic uptake on liver–spleen scans.

Findings
Although the primary end points did not differ significantly by treatment group, hydroxyurea was extremely well tolerated. The haematologic response was robust (hydroxyurea was associated with increases in haemoglobin levels). Hydroxyurea was associated with reductions in pain (177 events in 62 patients vs 375 events in 75 patients in the placebo group) and dactylitis (24 events in 14 patients vs 123 events in 42 patients in the placebo group) that were highly statistically significant. Increase in transcranial Doppler ultrasound velocity from entry to exit was lower in the hydroxyurea group.

Commentary
This was a well-designed and carefully conducted study. Masked readings of splenic scans were the strength of the study and may explain the difference in outcome in comparison with the earlier studies. However, given the qualitative nature of these scans and trend towards improvement on quantitative studies, it is biologically plausible that a longer duration of follow-up will show preservation of splenic function. Likewise, documenting delayed renal toxicity will likely require longer follow-up and perhaps a slightly older cohort.

On the basis of this study, use of hydroxyurea in infants and very young children with SCA who have had vaso-occlusive crises and dactylitis is warranted. Using it for the treatment for severe anaemia in this age group is also a rational approach. It is important to note that the secondary end points for splenic (Howell jolly body counts and Pitted cell counts) and renal (urine osmolality and specific gravity) function, based on the authors’ stated criteria of a p<0.01, were also not statistically improved in comparison with the earlier studies. However, given the stage for serious consideration and further examination, it is not yet clear that hydroxyurea should be recommended for all SCA infants as ‘prophylactic’ therapy. Ideally, a registry would best provide these answers as well as surveillance for any longer term toxicity.

Competing interests None.

References

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