

Finally a stroke prevention strategy that requires less blood transfusion therapy in sickle cell anaemia: the Transcranial Doppler (TCD) With Transfusions Changing to Hydroxyurea (TWiTCH) Trial

The North American TWiTCH Trial has established a new standard of care for primary stroke prevention in children with sickle cell anaemia and elevated transcranial Doppler (TCD) measurements, who, if untreated, have approximately a 10% annual stroke rate. In this high risk group, with the use of regular blood transfusion therapy, when compared to observation, there is 92% relative risk reduction of strokes with < 1% annual stroke rate. However this efficacious treatment comes with an intense family burden, typically requiring at least monthly blood transfusions, with each visit lasting for up to 6 hours and resulting in the anticipated medical complications, including red blood cell allo-immunization (1), which may preclude further transfusion, risk of the transmission of infectious agents, and excessive iron stores eventually requiring subcutaneous or oral chelation therapy (2) or phlebotomy. The primary question addressed by Ware et al. was exactly the question that every family asks when told that their child has an elevated TCD velocity that necessitates blood transfusion therapy to prevent a first time stroke: “how long must my child be on blood transfusion therapy?” Up until now the unsatisfactory answer has been “indefinite”.

Based on the results of the TWiTCH Trial, after least a year of blood transfusion therapy, the providers and family will now have an evidence base to consider their options of continued blood transfusion therapy or switching to hydroxyurea therapy. Unfortunately, monitoring TCD velocities after the start of hydroxyurea therapy may provide a false sense of security because the

TCD velocities are only predictive of strokes in untreated children with SCA and may not predict strokes once blood transfusion therapy begins. In STOP, TCD velocities remained abnormal in 21% of the participants after a mean of 2.4 years of transfusion;(3) small studies have not found evidence that these children are at higher risk of stroke but follow-up has been short.(4) Based on the compelling results of the TWiTCH Trial, we anticipate that persistence of elevated TCD velocities after the start of hydroxyurea therapy will not predict a future stroke; however, without longer term follow up we simply do not know if this will be the case. What is initially reassuring is that once the velocity had reduced to < 200 cm/sec while being transfused, no participant had an increase to > 200 cm/sec after being placed only on hydroxyurea therapy. The only way of knowing if children placed on hydroxyurea therapy with elevated TCD measurements will have sustainable protection for primary stroke prevention is to continue to follow the current cohort for a much longer period of time or create a new cohort for this purpose. Given the pre-existing clinical trial infrastructure, expertise and pre-selected participants, consideration of a TWiTCH II to better define the long term benefits of hydroxyurea therapy for primary prevention of strokes should be considered.

What about primary stroke prevention for the populations of sub-Saharan Africa and India, where $> 80\%$ of the 300,000 children with sickle anaemia are born?(5) In this high risk stroke population, access to monthly blood transfusion therapy, even for one year, is not feasible for most children.(6) The results of the TWiTCH trial are encouraging for this vulnerable population as well. Although, we do not know if starting hydroxyurea therapy immediately after detection of an elevated TCD velocity is efficacious in preventing strokes, the TWiTCH trial has provided further evidence that primary stroke prevention for children living in sub-Saharan Africa and India is possible with hydroxyurea therapy. What is not known for primary stroke prevention in

low and middle income countries is the optimal dose of hydroxyurea therapy that maximizes benefit whilst minimizing risks of treatment and the financial and human burden of laboratory surveillance for hydroxyurea related toxicity. Based on preliminary evidence from a feasibility trial,(7) the National Institute of Neurological Disorders and Strokes has just funded a randomized clinical trial (NCT02560935) in Nigeria for children with SCA elevated TCD velocities who will be started on hydroxyurea therapy immediately after detection of abnormal TCD velocities. Perhaps completion of this trial will fill some of the knowledge gaps that will facilitate care for children with sickle cell anaemia and elevated TCD velocities in both low and high income countries. We salute the hard work of the TWITCH investigator team and the trust of the families in completing yet another randomized clinical trial to decrease stroke morbidity in children with sickle cell anaemia.

Reference List

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