To the editor:

Use of hydroxyurea in prevention of stroke in children with sickle cell disease

We carefully read the paper by Zimmerman and colleagues[1] about the possible effect of hydroxyurea on the transcranial doppler flow velocities in children with sickle cell disease. We reviewed the transcranial dopplers (TCD) performed on the children with sickle cell disease in our hospital from 0 to 25 years old, treated or not treated with hydroxyurea, and we compared the trend of the time-averaged maximum velocity (TAMV) measured in the middle cerebral arteries and the incidence of stroke.

Among our 119 patients, we found that in the patients not treated with hydroxyurea, the velocity increased with age to a maximum between 6 and 9 years old ($P < .05$). This significant increase does not appear in the patients treated with hydroxyurea (Figure 1). Following the 85 patients who had repeated TCD after a mean duration of 3.1 ($\pm$ 1.5) years, we noticed that the velocity was increasing in the patients whose first TCD was normal (148 $\pm$ 16 cm/s to 172 $\pm$ 21 cm/s, n = 34, $P < .01$), stabilizing in the patients whose first TCD was conditional (181 $\pm$ 8 cm/s to 181 $\pm$ 25 cm/s, n = 30, $P = .75$); and decreasing in the patients whose first TCD was abnormal and who were thereafter treated by hydroxyurea between the first and the second TCD (235 $\pm$ 18 cm/s to 202 $\pm$ 34 cm/s, n = 21, $P < .01$). In these 21 patients with an abnormal first TCD, the velocities decreased to the normal/conditional range in 8 of them. This strengthens the observation of Zimmerman and colleagues[1] that children with the highest baseline doppler velocity had the greatest decrease in response to hydroxyurea.

In the 80 patients treated with hydroxyurea with a follow-up of 555 patient-years, 2 presented stroke, and of the 4 patients with a previous history of stroke, only one presented a new episode for a follow-up of 35 patient-years. For the 23 patients receiving hydroxyurea based on an abnormal TCD and no other clinical risk, no stroke was recorded for 84 patient-years. Seventeen of these 23 patients (mean age 5.5 $\pm$ 1.8 years) had repeated TCD after a mean duration of hydroxyurea treatment of 31 ($\pm$ 14) months. Their mean velocity dropped from 231 ($\pm$ 22) cm/s to 208 ($\pm$ 24) cm/s ($P < .01$). Magnetic resonance angiography (MRA) from 14 of these patients showed vascular stenosis in 6 of them. This stenosis persisted in 2 of the 5 patients on repeated MRA performed after a mean time of 4 ($\pm$ 1) years.

Concerning the secondary prevention of stroke, the recurrence rate of stroke in our patients treated with hydroxyurea was 2.9 for 100 patient-years, similar to that recorded in chronically transfused patients.[2,3] However, in the primary prevention of stroke, the incidence of first stroke in our patients with hydroxyurea was 0.36 for 100 patient-years, lower than in nontransfused patients of other larger cohorts[4] and lower than in the cohort of Zimmerman and colleagues (0.52 for 100 patient-years),[1] without using maximum tolerated dose of hydroxyurea.[5]

Our preliminary results therefore indicate that, in the patients at risk for stroke on the basis of transcranial doppler, hydroxyurea might be an effective and simpler alternative to chronic transfusion, as already observed in previous studies.[1,6]

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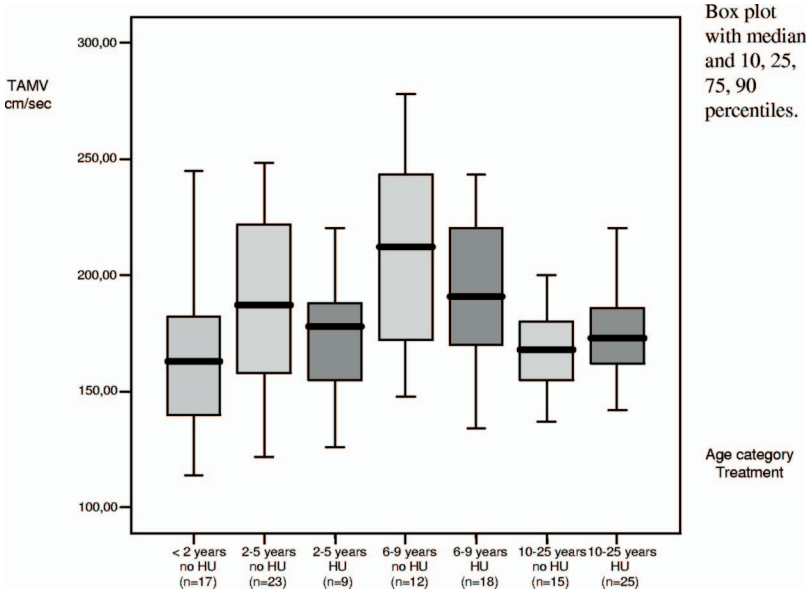

Figure 1. Median time-averaged maximum velocity (TAMV) at the first transcranial doppler (TCD) in patients treated and not treated with hydroxyurea for each age category. Box plots show medians with 25 percentiles; bars represent percentiles 10-90 sd.

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Response:

TCD response to hydroxyurea therapy

We thank the authors for summarizing the Belgian experience with transcranial doppler (TCD) for children with sickle cell disease (SCD). Although their data are retrospective, they describe significant differences in the TCD velocities of children treated with hydroxyurea compared with those who were not. Similar to our findings,[1] children with highest baseline TCD velocities had the greatest treatment-related decreases. Their data also provide additional support for the use of hydroxyurea for primary and even secondary stroke prevention in children with SCD. We are encouraged that these pilot data further document the benefits of hydroxyurea for children with SCD, yet we maintain that treatment at the maximum tolerated dose is preferred.[2] As we concluded in our paper, controlled multicenter prospective trials are needed to determine the efficacy of hydroxyurea therapy in these clinical settings.

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To the editor:

Hydrolysis of extracellular ATP and immune suppression: humans versus mice

We read with interest the recent article by Borsellino and colleagues on the role of CD39 and CD73 for the suppressor activity of $Foxp3^+$ regulatory T cells (T regs).[1]

Because the major sources of extracellular ATP are injured cells leaking cytoplasmic content, degranulating platelets, and endothelial cells under shear stress, extracellular ATP may represent a constitutive endogenous molecule that signals tissue stress and injury. Borsellino and colleagues proposed that the immune suppressive activity of T regs is due, at least in part, to their capacity to remove ATP from the extracellular space through the enzymatic activity of CD39 and CD73 expressed on their membrane.

It has been recently shown that T regs exert immune suppression by elevating intracellular cyclic AMP (cAMP) concentration in target cells.[2] As suggested by Borsellino and others, T regs might do so by degrading ATP to adenosine. In turn, adenosine activates adenylyl cyclases by triggering the cognate Gs-protein coupled receptor A2a.[1,3] However we would like to point out that in human cells ATP can act as a direct cAMP-elevating agent thus delivering a potent anti-inflammatory signal. This is because human, but not murine, cells express the purinergic receptor $P2Y_{11}$ that is the only P2 purinergic receptor coupled to adenylyl cyclases activation.[4]

Cells expressing $P2Y_{11}$ include dendritic cells (DCs), macrophages, T lymphocytes, and natural killer cells. Human DCs-exposed to micromolar concentrations of extracellular ATP do not undergo "classic" maturation. In fact, although ATP-stimulated DCs up-regulate costimulatory membrane molecules, they also display blocked pro-inflammatory cytokine and chemokine production including tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-12, CCL2, CCL3, CCL5, and CXCL10, while IL-10 and IL1Ra are either unaffected or up-regulated.[5-7] Moreover, extracellular ATP induces DCs to produce large amounts of Thrombospondin-1 and synergyzes with interferon-γ (IFN-γ) in up-regulating indoleamine 2,3 dioxygenase, turning DCs into tolerogenic antigen presenting cells.[8] These effects are mimicked by the nonhydrolyzable ATP analog ATP-γ-S and by several cyclic AMP elevating agents, as well as by the administration of cell permeable cAMP analogs.[8,9] Moreover, extracellular ATP has proven able to inhibit T lymphocyte and NK cell proliferation and cytokine production as well as NK-mediated cytotoxicity, associated with increased intracellular cAMP concentration.[10]

Extracellular ATP released from injured cells might not act as an activating danger signal but it might rather represent a negative feedback for immune cells to limit self-harmful excessive inflammation in the context of extensively damaged human tissues. This view suggests that extracellular ATP hydrolysis operated by human $CD39^+$ T regs might have more complex physiologic consequences than blunt immune suppression.

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