MEMSID: Results From a Phase 2 Pilot Study on Memantine Treatment for Sickle Cell Disease

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The World Health Organization (WHO) considers symptomatic sickle cell disease (SCD) the most deadly genetic disease worldwide.1 Recently, the European Hematology Association (EHA) reported that due to migration, an increasing number of patients suffering from SCD are living in almost every European country.2 Often combined with blood transfusions, approved drugs are currently used to reduce the incidence and severity of pain crises, hemolysis and vaso-occlusive events (VOC). The main biological effect of the standard-of-care treatment hydroxyurea is induction of fetal hemoglobin (HbF) synthesis.3 Several new compounds with different modes of action have been evaluated and licensed recently including L-Glutamine, that decreases red blood cell oxidative injury4; Voxelotor, that elevates the oxygen affinity to Hb, thus stabilizing the RBC in the oxygenated state, thereby preventing HbS fiber formation5 and Crizanlizumab, an anti-P-selectin antibody targeting adhesion of sickled RBCs to endothelium and activation of platelets in VOCS.6

Earlier we reported that intracellular Ca2+ concentration in human RBCs depends on the abundance and activity of N-methyl-D-aspartate receptors (NMDARs) that are present on the RBC’s membrane.7 These non-selective cation channels are activated when stimulated upon exposure to glutamate (homocysteine, homocysteic acid) and glycine as well as by mechanical stimuli in a variety of cell types including RBCs. Their activation results in a transient excess of cellular Ca2+ uptake.7,8 NMDARs are essential for cytoprotection and during maturation, of erythroid precursors the number or receptors drops from hundreds of thousands in a single proerythroblast to as little as 30 in young healthy RBCs.9,10 Inhibition of NMDARs using the channel inhibitor memantine (an approved anti-Alzheimer drug) resulted in an acute decrease in intracellular free Ca2+ levels in RBCs of healthy volunteers and SCD patients.7,9 Cells of SCD patients responded to NMDAR inhibition with rehydration, sickling reduction upon deoxygenation and with amelioration of oxidative stress. Based on these ex vivo findings, we hypothesized that NMDARs in the RBCs of SCD patients are a potential target for pharmacological intervention. Memantine represents a second generation NMDAR inhibitors combining safety and low price and is used to treat dementia, autism and other psychiatric conditions in adults, adolescent and children.11,12

In this proof-of-principle clinical phase 2 study termed MemSID, 6 SCD patients (Fig. 1A) were enrolled and four treated for up to 44 weeks with 5 to 20mg memantine (clinicaltrials.gov: NCT02615847). The primary objective was to test for safety and tolerability of the drug by SCD patients. The impact of the therapy on quality of life (QoL) and major hematological parameters were secondary objectives. The study was divided into 5 periods (Fig. 1C): (i) screening (up to 4 weeks), (ii) up-titration (4 weeks), (iii) treatment with 20mg memantine (41–44 weeks), (iv) down-titration (3 weeks) and (v) follow-up period (8 weeks). The planned total duration of the study was 56 to 59 weeks. For further information concerning demographics, characteristics and co-medication with hydroxyurea (see Fig. 1A). Two of 6 patients discontinued the study due to an adverse event (AE; dizziness/vertigo, P6) and a severe AE (SAE; psychosis, P5, see below and Fig. 1D). Memantine intake was monitored by determining plasma levels (Fig. 1B). After up-titration memantine levels were in a range of 30 to 90ng/ml reflecting overall good compliance by the patients with three exceptions that are mentioned below.

Figure 1D shows all AEs and SAEs of all 6 patients that started the trial. Dizziness/vertigo and tachycardia were judged as AEs possibly related to memantine, whereas dizziness/vertigo was found to be the most common symptom in 4 out of 6 patients (Fig. 1D, top). Accordingly, memantine dose was adjusted in 2 patients. One adjustment (P2 with grade III symptoms of
dizziness/vertigo) was transient, having no further consequence on the patient’s participation in the trial, while P6 (grade II dizziness/vertigo) withdrew from the study. Of note, P6 retrospectively reported suffering from dizziness even before the trial. The only observed SAE possibly related to memantine was an acute psychosis that occurred in P5 and consequently, memantine therapy was stopped immediately. Post-study analysis of plasma memantine revealed that this symptom was timely associated with very high plasma memantine levels reaching values of 155 and 137 ng/ml at week 5 and 9, respectively (Fig. 1B, marked a), before withdrawing from the trial at week 11. This patient recovered completely without rebound effects. We observed 2 additional elevations in plasma memantine levels that did not lead to psychological changes. P3 increased drug intake on his own during a pain crisis (Fig. 1B, marked b) and P4 reached similar high memantine plasma levels by accidentally taking double doses at the beginning of the study (Fig. 1B, marked c).

More AEs and SAEs were recorded but rated as not likely related to treatment (Fig. 1D, bottom). Of these AEs some were disease-related like transient pain, pain crises for over 4 hours, as well as urine analysis abnormalities and also infectious complications. More non memantine-related SAEs were patellar instability (with planned surgery) and disease-related priapism in P1 as well as severe pain crises, pneumonia and gastroenteritis in P4. Again, only one SAE (psychosis due to suspected overdose) was likely related to memantine. Two transfusion episodes were required during the study, one in the case of patient P1 before planned surgery and the second (2 units) in the case of P4 during pain crisis (1 unit). Knee surgery in P1 was associated with interruption of blood supply in the extremity, but the following hypoxemia did not lead to pain crises.

Patients’ QoL was continuously scored throughout the trial and the total score is summarized for each individual patient in Figure S2, http://links.lww.com/HS/A89. Pain crisis and infections were found to be the most important factors that influenced the scoring of the QoL. Three out of 4 patients showed a tendency of improvement in total QoL score: patient P1 and P2 (the latter upon reaching the full memantine dose) reported steady...
The impact of memantine on some RBC-related parameters

Figure 2. The impact of memantine on some RBC-related parameters. Means and 95%-CIs of RBC count, Hb, reticulocyte count, lactate dehydrogenase (LDH) activity, ferritin and total bilirubin in plasma as well as percentage of hypochromic and hyperchromic RBC isolated from patients 1 to 4 before enrolment and during the trial are shown. Note that the ferritin values for P4 reach levels around 1500 µg/l and thus are not shown here but appear in Table S2, http://links.lww.com/HS/A89. Screening has no 95%-CI since there is only one measurement. Symbols (dot, bar, * meaning p < 0.1, p < 0.05, p < 0.01, respectively; values are compared with screening value using Welch t test, not adjusted). Periods: Pre = pre-screening, Scr = screening, Up = up-titration, Trt = treatment, Dwn = down-titration, Fup = follow-up.

In agreement with ex vivo findings on rehydration of RBC upon memantine treatment we observed an increase in hypochrom and a decrease in hyperchrome RBC abundance in all four patients (Fig. 2). P1 showed an increase of hypochrome RBC from 7.5% to 29.7% (95%-CI: 29.0, 30.3%) and P2, P3 and P4 from 9.6, 4.6 and 2.0% to 24.3% (95%-CI: 20.1, 28.5%), 6.6% (95%-CI: 2.8, 10.4%) and 7.8% (95%-CI: 6.5, 9.1%), respectively (Fig. 2 and Table S2, http://links.lww.com/HS/A89). Dehydration of RBCs of SCD patients facilitates formation of HbS fibers that damage the cell membrane and compromise deformability promoting hemolysis and VOCs. Earlier, application of the Gardos channel blocker Senicapoc that interferes with RBC’s water balance by retention of intracellular K⁺ was not found to reduce pain and VOCs. Memantine, acting upstream from the inhibition of Ca²⁺-dependent Gardos channels, might have the potential to reduce VOCs.

In conclusion, our study on memantine in SCD patients demonstrated comparable safety profile as described before for memantine in Alzheimer’s disease. All side effects were transient and manageable and we observed a tendency to improve QoL. More in depth analysis of memantine’s impact on RBC characteristics is published elsewhere. Our study is not powered to make any final conclusions on efficacy but the obtained results on four patients that completed the study for one year served as a precedent to conduct a larger trial including young adults and adolescents that is now ongoing. Assuming that memantine reduces SCD symptoms, this drug – in combination with other already approved compounds – has a very cost effective potential.
**Sources of Funding**

The present work has been partially supported by the following foundations: Baugarten Zürich Genossenschaft und Stiftung, the Ernst Goehner Stiftung, the René und Susanna Braginsky Stiftung, the Stiftung Symphasis and the Botnar Foundation. We are also grateful to the Foundation for Clinical Research Hematology for supporting the clinical trial at the Division of Hematology, University Hospital Zurich.

**Disclosures**

The authors have no conflicts of interest to disclose. The University of Zurich holds the patent to use memantine against sickle cell disease.

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