Correspondence

Letter to the editor: the application of Interleukin-1 antagonists in MLC patients: caution warranted

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Dear Editor,

We read with interest the article by Sönmez et al.[1], describing therapy with interleukin (IL)-1 antagonist Anakinra in two patients with Megalencephalic Leukoencephalopathy with subcortical Cysts (MLC).

The pathomechanisms of MLC are still unclear, but loss of MLC1 function and disturbed brain ion–water homeostasis are central.[2] Recent *in vitro* studies by Brignone et al. on mouse-derived astrocytoma cell-lines suggest that loss of MLC1 activates IL-1β–induced inflammatory signals.[3] Based on these findings, the authors treated two MLC patients with Anakinra. Patient 1 was treated from age 31 months and showed improved motor skills and attention span after 7 months. Patient 2 used Anakinra from age 13 years; seizure control and clinical improvement, including cognitive and social functions, were described after 18 months. MRI brain volumetry demonstrated reduced cerebral and cerebellar white matter (WM) volume (5-7% and 13-16%, respectively) and increased cerebral and cerebellar gray matter (GM) volume (2-7% and 23-28%, respectively). WM volume decrease was interpreted as resolution of edema; improvements were attributed to Anakinra.

We would like to express our reservations. In MLC, cerebellar WM is mildly abnormal and not swollen, while cerebral WM is prominently abnormal and swollen.[4,5] Yet the biggest WM volume change after Anakinra concerned cerebellar WM. The increase in GM volume after Anakinra is unexplained. The test-retest variability of the volumetric assessments is unknown. MRI pictures substantiating decreased cerebral WM edema were not shown. No quantitative motor test (e.g., GMFM88) was performed. The psychometric scores do not support robust clinical effects, rather some worsening in patient 2. Most importantly, the

treatment was not part of a placebo-controlled clinical trial. At age 3 years most MLC patients still make developmental progress and slow decrease of WM swelling is part of the natural disease course, so findings should be compared to controls.

The publication of Sönmez et al.[1] has not provided convincing evidence to support efficacy of IL-1 antagonists in MLC patients. Anakinra is expensive[6] and not harmless. Daily painful subcutaneous injections are required.[7] The incidence of injection-site reactions is high and serious immune-mediated adverse events have been reported (e.g., severe infections, allergic reaction).[8] The question is whether results of *in vitro* studies are sufficient to justify application of Anakinra in patients. We would recommend the assessment of Anakinra in multiple model systems, including mouse models, to better understand scientific rational, and the conduction of a controlled clinical trial with validated meaningful outcome measures.

References

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Statement by the MLC clinical expert consortium on the application of Interleukin-1 antagonists in MLC patients

The research field of MLC is moving forward and the progress being made in the understanding of the disease gives hope for the development of therapies. Before a target drug can be applied in patients, a careful evaluation of benefits and risks is required. Recently, a research paper by HE Sönmez and colleagues was published, which describes the use of Anakinra, a drug in the group of Interleukin-1 (IL-1) antagonist, in two MLC patients. This drug is widely used in other fields of medicine, for instance for children with arthritis. We value the attempt to explore therapeutic options for MLC, but at this moment, convincing evidence is lacking to support the use of this drug in MLC patients. The researchers reported that the patients experienced no side effects and both showed some clinical improvement regarding cognitive functions and social interactions, but the data presented are equivocal. They also describe that the treatment resulted in reduction of brain white matter volume on MRI, especially for the cerebellar white matter, but the cerebellar white matter is not swollen in MLC. Notably, treatment with Anakinra is not harmless. It involves daily injections, which can be painful and result in skin reactions. In rare occasions, the treatment leads to serious immune-mediated adverse events (e.g., severe infections, allergic reaction). Further evidence is needed. We propose to test the drug in additional models, for instance MLC mice, first. If positive results are obtained, a clinical trial may be warranted, in which IL-1 antagonists are compared to controls in a larger group of MLC patients. We recommend to await additional evidence before using Anakinra and other IL-1 antagonists in MLC patients.