**A New Hose to Extinguish the FIRES?**

**Tocilizumab Treatment for New Onset Refractory Status Epilepticus**

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We investigated the therapeutic potential of the interleukin-6 receptor inhibitor tocilizumab in 7 patients with new-onset refractory status epilepticus (NORSE) who remained refractory to conventional immunotherapy with rituximab (n = 5) or without rituximab (n = 2). Status epilepticus (SE) was terminated after 1 or 2 doses of tocilizumab in 6 patients with a median interval of 3 days from the initiation. They had no recurrence of SE during the observation. However, 2 patients experienced severe adverse events related to infection during the tocilizumab therapy. Further prospective controlled studies are warranted to validate the efficacy and safety of tocilizumab in patients with NORSE.

**Commentary**

New-onset refractory status epilepticus (NORSE) is a clinical presentation, not a specific diagnosis, in a patient without active epilepsy or other preexisting relevant neurological disorder who has NORSE without a clear acute or active structural, toxic, or metabolic cause. When preceded by a febrile infection, it is referred to as febrile infection–related epilepsy syndrome (FIRES). The pathophysiology of FIRES and NORSE is largely unknown. Thorough investigations of etiology are often unrevealing, with a clear cause, mostly autoimmune encephalitis, being disclosed in only half of cases. The occurrence of a mild febrile illness days prior to the onset of status epilepticus (SE) suggests that cryptogenic cases might be a postinfectious syndrome. This hypothesis is further supported by the fact that children with FIRES exhibit very high levels of cytokines, including interleukin (II)-6, in the serum and, even more so, in the cerebrospinal fluid (CSF). Another study identified an association between FIRES and polymorphisms in the IL-1 receptor antagonist gene.

These findings have generated an interest in the use of immune therapies in cryptogenic NORSE and FIRES. However, conventional immune approaches such as steroids, intravenous immunoglobulins, and plasma exchange have been disappointing. The ketogenic diet, which possesses anti-inflammatory effects, appears more efficacious. More recently, the successful use of anakinra in a single case report has rekindled this interest.

Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor. It is currently used mainly for the treatment of rheumatoid arthritis, systemic juvenile idiopathic arthritis, and giant cell vasculitis. It has also been tried in cytokine release syndrome and antibody-mediated encephalitis.

In this retrospective observational case series, the authors report the use of tocilizumab in 7 adult patients with NORSE. One case was attributed to anti-N-methyl-D-aspartate receptor antibodies but the others remained cryptogenic despite an extensive standardized workup. As is typically the case in NORSE, all patients had a prolonged course of SE ranging from 16 to 75 days (median: 30 days) requiring ICU admission and failed to respond to multiple anti-seizure medications (median: 6; range: 5-7) and up to 3 anesthetic drugs. According to a local clinical protocol, patients received a standardized regimen of conventional immune therapies, consisting of intravenous (IV) steroids and IV immunoglobulins, and in some cases rituximab. Tocilizumab was started if SE persisted despite the combination of these immune therapies with anti-seizure medications and anesthetics, after a median of 25 days after SE onset. It was given at a dosage of 4 mg/kg once a week for 2 weeks, a regimen similar to what is used in cytokine release syndrome. Administration of tocilizumab was followed by SE termination in all but one case, with a latency period of 2 to 10 days, during which no other change in treatment was made. Adverse events occurred in 5 patients. Three developed leukopenia and 2 developed severe infections. Although these adverse events could be attributed to tocilizumab—the Federal Drug Administration issued a black box warning of life-threatening infections—they are also frequently observed in patients with refractory SE who do not receive tocilizumab or any other immune therapies. They are also more likely to
occur when other immune therapies, including steroids, are combined with tocilizumab. Closely monitoring for early signs of infection is an important component of the critical care of patients with refractory SE.

Outcome in this series was not substantially different from prior series, with only 3 patients achieving fair or good outcome, thus questioning the impact of tocilizumab on functional outcome. However, as pointed out by the authors, their series may have been biased toward severe and prolonged cases. Interestingly, patients with good or fair outcome had a non-significantly shorter duration of SE before tocilizumab (median = 11 days vs 42 days), suggesting that early treatment with tocilizumab may result in better functional outcomes, echoing similar observations that were recently made with other immune therapies in this setting.8,9

Although the findings of this observational study await confirmation, ideally in a randomized controlled trial, they further highlight the key role of inflammation in NORSE and FIRES.

The authors confirmed prior reports of abnormally high levels of cytokines—in particular IL-6 and tumor necrosis factor-α—in the CSF and serum of affected patients.

Interleukin-6 is an important mediator of the acute phase response and of the transition from innate to acquired immunity.10 Among other functions, it is required for B- and T-cell activation and recruitment, in part by regulating the expression of multiple cytokines and chemokines. It crosses the blood–brain barrier and is expressed peripherally and in the central nervous system. Its receptor is expressed by neurons. Its effect on seizures and seizure susceptibility is not yet fully elucidated, as pro- and anticonvulsant has been reported in various animal models. Further, seizures themselves can increase IL-6 levels in the CSF. So it is unclear if IL-6 itself is responsible for the development of SE in NORSE and FIRES. However, given its pivotal pro-inflammatory role, it might be operating upstream of other cytokines, such as IL-1β, which have clear direct proconvulsant effects, and might act as an amplifying factor in a positive feedback loop between inflammation and seizures. Another puzzling point that requires elucidation is that tocilizumab, as well as anakinra, poorly cross the blood–brain barrier, suggesting that their primary site of action—and the onset of NORSE and FIRES—is outside the central nervous system.

Clearly, much still needs to be elucidated of the mechanisms of these rare but devastating conditions. A clinical registry with a biobank is currently run by the Critical Care EEG Monitoring Research Consortium (https://www.acns.org/research/critical-care-eeg-monitoring-research-consortium-ccemrc) and the NORSE Institute (http://www.norseinstitute.org/) and might provide more information in the near future. In the meanwhile, this study brings hope for an effective treatment of NORSE and also serves as a reminder that seizures in RSE are often the symptoms of an underlying disorder that might require specific interventions beyond anti-seizure medications.

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