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Original Article

Dexamethasone, Intravenous Immunoglobulin, and Rituximab Combination Immunotherapy for Pediatric Opsoclonus-Myoclonus Syndrome

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ABSTRACT

BACKGROUND: Although pulse-dose dexamethasone is increasingly favored for treating pediatric opsoclonus-myoclonus syndrome (OMS), and multimodal immunotherapy is associated with improved clinical response, there have been no neuroimmunologic studies of dexamethasone-based multimodal disease-modifying therapy. **METHODS:** In this observational retrospective study, 19 children with OMS (with or without associated neuroblastoma) underwent multibiomarker evaluation for neuroinflammation. Nine children of varying OMS severity, duration, and treatment status were treated empirically with pulse dexamethasone, intravenous immunoglobulin (IVIg), and rituximab combination immunotherapy (DEXIR-CI). Another 10 children on dexamethasone alone or with IVIg at initial evaluation only provided a comparison group. Motor severity (total score) was scored rater-blinded via videotapes using the validated OMS Evaluation Scale. **RESULTS:** DEXIR-CI was associated with a 69% reduction in group total score ($P = 0.004$) and was clinically well tolerated. Patients given the dexamethasone combination exhibited significantly lowered B cell frequencies in cerebrospinal fluid (−94%) and blood (−76%), normalizing the cerebrospinal fluid B cell percentage. The number of patients with positive inflammatory markers dropped 87% ($P = 0.002$) as did the number of markers. Cerebrospinal fluid oligoclonal bands were positive in four of nine pretreatment patients but zero of six post-treatment patients. In the comparison group, partial response to dexamethasone alone or with IVIg was associated with multiple positive markers for neuroinflammation despite an average of seven months of treatment. **CONCLUSIONS:** Multimechanistic dexamethasone-based combination immunotherapy increases the therapeutic armamentarium for OMS, providing a viable option for less severely affected individuals. Partial response to dexamethasone with or without IVIg is indicative of ongoing neuroinflammation and should be treated promptly and accordingly.

Keywords: chemokines, CSF immunophenotyping, immunobiomarkers, neuroblastoma, neuroinflammation, OMS, paraneoplastic syndrome, pediatric neuroinflammatory disorders

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Introduction

First synthesized in 1957, dexamethasone is a fluorinated pharmaceutical steroid that binds to the glucocorticoid receptor and exerts powerful anti-inflammatory and immunosuppressive properties.[1] A number of favorable pharmacokinetic properties, such as 80% to 90% bioavailability, a long half-life of 190 minutes, and deliverability by a variety of routes, have led to its designation as an essential medication.[2-4] Dexamethasone, with its 25-fold greater potency than short-acting corticosteroids, is used in the management of a bevy of disorders, including neurological indications.[5-11]

The therapeutic application of dexamethasone to opsoclonus-myoclonus syndrome (OMS), a neuroinflammatory disorder known to be associated with neuroblastoma in at least half of the patients,[12] dates back to 1969,[13] 7 years after the first description of OMS, which introduced adrenocorticotropic hormone (ACTH) as a therapy.[14] Dexamethasone is one of seven steroids tried in OMS, a list that also includes betamethasone, hydrocortisone, methylprednisolone, prednisolone,

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prednisone, and triamcinolone.[15] Other early reports of its use in OMS made similar observations.[16,17] More recently, interest in dexamethasone has been renewed as a pulse-dose therapy for OMS in anecdotal reports.[18-21] Partial response and relapse remain clinical challenges in OMS.[22]

In recent years, multimodality has been the vanguard of immunotherapy for many neuroinflammatory disorders. Cerebrospinal fluid (CSF) B cell expansion, the first biomarker of disease activity in OMS,[23] lead to the novel application of rituximab after a phase I clinical drug trial (ClinicalTrials.gov NCT00244361).[24] Neuroinflammation in OMS is multicomponent, occurring much earlier than previously appreciated. Consequently, the National Pediatric Myoclonus Center has advocated a biomarker-driven therapeutic approach using rapid deployment of multimodal, multimechanistic, combination immunotherapy. We introduced this technique in OMS as part of front-loaded ACTH-intravenous immunoglobulin (IVIg)-rituximab combination therapy (FLAIR-CI).[25] Increased immunosuppression with these agents has a favorable effect on developmental outcome in OMS.[26] However, when the cost of ACTH spiked and some insurance companies began denying it, we substituted dexamethasone in individuals with mild or moderate severity, still also giving IVIg and rituximab. One aim of the present exploratory study was a retrospective analysis of observations on the feasibility and clinical utility of dexamethasone-IVIg-rituximab combination immunotherapy (coined DEXIR-CI) in OMS.

Markers for neuroinflammation have expanded the diagnostic yield of lumbar puncture beyond reliance on leukocytosis,[27] which is minimal or absent in OMS.[28] Those best able to discriminate OMS from noninflammatory pediatric neurological disorders are CSF B cell percentage,[23] positive CSF oligoclonal bands (OCB),[28] and the concentrations of chemokines CXCL13[29] and CXCL10 in CSF[30] and CCL22 in serum.[31] The rationale for inclusion of inflammatory markers, such as chemokines, in this study is their capacity to orchestrate inflammation through chemoattraction of B cells (CXCL13, CXCL10), T helper type 1 (CXCL10), or T helper type 2 cells (CCL22) into the CNS. Although such a panel is not exhaustive, each component has been shown to have a high probability of revealing neuroinflammation in this disorder.[23,28-31] Another aim of the present study was to evaluate the yield of the commercial and research immunobiomarkers used in identifying neuroinflammation in OMS, their relation to partial clinical response, and whether DEXIR-CI reversed the abnormalities.

Methods

Study design

The purpose of the study was to retrospectively analyze clinical and neuroimmunologic observations on two groups of children with OMS, one of which went on to be treated with DEXIR-CI. On the basis of our previous research, we wished to address several questions:

(1) Is partial response to treatment indicative of ongoing neuroinflammation in OMS? Accordingly, the type and number of CSF/serum inflammatory markers in children with persistent OMS symptoms and signs despite previous immunotherapy were analyzed.
(2) Is dexamethasone with or without IVIg sufficient to reliably protect children with OMS from failure to remit? Observations from another group of children on dexamethasone alone or with IVIg at initial evaluation provided a comparison.
(3) Do more rigorous neuroinflammation diagnostic tools (beyond routine CSF studies) that are available to the clinician make a difference in understanding treatment failure and identifying patients for more intensive immunotherapy? Flow cytometric immunophenotyping and quantification of OCB were analyzed.
(4) Did DEXIR-CI redress neuroinflammation and have clinical benefit? Before and after clinical and neuroimmunological observations made in patients treated empirically with DEXIR-CI were compared.
(5) Was the combination therapy well tolerated? Observations available on safety and outcome were gathered, which may be useful to the design of a randomized clinical trial.

Patients

Patient characteristics were documented (Table 1). The 19 children with OMS reported in the present study were referred or recruited to the National Pediatric Myoclonus Center, an international center specialized for pediatric-onset OMS, and examined by two OMS experts. Parents signed consent for enrollment of their child in a case-control study approved by the local Institutional Review Board (SIU School of Medicine, Springfield, IL). In this translational research, which was part of a multiplex chemokine profiling project, additional CSF and serum for research purposes was collected at the time of the diagnostic lumbar puncture and venipuncture.

Published pediatric noninflammatory neurological control data from Dr. Pranzatelli's laboratory were used for comparison in neuroimmunologic studies,[23,28-31] because CSF sampling is not performed in healthy children. Briefly, the types of disorders included ataxia, developmental delay, headache, movement disorders, seizures, and miscellaneous disorders.

Nine children were treated with DEXIR-CI. The choice of treatment modality was empirical, not part of a clinical drug trial. Because of the very high morbidity rate in OMS, we introduced into our clinical practice retesting for neuroinflammation after immunotherapy,[25] subsequently known as testing for freedom from disease activity[32] or no evidence of disease activity.[33] Parents were reconsented.

The other ten children, arriving on dexamethasone monotherapy or dexamethasone and IVIg, provided a comparison group for analysis only at initial evaluation, not as part of any subsequent treatment they may or may not have received. Treatment and longitudinal data were analyzed retrospectively via exempt review status granted by Western Institutional Review Board (Wallup, WA).

DEXIR-CI treatment

Dexamethasone pulses of 7 mg/kg twice daily were given orally for three consecutive days (21 mg/kg/day total), repeated monthly. IVIg was 1 g/kg on each of two consecutive days (2 g/kg total) for induction, then 1 to 2 g/kg monthly. Rituximab was infused IV at 300 to 375 mg/m^2 on each of four consecutive weeks uninterrupted by IVIg. The order of the agents varied according to local logistics. Rituximab was the third agent delivered in 57% of the patients. As prophylaxis against gastritis and acid reflex, parents were instructed to give the children oral ranitidine during the days of the pulses. Sulfamethoxazole/trimethoprim was administered as intermittent antimicrobial prophylaxis.

Biomarker assessments

Flow cytometry was used to measure the frequency of CSF and blood lymphocyte subsets per our standardized protocol[23] in the Pathology Department at St. John's Hospital (Springfield, IL). Chemokine enzyme-linked immunoabsorbent assays for CXCL10, CXCL13, and CCL22 were performed in the investigator's laboratory as per the manufacturers' instructions and our previous publications.[29-31] OCB were measured in CSF and parallel serum samples using isoelectric focus with immunofixation at ARUP Lab (Salt Lake City, UT).[28] Immunoglobulins in CSF and serum were quantified in the clinical laboratory. In patients on IVIg, blood for immunoglobulin testing was drawn at the 4-week trough, just before the next monthly dose, in an effort to minimize false positive