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New feasible treatment for refractory autoimmune encephalitis: Low-dose interleukin-2

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ABSTRACT

Low-dose interleukin-2 (IL-2) restores the balance of regulatory and effector T cells. We aimed to determine the feasibility of low-dose IL-2 as a treatment for refractory autoimmune encephalitis (AE). Ten patients who had received low-dose IL-2 were retrospectively identified. We observed an improvement in the modified Rankin Scale scores of six patients at the last follow-up compared with the scores at the initiation of low-dose IL-2 ($p = 0.014$). One patient experienced treatment-related grade 3 neutropenia. Overall, low-dose IL-2 is a feasible and relatively safe treatment for AE patients who are refractory to the first- and second-line immunotherapies.

1. Introduction

Autoimmune encephalitis (AE) is now a well-established type of encephalitis that presents with subacute memory deficits and psychiatric symptoms, which are often followed by an altered mental status and seizures (Armangue et al., 2014; Zuliani et al., 2012). The recognition of AE is important because these patients generally respond well to immunotherapies (Dalmau et al., 2011; Titulaer et al., 2013), and early treatment is a predictor of good outcome (Titulaer et al., 2013). Although there are no standard, evidence-based treatments, steroid, intravenous immunoglobulin (IVIG), and/or plasmapheresis treatments are used as a first-line immunotherapy in these patients, and those who exhibit an inadequate response receive rituximab and/or cyclophosphamide as a second-line immunotherapy (Lee et al., 2016; Titulaer et al., 2013). However, a considerable number of patients still have unfavourable clinical outcomes despite those immunotherapies (Lee et al., 2016; Titulaer et al., 2013). Therefore, immune-modulating therapies with different mechanisms are warranted.

Interleukin (IL)-2 plays a critical role in the differentiation, survival, and function of regulatory T cells (Tregs) (Boyman and Sprent, 2012; Liao et al., 2013; Malek, 2008). IL-2 receptor signalling is important to both Tregs and effector T cells (Malek, 2008). IL-2 treatments were originally administered at high doses to patients with cancer. While the high-dose IL-2 treatments were effective in some patients with melanoma or renal cell carcinoma, the mechanism was unclear and the therapy was highly toxic, causing such side effects as vascular leak syndrome and severe bacteremia (Klatzmann and Abbas, 2015). However, Tregs have a lower activation threshold for IL-2 than do effector T cells (Yu et al., 2009), and the number and function of Tregs are dysregulated in most autoimmune diseases (Buckner, 2010), including those of the central nervous system (CNS) (Carbone et al., 2014; Haas et al., 2007; Viglietta et al., 2004). The high sensitivity of Tregs to IL-2 led to clinical trials of low IL-2 doses as a novel class of immune-modulating drugs for treating several autoimmune and alloimmune inflammatory disease. Several studies not only have reported the clinical benefits of low-dose IL-2 but have also demonstrated its tolerability (Castela et al., 2014; Humrich et al., 2015; Koreth et al., 2011; Saadoun et al., 2011). However, the efficacy of low-dose IL-2 in AE has not yet been studied.

In this study, we aimed to assess the feasibility of low-dose IL-2 as a treatment for AE in patients who are resistant to both first- and second-line immunotherapies. We also evaluated the safety of the administration of low-dose IL-2.

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2. Methods

2.1. Study population

The Korea Autoimmune Synaptic and Paraneoplastic Encephalitis Registry (KASPER) is a prospective, nation-wide, multicentre registry for AE (Byun et al., 2016; Lee et al., 2016). From this registry, we selected patients with AE who were treated in our institution (Seoul National University Hospital [SNUH]) with low-dose IL-2 between Oct 2015 and March 2016 and reviewed medical records retrospectively. The institutional review board of the SNUH approved this study, and written, informed consent was obtained from the enrolled patients.

The clinical diagnosis of AE includes the following criteria (Graus et al., 2016): (1) subacute onset (i.e., rapid progression over <3 months) of psychiatric symptoms, working (short-term) memory deficits, or altered mental status; (2) at least one of the following: new focal CNS findings, seizures not explained by a previously known seizure disorder, cerebrospinal fluid (CSF) pleocytosis (white blood cell count >5 cells/mm^3), or magnetic resonance imaging (MRI) features suggestive of encephalitis; and (3) reasonable exclusion of alternative causes. We excluded patients with Bickerstaff's brainstem encephalitis and acute disseminated encephalitis (ADEM). The presence of brain-reactive autoantibodies was initially screened by immunostaining rat brain sections with patient serum (1:100) and CSF (1:10) samples, as previously described (Lancaster et al., 2010). Then, the presence of autoimmune synaptic antibodies including *N*-methyl-D-aspartate (NMDA) receptor, leucine-rich glioma-inactivated 1, contactin-associated protein-like 2, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic-acid-receptor 2, γ-aminobutyric acid receptor b, and amphyphisin was determined using a cell-based immunocytochemistry method (EUROIMMUN AG, Germany). Autoantibodies to classic paraneoplastic antigens including Hu, Yo, Ri, Ma2, CV2/CRMP5, and recoverin were tested for using the immunoblotting method (EUROIMMUN AG, Germany). Although antibodies were not detected, the patients were considered to have autoantibody-negative AE based on the proposed diagnostic criteria (Graus et al., 2016).

2.2. Analysis of clinical, laboratory and treatment profiles

We obtained clinical information by reviewing medical records. Symptoms were categorized into eight groups (Dalmau et al., 2008; Titulaer et al., 2013): seizures, memory dysfunction, language dysfunction, psychiatric symptoms, movement disorders, autonomic dysfunction, and altered mental status. CSF examinations, brain MRI scans, and electroencephalography (EEG) data from the time of diagnosis were reviewed. The neoplasm screening included chest and abdomen/pelvis computed tomography (CT) scans and mammographic and gynaecologic evaluations.

First-line immunotherapy was defined as use of corticosteroid, IVIG, and/or plasmapheresis treatments. Second-line immunotherapy was defined as the administration of rituximab and/or cyclophosphamide. Other immunotherapies included tocilizumab, cyclosporine A, mycophenolate mofetil, and tacrolimus. Low-dose IL-2 (aldesleukin [Proleukin]) was administered as follows: one course of subcutaneous IL-2 (1.5 million IU/day) for 5 days, followed by three 5-day courses of 3 million IU/day at weeks 3, 6, and 9 (Saadoun et al., 2011). We included patients who had completed at least four cycles of low-dose IL-2.

We assessed treatment effects and outcomes using the modified Rankin Scale (mRS) at the initiation of the first- and second-line immunotherapies, at the initiation of other immunotherapies, at the initiation of low-dose IL-2, and at the last follow-up. A decrease in at least one mRS score was defined as a clinical improvement.

We investigated the safety of the administration of low-dose IL-2. Adverse events were recorded and classified according to the Common Terminology Criteria for Adverse Events (CTCAE) 4.03. We recorded all adverse events, including serious adverse events and the withdrawal of low-dose IL-2 treatment due to adverse events.

2.3. Statistical analysis

The results are presented as median (range) or number (%). The Wilcoxon signed-rank test was employed to compare mRS scores among the immunotherapies. SPSS 21 was used for all statistical analysis, and two-tailed p values <0.05 were considered significant.

3. Results

3.1. Patient characteristics

Ten patients with AE received at least four cycles of low-dose IL-2 during the study period. Their median age was 22 years (ranging from 17 to 48 years), and six (60.0%) of them were female. All of the patients had seizures, six (60.0%) had memory deficits, four had language deficits (40.0%), six (50.0%) had an altered mental status, and seven (70.0%) had psychiatric symptoms.

All of the patients had abnormal CSF findings, with either both pleocytosis and elevated protein level together or one of the two individually. Five patients (40.0%) had MRI features suggestive of encephalitis, and four (40.0%) had focal epileptiform discharges on their first EEG. Anti-NMDA receptor antibodies were detected in four patients. Two patients with anti-NMDA receptor encephalitis also had an ovarian teratoma. Table 1 summarizes the clinical characteristics of the patients.

The patients received a first-line immunotherapy at a median of 0.6 months (ranging from 0 to 97 months) from symptom onset (Table 2). Two (20.0%) received IVIG treatment only, seven were treated with steroids and IVIG, and one patient underwent plasmapheresis in addition to steroid and IVIG treatments. All of the patients were treated with rituximab as a second-line immunotherapy but required additional immunotherapy due to inadequate responses. The median time from symptom onset to second-line immunotherapy was 1.5 months

Table 1
Characteristics and clinical features of patients.

Subject characteristics	
Age	22 (17–48)
Female sex	6
Presence of autoantibodies	4
Clinical symptoms	
Seizures	10
Memory dysfunction	6
Language dysfunction	4
Psychiatric symptoms	7
Movement disorder	5
Autonomic dysfunction	6
Consciousness decrement	6
Hypoventilation	2
Initial CSF profile	
Pleocytosis[a] only	1
Elevated protein[b] only	1
Pleocytosis and elevated protein	8
CSF WBC level, cells/μL	18 (0–387)
CSF protein level, mg/dL	52 (18–171)
Initial MRI	
Abnormal MRI enhancement	1
Medial temporal T2 HSI	3
Abnormal T2 HSI in any other site	1
Initial EEG	
Focal epileptiform discharge	6
Regional slow activity	0
General slow activity	4

Abbreviations: CSF = cerebrospinal fluid; WBC = white blood cell; MRI = magnetic resonance imaging; HSI = high signal intensity; EEG = electroencephalography. Data are reported as number or median (range).
[a] CSF WBC ≥5 count/mm^3.
[b] CSF protein ≥45 mg/dL.