Anakinra Treatment for Refractory Cerebral Autoinflammatory Responses

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Short report

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Abstract

Background

Refractory cerebral autoinflammatory-autoimmune diseases are often associated with dysregulated innate immunity, which are targeted by anakinra, an interleukin-1 receptor antagonist. Here, we analyzed the therapeutic effect of anakinra in refractory cerebral autoinflammatory response (CAIR).

Methods

We analyzed single institutional patients treated with anakinra for CAIR from January 2017 to May 2021. Anakinra was sympathetically used for patients with intractable CAIR at 100 mg/day subcutaneously. A good response was defined as any improvement of the modified Rankin Scale, Clinical Assessment Scale in Autoimmune Encephalitis, or Expanded Disability Status Scale.

Results

A total of twelve patients with various diagnostic etiologies were treated with anakinra (mean age=45.1; male=7). Four patients showed good responses, and eight patients had unclear responses. Among the good responders, 75% of the patients had pathologically demonstrated CAIR. The two very good responders had primary progressive multiple sclerosis and cerebral granulomatosis with polyangiitis in each, and microglia/macrophage infiltration was prominent in their brain biopsies. No patient had a serious adverse effect.

Conclusions

Anakinra may be a therapeutic option for refractory cerebral autoinflammatory diseases with microglia and macrophage infiltrations.

Background

Cerebral autoinflammatory-autoimmune diseases, including autoimmune encephalitis, multiple sclerosis (MS), acute disseminating encephalomyelitis (ADEM), cryptogenic new-onset refractory status epilepticus (NORSE), and other miscellaneous diseases, are often refractory to conventional immunosuppressive treatments, such as intravenous immunoglobulin (IVIg), plasmapheresis, rituximab, and tocilizumab, which target adaptive immune-mediated responses, such as B and T cells.[1-5] However, accumulating evidence suggests that dysregulated innate immunity mediated by microglia, macrophages, and interleukin-1 (IL-1) has key roles in refractoriness, which is called the cerebral autoinflammatory response (CAIR).[6-8]

Anakinra is an interleukin-1 receptor (IL-1R) antagonist that has shown efficacy and safety in refractory rheumatoid diseases[9, 10] by inhibiting an innate immune response mediated by IL-1, macrophages, and proinflammatory cascades.[11] Anakinra has a low molecular weight that has the potential for blood–

brain barrier penetrance[12] and has shown possible therapeutic potential in cases with febrile infection-related epilepsy syndrome and CAIR.[7, 13] After selecting patients with CAIR by brain biopsy or by clinical implication, anakinra might be used to treat the unbalanced innate immunity pathogenesis in monotherapy or in combination with adaptive immunotherapeutic drugs.

Here, we aimed to analyze the therapeutic potential of anakinra in patients with CAIR that was evident in brain biopsy or theoretically. The patients were from a single institutional cohort that included all consecutive patients who had received therapy for a sympathetic purpose for intractable cerebral autoinflammatory-autoimmune diseases.

Methods

From a single institutional cohort, we selected patients who had received anakinra treatment from January 2017 to May 2021. Anakinra was sympathetically used for patients with intractable central nervous system (CNS) diseases caused by autoimmune, autoinflammatory, postviral, or other miscellaneous diseases and having evidence of innate immunity pathogenesis based on brain biopsies or clinical implications. For the patients, CAIR was demonstrated by pathology of macrophage infiltration greater than a moderate degree. Moreover, refractory cerebral autoinflammatory-autoimmune diseases were also included, such as seronegative autoimmune encephalitis, MS, ADEM, neurotoxic encephalitis, and cryptogenic NORSE, which were unresponsive to previous immunotherapies (steroid, IVIg, rituximab, tocilizumab, tofacitinib, and other conventional immunosuppressant drugs).

Anakinra was administered daily by subcutaneous injection at 100 mg per day. Treating physicians decided the duration of therapy based on the clinical response. The outcome was evaluated with the modified Rankin Scale (mRS), Clinical Assessment Scale in Autoimmune Encephalitis (CASE), and Expanded Disability Status Scale (EDSS) for multiple sclerosis.[14] A good response to anakinra treatment was defined as any improvement of mRS, CASE, EDSS, or seizure cessation. A very good response was defined as an improvement to unassisted daily activity or mRS score of 2.

Results

Characteristics and treatment response of patients

A total of twelve patients were treated with anakinra (Table 1). The clinical diagnoses were primary progressive multiple sclerosis (PPMS) (Patient 1), granulomatosis with polyangiitis (GPA) (Patient 2), ADEM (Patients 3, 4, and 5), NORSE (Patients 6 and 7), seronegative autoimmune encephalitis (Patient 8), autoimmune meningitis (Patient 9), methotrexate-necrotizing leukoencephalopathy (Patient 10), Japanese B encephalitis (JBE) (Patient 11), and sporadic Creutzfledt-Jakob disease (CJD) (Patient 12). Brain biopsy was performed for seven patients (Patients 1, 2, 3, 5, 8, and 12), and three patients (Patients 1, 2, and 3) showed CAIR, defined by prominent CD68-positive macrophage/microglial infiltration. All the patients were refractory to previous immunotherapies (Table 1).

Anakinra treatment showed clear responses in four patients (Patients 1, 2, 3, and 4). In particular, all the patients with biopsy proven CAIR (Patient 1, 2, and 3) had favorable outcomes for anakinra. Patient 1 with PPMS showed dramatic improvement of gait and magnetic resonance imaging (MRI) lesions during anakinra treatment, but the disease recurred after switching anakinra to azathioprine (Figure 1A and C). Patient 2 was diagnosed with GPA and was unresponsive to previous immunotherapies, but anakinra had great efficacy in improving the clinical symptoms and MRI lesions (Figure 1B and C). Patients 3 and 4 who were diagnosed with ADEM also showed good responses to anakinra, and the clinical course and pathology of patient 3 have been previously described as a case report.[7] However, the other eight patients (Patients 5, 6, 7, 8, 9, 10, 11, and 12) showed unclear responses to anakinra treatment. Representative cases with very good responses to anakinra are described below.

Adverse events were reported in two patients (Patients 6 and 9). Patient 6 experienced mild neutropenia without fever. Patient 9 showed delirium during anakinra, resulting in the treatment discontinued.

Case 1 (Patient 1)

A 29-year-old female was referred to our clinic due to progressive gait disability (Figure 1A and C). She was previously healthy, but after delivery, she complained of gait disturbance with a tingling sensation in both legs, urinary retention, and fecal incontinence, worsening over a year. On the neurologic examination, she was alert with full orientation but could not walk without assistance, scoring EDSS of 6.5, mRS of 4, and CASE of 3. Brain MRI revealed T2 high signal intensities in the bilateral subcortical and periventricular white matter, middle cerebellar peduncle, and cerebellum (Figure 1 C). A cerebrospinal fluid (CSF) test showed mild leukocytosis with a high immunoglobulin G (IgG) index (8/μL white blood cells [WBCs], 100% leukocytes, 47 mg/dL protein, and 3.04 IgG index) and oligoclonal band (Type 3) (Table 1). Extensive laboratory evaluations of infection, autoimmune diseases, and malignancy were all negative, and empirical steroid treatment also failed. Therefore, a brain biopsy was performed, revealing CD68-positive microglia/macrophage infiltration with a few scattered CD3-positive T-cells (Figure 1A). She was clinically diagnosed with PPMS, in which no treatment was available and ocrelizumab was not regionally approved. Empirical immunotherapies, including IVIg, rituximab, tocilizumab, and tofacitinib, were ineffective.

Because the pathological findings indicated CAIR, anakinra treatment was sympathetically applied with the patient's consent at four and half years from disease onset. The treatment was very effective. Her symptoms improved dramatically, allowing her to perform daily activities and walk without any assistance, scoring EDSS of 2, mRS of 2, and CASE of 1. The brain lesions on MRI also disappeared during five months of treatment (Figure 1C). Anakinra treatment continued for 5 months without any side effects. However, after switching anakinra to azathioprine for maintenance treatment due to cost issues, the clinical symptoms and MRI lesions recurred in one month (Figure 1C), and she again continued anakinra afterward.

Case 2 (Patient 2)

A 51-year-old male was transferred to our hospital due to an altered mentality (Figure 1B and C). He previously suffered from chronic rhinitis with conjunctivitis. His symptoms started with headache and fever, and within a week, he experienced a rapid cognitive decline with memory loss to a point where he could not even recognize his own writing. On the neurologic examination, he was drowsy and disoriented to time and place with severe memory impairment, scoring CASE of 12, mRS of 5, and mini-mental status exam (MMSE) of 19. An initial CSF test showed leukocytosis with elevated protein (172/μL WBCs, 23% poly, 55% leukocytes, 22% others, and 85 mg/dL protein), and brain MRI revealed T2 lesions in the bilateral medial temporal lobes and basal ganglia with leptomeningeal enhancement (Figure 1C). Extensive evaluation of infectious etiologies (viral, fungal, bacterial, and mycobacterium), autoantibody-mediated diseases, and malignancy was negative. Because high-dose corticosteroids followed by serial immunotherapies, including IVIg, rituximab, and tocilizumab, were ineffective, a brain biopsy was performed and revealed chronic granulomatous and suppurative vasculitis with diffuse infiltration of CD68-positive macrophages (Figure 1B).

To target CAIR caused by GPA, we treated the patient with anakinra after ten weeks of disease onset and continued for two weeks. The patient responded very well to the treatment, showing rapid improvement of the symptoms. He recovered a CASE of 0 and mRS of 1 with minimal memory impairment, and the T2 lesions in the mesial temporal lobes also clearly decreased with no more leptomeningeal enhancement (Figure 1C). He returned to daily life without recurrence while taking oral prednisolone and azathioprine maintenance.

Discussion

The off-label use of anakinra in cerebral autoinflammatory-autoimmune diseases showed its therapeutic potential in four patients who had poor response to conventional immunotherapy. In particular, three patients with pathological findings of CAIR were clearly responsive to anakinra, and they were clinically diagnosed with PPMS, GPA, and ADEM. Therefore, these findings suggested that anakinra may be the primary treatment for a certain group of cerebral autoinflammatory-autoimmune diseases.

Anakinra controls dysregulated innate immunity by blocking IL-1-mediated autoinflammatory reactions.[11] Systemically, myeloid cells play a crucial role in generating autoinflammasomes by recognizing pathogen-associated molecular patterns or damage-associated molecular patterns and potentiating the autoinflammatory response by secreting IL-1 and IL-18.[8, 15] In our patients with CAIR, while the exact pathogenesis of activated microglia or macrophage infiltration across the blood–brain barrier remains to be studied, the secretion of IL-1 from microglia or macrophages may have maintained the CAIR through a vicious cycle. In Patient 1, who was clinically diagnosed with PPMS, the autoinflammatory response may have originated from peripherally infiltrated macrophages and activated microglia. Indeed, a high concentration of blood monocyte-driven IL-1β has been associated with a poor prognosis of PPMS.[16] Patient 2, who was diagnosed with GPA, showed a very good response to the short-term treatment of anakinra. As discussed in the previous case report of Patient 3,[7] persistent microglial dysregulation may have occurred, resulting in CAIR in Patient 2. Although we could not confirm the pathology of Patient 4,

the pathogenesis of ADEM may be similar to that of Patient 3 according to the response to anakinra treatment.[7] However, there were patients who did not respond to anakinra even if they were clinically diagnosed with ADEM or pathologically showed microglial infiltration. These results suggested that even with the same diagnosis, the pathogenesis may be different. Thus, the nonfoamy microglia in the pathology of Patients 8 and 9 may not play a major role in the pathogenesis. Moreover, although microglial activation has been reported in methotrexate-necrotizing leukoencephalopathy, JBE, and CJD, [17-19] the inhibition of IL-1 was ineffective in our patients, and dysregulated innate immunity may not be the main driving force in the pathogenesis.

Conclusions

The present study demonstrated the presence of CAIR in a selected population of patients with refractory cerebral autoinflammatory-autoimmune diseases, and anakinra was effective for these patients. Although this was a retrospective study with a small number of patients, our pilot data with anakinra treatment may provide a useful option for refractory cerebral autoinflammatory-autoimmune diseases. Further research is required to determine CAIR in patients with refractory cerebral autoinflammatory-autoimmune diseases and to analyze the optimal candidates for anakinra treatment.

List Of Abbreviations

ADEM = acute disseminated encephalomyelitis; CASE = clinical assessment scale in autoimmune encephalitis; CAIR = cerebral autoinflammatory response; CJD = Creutzfeldt–Jakob disease; CNS = central nervous system; CSF = cerebrospinal fluid; EDSS = Expanded Disability Status Scale; GPA = granulomatosis with polyangiitis; IgG = immunoglobulin G; IL-1 = interleukin-1; IL-1R = interleukin-1 receptor; IVIg = intravenous immunoglobulin; JBE = Japanese B encephalitis; MMSE = mini-mental status exam; MRI = magnetic resonance imaging; mRS = modified Rankin Scale; MS= multiple sclerosis; NORSE = new-onset refractory status epilepticus; PPMS = primary progressive multiple sclerosis; WBC = white blood cell

Declarations

Ethics approval and consent to participate

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This study was approved by the Seoul National University Hospital Institutional Review Board.

Consent for publication

Written informed consent was received from all patients and/or legal guardians.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Y.J. and S-T.L. wrote and revised the manuscript. Y.J. and S-T.L. reviewed patients' medical records. W-J.L., H.S.L., and S-T.L. collected clinical data. S-T.L. provided study concepts and funding. All authors revised the manuscript.

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Table

Due to technical limitations, table 1 docx is only available as a download in the Supplemental Files section.

Figures

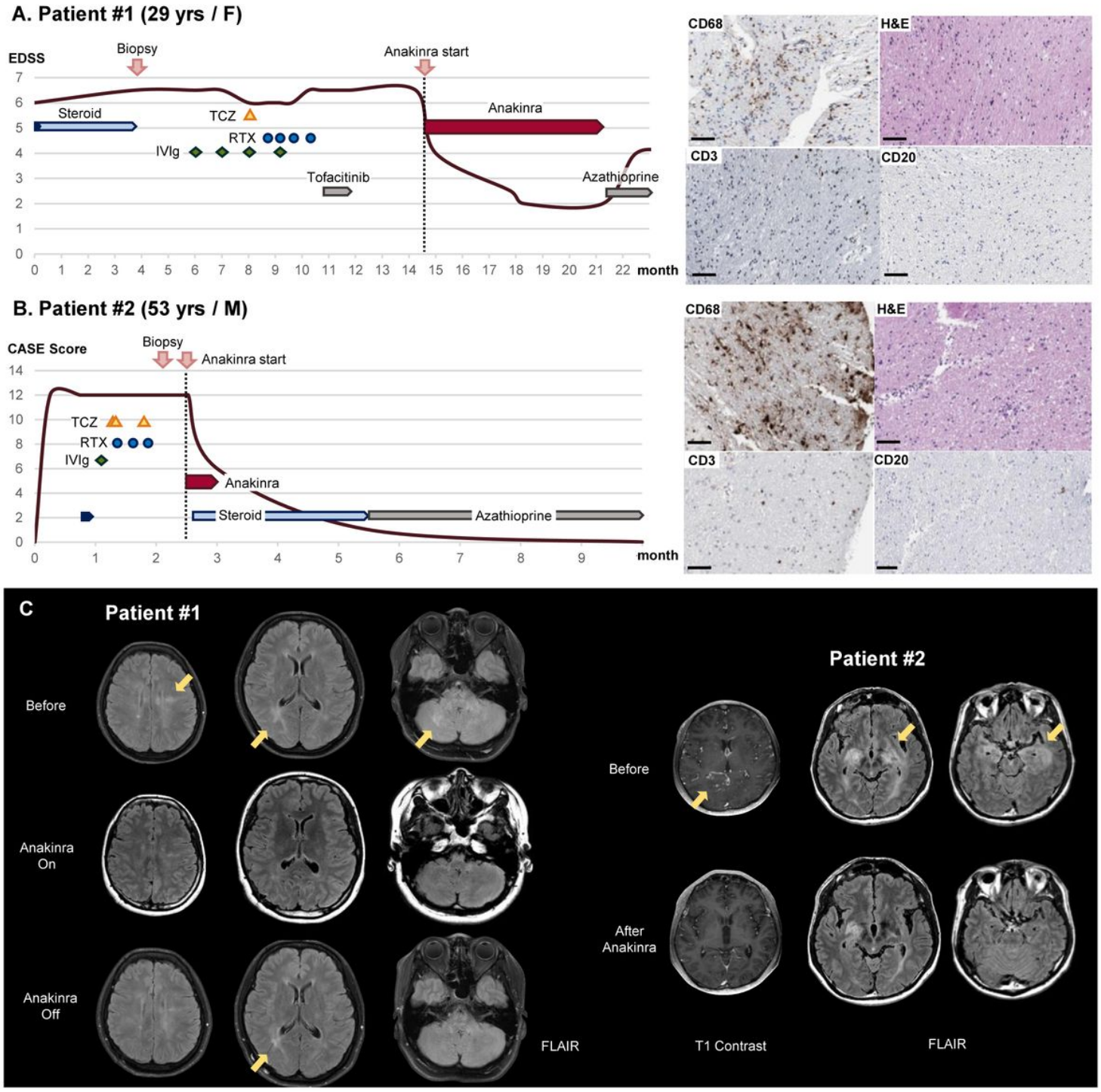

Figure 1

Clinical course, pathology, and brain images of Patients 1 and 2 who showed very good responses to anakinra treatment. A. A 29-year-old woman with primary progressive multiple sclerosis (PPMS) was pathologically identified as having cerebral autoinflammatory response (CAIR), which is CD68-positive macrophage infiltration. Anakinra treatment dramatically improved her symptoms from an expanded disability status scale (EDSS) score of 6.5 to 2.0, but after the discontinuation of anakinra, her symptoms aggravated again to an EDSS score of 4. B. A 51-year-old man with refractory granulomatosis with polyangiitis (GPA) showed CD68-positive microglia-dominant pathology on brain biopsy. He responded very well to the 14-day short-term anakinra treatment followed by steroids and azathioprine, recovering from a Clinical Assessment Scale in Encephalitis (CASE) score of 12 to 0. All of the immunotherapies administered during the clinical courses are presented schematically. IVIg, intravenous immunoglobulin; RTX, rituximab; TCZ, tocilizumab. Scale bar=100 μm. C. In Patient 1, brain magnetic resonance imaging (MRI) identified T2 hyperintensity lesions in the bilateral subcortical and periventricular white matter, middle cerebellar peduncle, and cerebellum. During anakinra treatment, the lesions disappeared but partially recurred after the discontinuation of anakinra. In Patient 2, brain MRI revealed the improvement of T2 lesions in the bilateral medial temporal lobes and basal ganglia with leptomeningeal enhancement after anakinra treatment.

Supplementary Files

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