

## Intractable Epilepsy (IE) and Responses to Anakinra, a Human Recombinant IL-1 Receptor Agonist (IL-1ra): Case Reports

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### Abstract

Patients with intractable seizures (IE) who failed to respond currently available treatment measures are clinically challenging, causing significant morbidity and even mortality. Better understanding of contributing factors for IE will be helpful for exploring additional treatment options. A role of inflammation has long been suspected in pathogenesis of epilepsy, especially in idiopathic epilepsy with diffuse epileptic activity. In rodent models of epilepsy, blockage of inflammatory mediators such as interleukin 1- $\beta$  (IL-1 $\beta$ ) and IL-6 attenuates epileptic activities. However, therapeutic effects of blockers of such inflammatory mediators have not been addressed in patients with IE.

This manuscript reports 4 IE cases in which anakinra, a human recombinant IL-1 receptor antagonist (IL-1ra), was clinically effective in controlling their epileptic activity in a dose-dependent manner. In these patients, we also observed changes in ratios of IL-1 $\beta$ /IL-10 produced by peripheral blood monocytes, surrogates of bone marrow derived microglial cells. These findings could be associated with seizure control status.

These presented cases indicate a possible therapeutic use of a commercially available IL-1 $\beta$  blocker (anakinra) and therapeutic utility of the IL-1 $\beta$ /IL-10 ratios produced by peripheral blood monocytes for assessing responses to this immune-modulating agent.

**Keywords:** Intractable epilepsy; IL-1 receptor antagonist; Peripheral blood monocytes

**Abbreviations** ADI-R: Autism Diagnostic Inventory-Revisited; ADOS: Autism Diagnostic Observational Scale; AEDs: Anti-Epileptic Drugs; ANA: Anti-Nuclear Antibody; APC: Antigen Presenting Cells; ASD: Autism Spectrum Disorder; BBB: Blood Brain Barrier; CNS: Central Nervous System; ELISA: Enzyme Linked Immune-Sorbent Assay; FS: Febrile Seizures; GABA: Gamma Aminobutyric Acid; IE: Intractable Epilepsy; IL: Interleukin; IL-1R: IL-1 Receptor; IL-1ra: IL-1 receptor antagonist; IRB: Institutional Review Board; IVIg: Intravenous Immunoglobulin; LPS: Lipopolysaccharide; Mo: Monocytes; NMDAR: N-Methyl-D-Aspartate Receptor; NOMID: Neonatal Onset Multifocal Inflammatory Disease; OCS: Oral Corticosteroid; PAMP: Pathogen Associated Molecular Pattern; PB: Peripheral Blood; PDD-NOS: Pervasive Developmental Disorder – Not Otherwise Stated; PRRs: Pattern Recognition Receptors; SPAD: Specific Polysaccharide Antibody Deficiency; sTNFR: Soluble TNF Receptor; TLR: Toll-Like Receptor; TNF: Tumor Necrosis Factor; vEEG: video-Monitor Electron Encephalogram; VNS: Vagal Nerve Stimulation

### Introduction

Despite advances in therapeutic measures for epilepsy, some patients (up to 30%) are still refractory to currently available anti-epileptic measures [1]. Although the complex pathogenesis of IE makes it difficult to elucidate the underlying molecular mechanisms,

mounting evidence supports a role of immune and inflammatory processes in its pathogenesis.

The immune system in the central nervous system (CNS) is less exposed to antigenic stimuli than other organs, largely due to the presence of the blood brain barrier (BBB), scant lymphoid tissue without lymphatic drainage, and limited numbers of antigen-presenting cells (APCs). Nevertheless, innate immune cells in the CNS (microglial cells, astrocytes, oligodendrocytes, and other types of macrophages) can mount an immune reaction in the CNS. These CNS innate immune cells are activated by the sensing of pathogen-associated molecular patterns (PAMPs) and danger signals via pattern recognition receptors (PRRs). Toll-like receptors (TLRs), the best studied PRRs, are found to be expressed by microglial cells, CNS vascular endothelial cells, neurons, and astrocytes [2,3].

CNS inflammatory conditions such as encephalitis and neuro-trauma are associated with acute symptomatic seizures and often lead to the development of epilepsy [4-6]. This process has been implicated in the activation of innate immune responses in the CNS, which can lead to increased excitability of neurons through the interleukin-1 receptor (IL-1R)/TLRs. In rodent models of epilepsy, aberrant innate immune responses and the subsequent overproduction of inflammatory cytokines (IL-1 $\beta$ , especially) affect neuronal excitability, inducing epileptic activity [4,7-13]. One of the possible mechanisms of IL-1 $\beta$ -mediated seizure activity is via N-methyl-D-aspartate receptor (NMDAR)-mediated signaling. *In vitro* analysis of hippocampal cells indicated that IL-1 $\beta$  may concurrently increase excitation of neuronal cells through alterations in NMDAR phosphorylation and influence GABAergic inhibition, which may promote the genesis of FS [14,15].

This was also shown in other rodent models of seizures where seizures are either provoked or spontaneous [16-19].

IL-1 $\beta$  is produced as an inactive precursor. Pro IL-1 $\beta$  must be cleaved into an active form before being secreted. This cleavage event is catalyzed by caspase 1 and the deregulation of this process, by genetic mutations, results in a number of primary auto-inflammatory disorders [20,21]. Even subtle changes in IL-1 $\beta$  synthesis due to single nucleotide polymorphisms can predispose individuals to certain inflammatory conditions. For example, one allele of IL-1 $\beta$ -511 is linked to FS by meta-analysis [22].

The actions of IL-1 $\beta$ , tumor necrosis factor (TNF)- $\alpha$ , and other pro-inflammatory cytokines are counter-regulated by a variety of anti-inflammatory factors to maintain immune homeostasis in physiological conditions. Such counter-regulatory cytokines/mediators include IL-1ra, soluble IL-1 receptor type II, and soluble TNF receptors (sTNFR). An imbalance of pro-inflammatory and counter-regulatory mediators in the CNS may lead to epileptic activity [6,23]. This imbalance, i.e. exaggerated IL-1 $\beta$  response, has been seen in leukocytes from children with both viral and bacterial infection in which IL-1 $\beta$  production is initially triggered by innate immune responses sensing viral RNA, viral/bacterial DNA, and bacterial byproducts [24,25]. In rodents, increased seizure susceptibility by peripheral inflammation was attributed to induction of neuroinflammation and oxidative stress in the hippocampus [26].

IL-1ra blocks the binding of IL-1 $\beta$  to IL-1R, thereby preventing IL-1 $\beta$ -mediated intracellular signaling and cell activation. Blocking IL-1-mediated inflammatory pathways via IL-1ra (anakinra) has been successful for treating auto-inflammatory disorders caused by mutations in IL-1 $\beta$ -signaling pathways [20,21]. Homozygous mutations of the IL-1RA allele 2 have been linked to development of IE [27].

The above-described findings indicate a role of IL-1 $\beta$  and potential therapeutic effects of IL-1ra in seizure activity. Furthermore, endogenous IL-1ra has been shown to be protective against FS in rodent models [23]. Exogenous IL-1ra has also been shown to control FS activity in these rodent models [23,28,29] as well as in rodent models of other seizures [5,7,11,18]. In non-human primates, anakinra was found to penetrate the BBB, albeit at lower concentrations [30].

Among IL-1 $\beta$  blockers, anakinra, a recombinant human IL-1ra, may have therapeutic advantages; its small molecular size that permits its penetrance to intact BBB, its short half-life with low risk of irreversible complications, and good safety profile, in contrast to monoclonal antibodies against IL-1 $\beta$  or a soluble decoy receptor conjugated with Fc portion of human IgG1. Herein, we describe our experience of the clinical benefits of IL-1ra in 4 IE patients. To our knowledge, this is the first report on the therapeutic effects of anakinra for IE.

## Case Presentation

### Case 1

A Caucasian male with IE (daily partial complex seizure and grand mal seizures 3-4 times/week since 4 weeks of age) presented for evaluation of recurrent infection in our clinic at 13 years of age. Multiple imaging studies failed to reveal any structural abnormalities. Multiple video-monitored EEG (vEEG) and subsequent evaluation of epileptic activity by subdural grid placement were significant for diffuse epileptic activity. Multiple anti-epileptic drugs (AEDs, more

than 20 AEDs tried) and vagal nerve stimulation (VNS) failed to control his seizures. He also exhibited impairment in speech, three-dimensional visual perception, and social skills. He also was found to suffer from Hashimoto's disease, and specific polysaccharide antibody deficiency (SPAD) with intermittently positive anti-nuclear antibody (ANA). SPAD was treated with intravenous immunoglobulin (IVIg) infusion (1 g/kg/dose every 3 weeks) from 13 years of age. Although frequency of infection has significantly reduced, IVIg treatment did not reduce frequency of his grand mal seizures.

At 17 years of age, after the exhaustion of other therapeutic options and a worsening of his epileptic activity, anakinra was added to his treatment regimen. With an initial dose of anakinra (100 mg once daily subcutaneous injection-2 mg/kg/day), there was no change in his epileptic activity. However, a higher dose of anakinra (200 mg/day-4 mg/kg/day) led to a marked decrease in frequency of grand mal seizures from 1-2x/week to 1x/3-4 weeks. Unfortunately, anakinra treatment had to be suspended 3 times due to his insurance change. Interruption of anakinra treatment resulted in worsening his epileptic activity (grand mal seizure 1-2x/week) each time. Parents reported that he became more alert, expressive, and attentive, with improved social interactions with anakinra. This was also noticed by his teachers and therapists, who were not aware of this treatment. His ophthalmologist documented marked improvement in his three-dimensional vision after starting a higher dose of anakinra (4 mg/kg/day). Parents also reported the loss of the gains in the above-described cognitive skills each time when anakinra treatment was interrupted.

### Case 2

An 8-year-old Caucasian female with daily partial complex seizures and clusters of grand mal seizures associated with microbial infection from 16 months of age presented for evaluation of frequent infections. She was also diagnosed with pervasive developmental disorder, not otherwise stated (PDD-NOS) when 8 years old and then diagnosed with autism with autism diagnostic observational scale (ADOS) and autism diagnostic inventory-revisited (ADI-R) at 12 years of age at a nationally known autism diagnostic center. Prior extensive neurology workup at another institution revealed diffuse epileptic activity by EEG without any structural abnormalities. Previous extensive metabolic/genetic workup was all negative. Multiple AEDs failed to control her seizure activity. Our immune workup revealed impaired humoral immunity that led a diagnosis of SPAD. IVIg treatment (1 g/kg/dose every 3 weeks) was initiated. IVIg with premedication of a steroid decreased frequency of seizures to once a week with a drastic decrease in sinopulmonary infection initially. However, her frequency of seizure surged and became uncontrollable 2 years later, resulted in multiple hospitalizations. Exhausting other options, at 10 years of age, anakinra (100 mg daily; 3 mg/kg/day) was added to her treatment regimen. While on anakinra, she remained seizure-free for one year, the longest stretch in her life. She experienced clusters of seizures (grand mal and partial complex seizures) every 2-3 weeks when her dose of anakinra was reduced from 100 mg to 75 mg per day. Once her dose was adjusted to her weight, the number of grand mal seizures was reduced to once every 2-3 months. Her recent seizures were associated with IVIg treatment, indicating that rapid immune complex formation by IVIg may be causing seizure clusters. Thus, the route of IVIg was switched to subcutaneous infusion 14 mo ago, and she remains seizure-free, since then with concurrent treatment of 150 mg anakinra daily.

### Case 3

A 6-year-old Caucasian male diagnosed with Landau-Kleffner syndrome and autism presented for evaluation of recurrent infection that has been a major trigger for his seizure activity. EEG showed nearly constant epileptic activity near the oromotor cortex, right hemisphere, and left temporal lobe. His seizure disorder was exacerbated by flare-ups of his severe colitis, which is secondary to food protein induced enterocolitis syndrome. Prior to presentation at our clinic, multiple AEDs were tried without symptomatic relief. Bihemispheric multiple subpial transection eliminated 90% of seizure activity for a few months, but he reverted back to having epileptic activity as seen previously. His seizure activity was best controlled by an anti-inflammatory medication, i.e., oral corticosteroids (OCS), but OCS caused significant neuropsychiatric symptoms including mood swings. Our initial immune workup led to a diagnosis of SPAD and IVIg therapy was initiated. Although IVIg effectively controlled his infection, it had no effect on his seizure activity. A combination of thalidomide and VNS initiated at another institution reduced the number of seizures from 301 (based on a 48-hour vEEG) to 3 in 6 months. However, thalidomide was discontinued due to its side effects (peripheral neuropathy and muscle wasting) after 9 months of trial. Secondary to exhaustion of therapeutic options, at 10 years of age, anakinra (3 mg/kg/day) was added to his treatment regimen. After starting anakinra, parents reported improvement in his fine motor skills (able to unbutton, etc.) and cognitive skills (speaking more frequently, better focusing, being more independent, and expressing his opinions), which was also documented by teachers and care-takers who were not aware of anakinra treatment. Caretakers also felt that he was less hyperactive. His ocular symptoms (photophobia and persistently dilated pupils) also resolved. He had dilated pupils with minimal reactivity to light prior to anakinra treatment; this was documented in our clinic as well as at clinics at other institutions. Discontinuation of anakinra resulted in recurrence of these symptoms and seizure activity. Currently with anakinra (3 mg/kg/dose), he has been seizure-free for over 4 years.

### Case 4

A 9-year-old Caucasian male diagnosed with IE and ASD (initial diagnosis: PDD-NOS) at 5 years of age, presented for evaluation of recurrent otitis media and sinusitis. vEEGs repeatedly revealed epileptic activity in the left parietal region prior to his initial visit. MRI of the brain was unremarkable except for chorocoid cyst, which was thought to be not associated with his IE. Extensive neurological and metabolic workups were unrevealing. Multiple AEDs failed to control his seizure activity but caused significant side effects including hepatotoxicity, and most AEDs had to be discontinued. Triggers of his seizure activity included microbial infection, dysbiosis (typically due to prolonged antibiotics), and exposure to offending foods (wheat). Workup for celiac disease was negative. Subsequent immune workup led to diagnosis of SPAD and IVIg treatment was initiated, resulting in better control of recurrent infection. His seizure activity, however, was not controlled by either IVIg (1 g/kg/dose every 3 weeks) or high dose of oral steroids (2 mg/kg/dose). After exhausting treatment options, anakinra (1.5 mg/kg/day) was added to his treatment regimen at 10 years of age. This resulted in a marked reduction of seizure activity; 1x grand mal seizure in a one-year period. The grand mal seizure occurred following the accidental ingestion of a wheat-containing product at 11 years of age. His mother also reported improvement in his cognitive skills (more attentive and focused) as well as reduced

irritability and hyperactivity. Improvement in irritability and hyperactivity was documented by the ABC (aberrant behavior checklist) as well. Discontinuation of anakinra led to a recurrence of his seizure activity within a few months. After resuming anakinra at a dose of 2 mg/kg/day, once again, he regained seizure-free status and has remained seizure-free since then over 3 years. vEEG also revealed disappearance of epileptic activity while he was on anakinra, but a recurrence of epileptic activity 3 months after discontinuation of anakinra.

### Laboratory Findings

IL-1 $\beta$  is mainly generated by innate immune responses, and peripheral blood monocytes (PB Mo) are major innate immune cells in the PB. Thus we tested cytokine production by PB Mo in Cases 2, 3, and 4; these measures were done following the IRB-approved protocol. Namely, PB Mo were isolated by Ficoll-Hypaque density gradient centrifugation, and then immunoaffinity column (monocyte separation kit II - human, MILTENYI BIOTEC, Cambridge, MA) [31]. PB Mo were then incubated overnight at a concentration of  $2 \times 10^5$  cells/ml in the presence of TLR4 agonist (lipopolysaccharide (LPS); 0.1  $\mu$ g/ml, GIBCO-BRL, Gaithersburg, MD, USA), TLR2/6 agonist (zymosan; 50  $\mu$ g/ml, Sigma-Aldrich, St. Luis, MO, USA), or TLR7/8 agonist (CLO97, 20  $\mu$ m, InvivoGen, San Diego, CA, USA) in RPMI 1640 with additives as previously described [31]. Internal control cells were incubated without a stimulus. Levels of IL-1 $\beta$  and IL-10 in the culture supernatant were then measured by enzyme-linked immunosorbent assay (ELISA) [32] (Figure 1). IL-10 has a crucial role in regulating immune-homeostasis including IL-1 $\beta$ -mediated inflammation [33,34]. Monocyte cytokine production assays were able to be conducted in cases 2-4, but not in case 1.

In case 2, assays were conducted when her anakinra dose was at 75 mg/day (data point 1) and then 150 mg/day (data point 2). With a higher dose of anakinra, IL-1 $\beta$  production is lower in response to LPS (endotoxin) and also IL-1 $\beta$ /IL-10 ratio was lower in response to CLO97, a TLR7/8 agonist. In case 3, despite the fact that his anakinra dose was properly adjusted to his weight without interruption, IL-1 $\beta$  production fluctuated and appears to have become more stable recently. This may be associated with improvement of GI symptoms following treatment of dysbiosis. In Case 4, all samples were obtained after stabilization of his seizures, following after resuming anakinra (100 mg daily) treatment and IL-1 $\beta$  production and IL-1 $\beta$ /IL-10 ratio remained stable.

### Conclusions

This study retrospectively reviewed clinical responses and laboratory findings in 4 IE patients for whom anakinra, a human recombinant IL-1ra, was added to their anti-seizure treatment regimen, after exhausting the treatment options. In these 4 subjects, anakinra treatment resulted in significant reduction in their clinical seizure activity. These presented cases indicate the promising therapeutic effects of anakinra in patients with IE as indicated in rodent models of epilepsy [5,11,18,35]. Interestingly, in addition to improvement of seizure activity, parents of three out of 4 of these subjects report improvement in cognitive skills. In 2 of these subjects presented in this paper, objective improvement of ocular functions was also reported; one showed improvement of three dimensional vision and the other had normalization of dilated pupils and photosensitivity. To address such parental observation, prospective studies carefully assessing changes in cognitive skills before and after anakinra

treatment will be required. Nevertheless, our findings may indicate a possibility that IL-1 $\beta$ -mediated CNS inflammation not only caused seizure activity but also affected cognitive activity.

It should be noted that impaired cognitive activity has been reported in autoinflammatory syndrome in which gene mutations result in uncontrolled IL-1 $\beta$ -mediated inflammation [21]. In patients with NOMID (Neonatal onset multifocal inflammatory disease), one of these conditions, IL-1 $\beta$ -mediated CNS inflammation leads to multiple neuropsychiatric symptoms including mental retardation, seizures, developmental delay, and hearing/vision loss [21]. These symptoms were greatly improved after treatment with anakinra.

Doses of 1–5 mg/kg of anakinra were investigated in a clinical trial of anakinra for NOMID patients and a higher dose of anakinra revealed better therapeutic efficacy [36]. Similar to NOMID subjects, in the presented cases, we found that higher doses of anakinra were more effective in controlling seizure activity. This might be associated with the relatively low delivery of anakinra to the CNS reported in non-human primates [30]. Despite the use of higher than generally recommended doses of anakinra, we have not observed any major side effects that required discontinuation. WBC count, which may be affected by anakinra, remained stable in the presented cases. These results indicate that anakinra may be a safe therapeutic option for IE children after other treatment options have been exhausted.

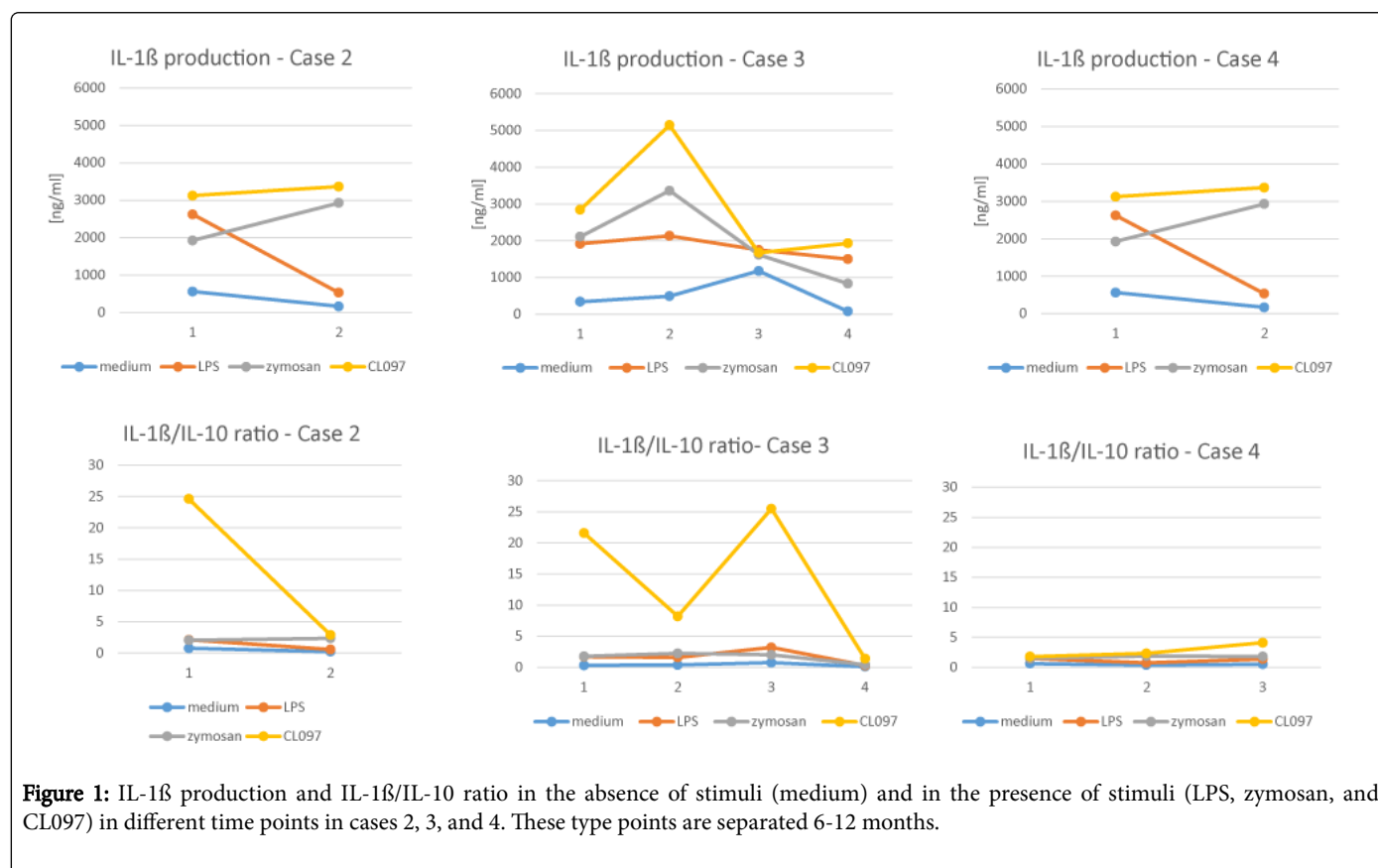
Human PB monocytes can be recruited to the CNS and changed into bone marrow-derived microglial cells. These cells are thought to play a crucial role in the CNS inflammation. Thus we tested IL-1 $\beta$  production by purified PB monocytes as a surrogate for brain

microglial cells in 3 out of 4 cases presented in this paper. Unfortunately, we were unable to check IL-1 $\beta$  production prior to the start of anakinra therapy, since these assays were not established in our laboratory at that time. We found stable IL-1 $\beta$  production in Case 4. In Case 2, lowering in IL-1 $\beta$  production (with LPS) and IL-1 $\beta$ /IL-10 ratio (with CL097) were observed. Case 3 suffered from persistent GI symptoms associated with dysbiosis and delayed type food allergy, and both the IL-1 $\beta$  and IL-1 $\beta$ /IL-10 ratios became more stable after the improvement of gastrointestinal symptoms, irrespective of anakinra treatment. These results may indicate that these immunoparameters can be utilized as biomarkers for the efficacy of anakinra. However, effects of other co-morbid conditions may need to be taken into consideration when evaluating the results.

In summary, we have presented favorable seizure-controlling effects of anakinra in 4 IE patients. Our results indicate that anakinra and possibly other IL-1 $\beta$  blockers can serve as an additional therapeutic action for IE subjects when other therapeutic options are exhausted and a role of immune-mediated inflammation is suspected in its pathogenesis. Controlling the CNS inflammation by anakinra may also be helpful for the improvement of cognitive activity in some subjects, as observed in these presented cases.

## Consent

The presented cases entered the IRB approved study protocols and consent of case presentation without personal health information was obtained when entering the study.



**Figure 1:** IL-1 $\beta$  production and IL-1 $\beta$ /IL-10 ratio in the absence of stimuli (medium) and in the presence of stimuli (LPS, zyosan, and CL097) in different time points in cases 2, 3, and 4. These type points are separated 6-12 months.

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## References

1. Akin D, Ravizza T, Maroso M, Carcak N, Eryigit T, et al. (2011) IL-1beta is induced in reactive astrocytes in the somatosensory cortex of rats with genetic absence epilepsy at the onset of spike-and-wave discharges, and contributes to their occurrence. *Neurobiol Dis* 44: 259-269.
2. Arroyo DS, Soria JA, Gaviglio EA, Rodriguez-Galan MC, Iribarren P (2011) Toll-like receptors are key players in neurodegeneration. *Int Immunopharmacol* 11: 1415-1421.
3. Auvin S, Shin D, Mazarati A, Sankar R (2010) Inflammation induced by LPS enhances epileptogenesis in immature rat and may be partially reversed by IL1RA. *Epilepsia* 51 Suppl 3: 34-38.
4. Balosso S, Maroso M, Sanchez-Alavez M, Ravizza T, Frasca A, et al. (2008) A novel non-transcriptional pathway mediates the proconvulsive effects of interleukin-1beta. *Brain* 131: 3256-3265.
5. De Simoni MG, Perego C, Ravizza T, Moneta D, Conti M, et al. (2000) Inflammatory cytokines and related genes are induced in the rat hippocampus by limbic status epilepticus. *Eur J Neurosci* 12: 2623-2633.
6. Dedeurwaerdere S, Friedman A, Fabene PF, Mazarati A, Murashima YL, et al. (2012) Finding a better drug for epilepsy: antiinflammatory targets. *Epilepsia* 53: 1113-1118.
7. Devinsky O, Vezzani A, Najjar S, De Lanerolle NC, Rogawski MA (2013) Glia and epilepsy: excitability and inflammation. *Trends Neurosci* 36: 174-184.
8. Dinarello CA, Simon A, van der Meer JW (2012) Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. *Nat Rev Drug Discov* 11: 633-652.
9. Dubé C, Vezzani A, Behrens M, Bartfai T, Baram TZ (2005) Interleukin-1beta contributes to the generation of experimental febrile seizures. *Ann Neurol* 57: 152-155.
10. Fox E, Jayaprakash N, Pham TH, Rowley A, McCully CL, et al. (2010) The serum and cerebrospinal fluid pharmacokinetics of anakinra after intravenous administration to non-human primates. *J Neuroimmunol* 223: 138-140.
11. Gabryšová L, Howes A, Saraiva M, O'Garra A (2014) The regulation of IL-10 expression. *Curr Top Microbiol Immunol* 380: 157-190.
12. Goldbach-Mansky R (2012) Immunology in clinic review series; focus on autoinflammatory diseases: update on monogenic autoinflammatory diseases: the role of interleukin (IL)-1 and an emerging role for cytokines beyond IL-1. *Clin Exp Immunol* 167: 391-404.
13. Heida JG, Moshé SL, Pittman QJ (2009) The role of interleukin-1beta in febrile seizures. *Brain Dev* 31: 388-393.
14. Ho YH, Lin YT, Wu CW, Chao YM, Chang AY, et al. (2015) Peripheral inflammation increases seizure susceptibility via the induction of neuroinflammation and oxidative stress in the hippocampus. *J Biomed Sci* 22: 46.
15. Jyonouchi H, Geng L, Davidow AL (2014) Cytokine profiles by peripheral blood monocytes are associated with changes in behavioral symptoms following immune insults in a subset of ASD subjects: an inflammatory subtype? *J Neuroinflammation* 11: 187.
16. Jyonouchi H, Geng L, Ruby A, Zimmerman-Bier B (2005) Dysregulated innate immune responses in young children with autism spectrum disorders: their relationship to gastrointestinal symptoms and dietary intervention. *Neuropsychobiology* 51: 77-85.
17. Librizzi L, Noè F, Vezzani A, de Curtis M, Ravizza T (2012) Seizure-induced brain-borne inflammation sustains seizure recurrence and blood-brain barrier damage. *Ann Neurol* 72: 82-90.
18. Maroso M, Balosso S, Ravizza T, Iori V, Wright CI, et al. (2011) Interleukin-1beta biosynthesis inhibition reduces acute seizures and drug resistant chronic epileptic activity in mice. *Neurotherapeutics* 8: 304-315.
19. Maroso M, Balosso S, Ravizza T, Liu J, Aronica E, et al. (2010) Toll-like receptor 4 and high-mobility group box-1 are involved in ictogenesis and can be targeted to reduce seizures. See comment in PubMed Commons below *Nat Med* 16: 413-419.
20. Matsuo M, Sasaki K, Ichimaru T, Nakazato S, Hamasaki Y (2006) Increased IL-1beta production from dsRNA-stimulated leukocytes in febrile seizures. See comment in PubMed Commons below *Pediatr Neurol* 35: 102-106.
21. Peltola J, Keränen T, Rainesalo S, Hurme M (2001) Polymorphism of the interleukin-1 gene complex in localization-related epilepsy. *Ann Neurol* 50: 275-276.
22. Pitkänen A, Ndoe-Ekane XE, Łukasiuk K, Wilczynski GM, Dityatev A, et al. (2014) Neural ECM and epilepsy. *Prog Brain Res* 214: 229-262.
23. Sabat R, Grütz G, Warszawska K, Kirsch S, Witte E, et al. (2010) Biology of interleukin-10. *Cytokine Growth Factor Rev* 21: 331-344.
24. Saghazadeh A, Gharedaghi M, Meysamie A, Bauer S, Rezaei N (2014) Proinflammatory and anti-inflammatory cytokines in febrile seizures and epilepsy: systematic review and meta-analysis. *Rev Neurosci* 25: 281-305.
25. Sasaki K, Matsuo M, Maeda T, Zaitsumi M, Hamasaki Y (2009) Febrile seizures: characterization of double-stranded RNA-induced gene expression. *Pediatr Neurol* 41: 114-118.
26. Serdaroglu G, Alpman A, Tosun A, Pehlivan S, Ozkinay F, et al. (2009) Febrile seizures: interleukin 1beta and interleukin-1 receptor antagonist polymorphisms. *Pediatr Neurol* 40: 113-116.
27. Sibley CH, Plass N, Snow J, Wiggs EA, Brewer CC, et al. (2012). Sustained response and prevention of damage progression in patients with neonatal-onset multisystem inflammatory disease treated with anakinra: a cohort study to determine three- and five-year outcomes. *Arthritis Rheum* 64: 2375-2386.
28. Vezzani A, Conti M, De Luigi A, Ravizza T, Moneta D, et al. (1999) Interleukin-1beta immunoreactivity and microglia are enhanced in the rat hippocampus by focal kainate application: functional evidence for enhancement of electrographic seizures. *J Neurosci* 19: 5054-5065.
29. Vezzani A, French J, Bartfai T, Baram TZ (2011) The role of inflammation in epilepsy. *Nat Rev Neurol* 7: 31-40.
30. Vezzani A, Friedman A, Dingledine RJ (2012) The role of inflammation in epileptogenesis. *Neuropharmacology* 69: 16-24.
31. Vezzani A, Moneta D, Conti M, Richichi C, Ravizza T, et al. (2000) Powerful anticonvulsant action of IL-1 receptor antagonist on intracerebral injection and astrocytic overexpression in mice. *Proc Natl Acad Sci U S A* 97: 11534-11539.
32. Vezzani A, Moneta D, Richichi C, Aliprandi M, Burrows SJ, et al. (2002) Functional role of inflammatory cytokines and antiinflammatory molecules in seizures and epileptogenesis. *Epilepsia* 43 Suppl 5: 30-35.
33. Vezzani A, Viviani B (2015) Neuromodulatory properties of inflammatory cytokines and their impact on neuronal excitability. *Neuropharmacology* 96: 70-82.
34. Viviani B, Bartesaghi S, Gardoni F, Vezzani A, Behrens MM, et al. (2003) Interleukin-1beta enhances NMDA receptor-mediated intracellular calcium increase through activation of the Src family of kinases. *J Neurosci* 23: 8692-8700.
35. Wang S, Cheng Q, Malik S, Yang J (2000) Interleukin-1beta inhibits gamma-aminobutyric acid type A (GABA(A)) receptor current in cultured hippocampal neurons. *J Pharmacol Exp Ther* 292: 497-504.
36. Washington J 3rd, Kumar U, Medel-Matus JS, Shin D, Sankar R, et al. (2015) Cytokine-dependent bidirectional connection between impaired social behavior and susceptibility to seizures associated with maternal immune activation in mice. *Epilepsy Behav* 50: 40-45.