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RECENT ANTI-INFLAMMATORY AND IMMUNOMODULATORY DRUGS IN EPILEPSY

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Abstract:

Epilepsy is a neurological illness that is caused when nerve cells in the brain fire electrical impulses at a high rate that causes a sort of electrical storm in the brain, known as a seizure. A repeated episode of seizure is known as epilepsy. Mostly epilepsy is caused by infection, illnesses, head injuries, brain tumors and lead poisoning. At least one-third of epileptic patients have seizures that cannot be controlled with the traditional anti-epileptic medications. Inflammatory reaction that releases neuromodulator molecules and inflammatory mediators that are involved in the pathophysiology of seizures can stimulate epilepsy. In this review we highlighted most promising components to control the epilepsy cases. It is concluded that anti-inflammatory and immunomodulatory drugs have a positive role to decrease the bouts of epilepsy and limit it. They can be effective in improving the outcomes of patients with refractory epilepsy and status epilepticus as per the published studies.

Keywords: *Epilepsy, Drugs, Anti-inflammatory, Immunomodulatory*

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1.INTRODUCTION:

Epilepsy stands third among the most common chronic brain disorders that affects approximately 65 million people worldwide.[1,2] Almost one-third of the patients with epilepsy, have seizures that cannot be controlled with anti-epileptic medications.[2] Refractory epilepsy has severe consequences, including interference with daily life activities, social isolation and loss of independence, as well as increased risk of injury, depression, and suicide. Surgery has its limitations; it can only be used if the seizure has originated from a region that can be removed with minimal risk of disabling neurologic function or cognitive dysfunction. Vagus nerve stimulation is not more effective than antiepileptic drugs.[3]

Recently, evidence has developed that supports the involvement of inflammatory mediators in both the origin of individual seizures and the epileptogenic process. These inflammatory mediators are released by brain cells and peripheral immune cells in both the origin of seizures and epilepsy. Chronic brain inflammation involves activation of astrocytes, microglia, endothelial cells of the blood brain barrier (BBB), and peripheral immune cells. The relation between limbic encephalitis and epilepsy suggests that there is an inflammatory mechanism, and immune system has a role in some forms of epilepsy.[2] Immune therapy options for epilepsy treatment include medications such as corticosteroids, plasmapheresis, immunoglobulins, or steroid-sparing drugs such as azathioprine. Recent alternatives have involved more aggressive treatment like cyclophosphamide, anti-pre-B-lymphocyte monoclonal antibody rituximab, and monoclonal antibodies such as natalizumab or efalizumab.[4] Reviewing recent anti-inflammatory and immunomodulatory drug's efficacy in improving the outcomes of patients with refractory epilepsy was the aim of this review.

2.Anti-inflammatory drugs

Inflammatory reactions in the brain occur in various CNS diseases, including autoimmune, neurodegenerative, and epileptic disorders.[5] Clinical and experimental researches suggest that infection or inflammation may be a trigger to seizure predisposition and occurrence, also seizure can be caused by brain injury. About 1 to 5% of incidence of epilepsy cases are presumed to be due to CNS infection.[6]

Several reports have showed that the proinflammatory cytokines are involved in the pathophysiology of seizures,[7] and proconvulsant events that can activate microglia and astrocytes to release several proinflammatory mediators. Proinflammatory cytokines initiate a cascade of inflammatory processes in the brain parenchyma and can change neuronal excitability and influence the physiological functions of glia by autocrine or paracrine actions, this perturbs the glioneuronal communications.[8]

a. Minocycline

Minocycline is an antibiotic which was proven to have an anti-inflammatory effect that is not related to its antimicrobial effect.[9] According to a study done by Wang, et al., aimed to investigate whether minocycline could exert antiepileptogenic effects in a rat lithium- pilocarpine model of temporal lobe epilepsy. It was found that minocycline decreased interleukin 1 beta (IL-1b) and tumor necrosis factor-alpha (TNF-α) concentration, reduced the neuronal loss in status epilepticus induced mice, and reduced the frequency and severity of spontaneous recurrent attacks of seizures. All these results indicate that minocycline can reduce status epilepticus induced inflammation and decrease the frequency of recurrent attacks.[10] In another study it was also found that minocycline has a role in reducing TNF-α production by 50% as an effect of minocycline on brain tissue after hypothermic cardiac arrest in rats.[11] Another study was able to determine the anti-inflammatory and anti-apoptotic influence of minocycline in early brain injury after subarachnoid hemorrhage in male Sprague–Dawley rats.[12] In a recent study investigated minocycline's anticonvulsant properties in LPS-treated animals. It was found that co-treatment of minocycline and aminoguanidine (AG) dissimilar to 7-Nitroindazole (7-NI) could increase the seizure threshold of LPS-treated animals. L-arginine reversed the anticonvulsant effect of minocycline. Also, molecular evaluations showed that LPS could increase the adenosine triphosphate (ATP) levels, glutathione (GSH) levels, and reactive oxygen species formation. However, minocycline significantly reversed the effects of LPS. Minocycline counteracts the proconvulsant effects of LPS through regulating the mitochondrial function and decreasing neuro-inflammation. Also, co-administration of minocycline and inducible nitric oxide synthases (i-NOS) inhibitors could intensify anticonvulsant effects of minocycline.[9] One study elucidated the effect of minocycline on histological structures of cerebellar Purkinje neurons in epileptic rats induced by pentylenetetrazole. It was found that treatment with minocycline has protective effect on Purkinje neurons in the cerebellum of epileptic rats.[13]

b. VX-765 and Cyanobacterial LPS Combination

High-mobility group box-1 (HMGB1) protein is a highly abundant protein that can promote the pathogenesis of inflammatory and autoimmune diseases.[14] Toll-like receptor 4 (TLR4) belongs to the toll-like receptor family, is a part of the innate immune system.[15] It was found that expressions of HMGB1 and TLR4 is correlated with increased severity and risk of epilepsy. In addition, their level was higher in patients who were resistant to anti-epilepsy drugs.[16] VX-765 is an IL-converting enzyme/caspase-1 inhibitor that inhibits the production of HMGB1 and interleukin-1-beta (IL-1b).[17] Cyanobacterial lipopolysaccharide (Cyp) is a TLR4 antagonist.[17] Some experiments were done to test the anticonvulsant activity of VX-76. It was found that there was a decrease on an average of 50% and 64% in the number of the seizures and their total duration respectively, with 50 to 200 mg/kg VX-765. In addition, there was a significant delay in the time of onset of the first seizure at doses of 100 and 200 mg/kg.[18] It was also found that inhibition of Interleukin-1 receptor type-I (IL-1R1) alone is not effective to prevent activation of TLR4 that contributes in the inflammation cascade, which results in spontaneous seizer production by itself.[19] Thus, combination of both drugs (VX-765 and Cyanobacterial LPS) showed decrease in seizure frequency by 90% and prevented its progression.[17]

c. SB225002

SB225002 is a C-X-C motif chemokine receptor-2 (CXCR2) antagonist, was investigated in a study in a mouse model, the seizure in mice was induced by pilocarpine. SB225002 was found to decrease the frequency of spontaneous recurrent attacks by 50% and increase the latency of spontaneous recurrent attacks by 40%.[20]

d. 5Z-7- Oxozeaenol

5Z-7-Oxozeaenol is a transforming growth factor 3 beta-activated kinase (TAK1) inhibitor, which participate in TNF-α and IL-1 signaling pathways (The NF-kkB and c-Jun N-terminal kinase (JNK) pathways).[21] A study explored the role of TNF receptor-associated factor-6 (TRAF6) and TAK1 in pilocarpine-induced epileptic rat model and found that 5Z-7- oxozeaenol decreased IL-1b expression. The study indicated that there was an upregulation of TRAF6 and TAK1. Besides, there was significant reduction of neuron death in addition to seizure durations with early inhibition of TAK1.[21]

d. Methylated Flavonoids

Flavonoids are polyphenolic in structure that present in almost all terrestrial plants and it is safely consumed with no adverse effect.[22] These structures are found to exert a potent anti-inflammatory effect.[23] Flavonoid pharmaceutical potential is often restrained by their metabolic instability and low oral bioavailability. It was found that methylation of their free hydroxyl groups can improve absorption, metabolic stability and increase bioavailability.[24] The anticonvulsive effect of methylated flavonoid in zebrafish and two mouse models was investigated. Zebrafish seizure was induced by pentylenetetrazol (PTZ). And one mouse model was induced by PTZ, while the other was induced by 6-Hz psychomotor. Flavonoids that were used included naringenin (NRG), kaempferol (KFL) and their methylated derivatives included naringenin 7-O-methyl ether (NRG-M), naringenin 4 ′,7-dimethyl ether (NRG-DM), and kaempferide (4′-O-methyl kaempferol) (KFD). It was found that non- methylated flavonoids (NRG and KFL) had limited anticonvulsive activity in PTZ induced zebrafish, while KFD (methylated KFL) had only marginal activity. Also, methylated NRG (NRG-M and NRG-DM) had a clear anticonvulsive effect as it reduced the number and duration of the seizure attacks.[23]

e. Isoliquiritigenin (ISL)

ISL is one of the main compounds in licorice, which is a flavonoid with a chalcone structure with diverse pharmacological activities, including anti-inflammation, antioxidative stress, antiplatelet aggregation, and cancer-preventing properties.[25] ISL effectively inhibits the expression of multiple proinflammatory mediators, such as IL-6, TNF-α, and CCL2, in macrophage.[26] ISL pretreatment significantly attenuated the expression of TNF-α, IL-1β, and CCL3. Although the level of IL-6 was not significantly reduced, a slight decline was detected. These findings concluded that ISL is beneficial in the treatment of early-stage epilepsy because it suppresses the neuroinflammatory response. This study showed that ISL pretreatment significantly inhibited the protein levels of TLR4, MYD88, and p-NF-κB, and blocks the TLR4/NF-κB signaling pathway of attenuated KA-induced neuroinflammation and neuronal damage in the hippocampus. These findings indicated that ISL pretreatment has a neuroprotective effect on epileptogenesis, via the TLR4/MYD88 signaling pathway and reduces the neuronal apoptosis-like injury that occurs during epileptogenic processes.[27]

f. Silibinin

Ischemia and brain hypoxia can be a consequence of seizure. And it can increase hypoxia inducible

factor-1α (HIF-1α) overexpression. HIF-1α activates vascular endothelial growth factor (VEGF), multidrug resistance gene-1 (MDR1), glucose transporters, and erythropoietin (EPO).[28] Silibinin is a herb extract which is the major ingredient of the flavonoid compound silymarin, which is extracted from Silybum marianum, it considered to be non-toxic even at higher doses, silibinin noticed to have an anti-apoptotic and neuroprotective in cerebral ischemia, and can decrease neuro-inflammatory injury induced by lipopolysaccharides.[28] Silibinin effect was investigated in lithium-pilocarpine seizure induced rats in which silibinin reduced apoptotic cell death, neuronal loss, TNF-α, IL-1β, IL-6, caspase-3, cleaved caspase-3, and HIF-1α. Silibinin had anti-inflammatory and neuroprotective effects that most probably are results of HIF-1α signaling inhibition.[28]

g. N-acetylcysteine and Sulforaphane Combination

Epilepsy therapy was focused on oxidative stress since it is a pathophysiological process commonly occurring in experimental epileptogenesis and observed in human epilepsy. De novo brain and blood generation of high mobility group box 1 (HMGB1) was associated with oxidative stress.[29] Generation of the disulfide isoform of HMGB1 is a potential critical point of intersection between oxidative stress and neuroinflammation, HMGB1 is a protein crucially involved in the molecular cascade that contributes to seizure mechanisms.[29] It was hypothesized that the treatments (antioxidant drugs) given are either do not have a sufficiently rapid effect or too short-lived. This obstacle was overcome by using a combination of two antioxidant drugs that have a complementary mechanism of action, acting as an acute antioxidant using N-acetylcysteine (NAC and increasing the longer-term endogenous antioxidant system using sulforaphane (SFN).[29] A study found that combination of NAC and SFN reduces oxidative stress in brain and blood during epileptogenesis in a rat model in which seizure was induced by electrical current, and significantly improves pathological outcomes by providing blockade of spontaneous seizure progression, reduction of cell loss and rescue of comorbidities. This combination results in significant delay in the epilepsy onset, drastically reduces the frequency of spontaneous seizure that is measured at five months with no modification in the average duration of seizure or the incidence of animals' epilepsy, and blocks the progression of the disease between two- and five-months post-status epilepticus. Treatment also decreased hippocampal neuronal loss and rescued cognitive deficit.[29]

h. Pinoresinol-4-O-β-D-glucopyranoside

Pinoresinol-4-O-β-D-glucopyranoside (PGu) is a lignan glycoside isolated from an edible plant called Prunus domestica L, recently, it was proven that prunus domestica has a potent anti-inflammatory and anxiolytic activity.[30] COX-2 is an enzyme that affects nerve cell damage caused by excitotoxicity caused by glutamate or by prostaglandins' neurotoxic potential in addition to seizures via oxidative stress.[30] Meanwhile, elevated iNOS expression increases the susceptibility of seizure in sensitive brain areas.[30] In a study investigated PGu anti-inflammatory and anxiolytic activity in ithium/pilocarpine-induced rats' model. in was found that PGu exerted potent neuroprotective activity as anti-inflammatory and antioxidant activity via reducing seizure onset, severity, number of rats that developed seizures, and enhanced animal survival after seizure exposure, also, PGu decreased neurodegeneration caused by pilocarpine, and declined COX-2 level by 40% and iNOS expression by 18%.[30]

i. Daidzin

Daidzin is an isoflavone extracted from Pueraria lobata (Fabaceae) and known to have an anti-inflammatory and antioxidant effect for centuries.[31] In a study daidzin anti-epileptic potential was explored in a pentylenetetrazole (PTZ) seizure induced mice model. Results demonstrated that daidzin decreased the incidence of PTZ-induced seizures in a dose- dependent manner. And significantly prevented epileptogenesis and reversed histopathological changes in the hippocampus. Also, antioxidant levels were improved including (glutathione sulfotransferase, glutathione, catalase, and superoxide dismutase) while decreased MDA (malondialdehyde) and nitrite production in the brain. Protein damage was remarkably prevented in addition to modulation of oxidative stress, apoptotic signaling and BDNF/VEGF signaling in PTZ induced mice treated with daidzin. [31]

j. SMM-189

SMM-189 is a Cannabinoid receptor type 2 (CB2) selective inverse agonist that has emerged as an appealing anti-inflammatory target for brain conditions, CB2 is a G protein-coupled receptor that can be expressed by activated brain microglia.[32] A study conducted to evaluate the therapeutic potential of SMM-189 effect in kainate seizure induced rat model, it was reported that

SMM-189 largely prevented the rat primary microglia mediated inflammation and showed moderate neuroprotection against N-methyl-D-aspartic acid (NMDA) receptor mediated excitotoxicity, in addition to that SMM-189 prevented COX-2 induction in the brain, prolonged seizure-induced cytokine storm, neuronal death in the hippocampus, and behavioral deficits, also, in combination with diazepam, that was administered after status epilepticus, SMM-189 showed an anti-inflammatory effect, and protected pyramidal neurons in the hippocampus, leading to reductions in behavioral impairments that were associated with prolonged seizures. [32]

k. Celecoxib

Most investigators reported that pretreatment of animals with a COX-2 inhibitor before aconvulsant stimulus may lower seizure intensity.[33] None of the selective COX-2 inhibitors have shown slowing in epilepsy disease progression. The use of celecoxib (CCX) as a blocker of COX-2 and HMGB1/TLR-4 pathways in rats induced recurrent seizures with kainic acid (KA, 1.4 mg/k) was investigated. It was found that treatment with CCX after epileptic seizure was associated with reduction in seizure susceptibility, in addition to that it had a neuroprotective effect due to the inhibition of proinflammatory proteins and associated signaling pathways, And, additionally, the timely intervention of inflammatory pathways would reduce the risk of developing epilepsy in adulthood.[34]

l. Tumor necrosis factor-alpha (TNF-α)

TNF-α is rapidly induced during seizures in endothelial cells and glial and of the BBB in rodents where seizure was induced by neuroinflammatory response. A simultaneous reduction in neuronal tumor necrosis factor (TNF)-α receptor type 2 (TNFR2) and an increase of TNFR1 was found in neurons and astrocytes. TNF-α has either anticonvulsant or proconvulsant effects counting on its concentration within the brain in addition to the receptor subtype activated in diseased tissue. Furthermore, a protective role of TNF-α on seizures was found in mice with a genetic deletion of TNFR1.[35]

m. PMX53

Various complement related factors are induced in the brain during spontaneous seizures. Studies have shown that the sequential intrahippocampal injection of the complement factors C5b6, C7, C8, and C9 stimulate seizures in rats and hippocampal neuronal loss, and the administration of PMX53, a C5ar1 antagonist, resulted in anticonvulsive effects in various murine models of seizures. While, the blockade of C5ar1 during pilocarpine-induced spontaneous seizures reduced seizure power, spontaneous seizures associated mortality, and neurodegeneration within the hippocampus. Also, the transgenic mice lacked specific complement-related factors. Like C3-deficient mice developed significantly fewer behavioral seizures following Theiler's viral infection as compared to wild-type mice. [35]

n. Chemokines

Chemokines such as (CCL2 [MCP-1], CCL3 [MIP-1α], CCL4 [MIP-1β], and CCL5, and their receptors are increased in the brain tissue of patients with drug-resistant epilepsy and in experimental models in glial, endothelial cells and neurons, also in infiltrating leukocytes. CCR5 receptors activated by MIP-1α and RANTES contribute to neuroinflammation, cell loss, acute seizures, and BBB damage in experimental models. The spontaneous seizures in mice was induced by CCR2 which was activated by CCL2. [35]

Table 1: Clinical studies using anti-inflammatory treatments

Drug	Action	Effect	Reference
Minocycline	Decreased IL-1b and TNF-a concentration	Reduces the neuronal loss, frequency and severity of spontaneous recurrent attacks of seizures	**(9,10, 11,13)**
VX-765 + Cyp	Inhibit (HMGB1), (IL- 1b) + TLR4	Combination showed decrease in seizure frequency by 90% and prevented its progression	**(17)**
SB225002	a C-X-C motif chemokine receptor 2 (CXCR2) antagonist	Decreases the frequency of by 50% and increase the latency by 40%	**(20)**
5Z-7-Oxozeaenol	TAK1 inhibitor	Decreased IL-1b expression, neuronal death, and seizure duration	**(21)**
Methylated Flavonoids: (NRG-M, NRG-DM, and KFD)	--	NRG-M and NRG-DM reduced the number and duration of the seizure attacks, while KFD had only marginal activity.	**(23)**
Isoliquiritigen in	TLR4 inhibitor	Inhibited the protein levels of TLR4, MYD88, and p-NF-κB, reduces the neuronal apoptosis-like injury	**(27)**
Silibinin	HIF-1α inhibitor	Reduced apoptotic cell death, neuronal loss, TNF-α, IL-1β, IL-6, caspase-3, cleaved caspase-3, and HIF-1α	**(28)**
NAC + Sulforaphane	Anti-oxidant leading to HMGB1 reduction	Delayed epilepsy onset, blocked progression, reduced the frequency, and decreased hippocampal neuron loss and rescued cognitive deficit.	**(29)**
Pinoresinol-4- O-β-D- glucopyranoside	- Decreases COX-2 level and iNOS expression	reducing seizure onset, severity, number of rats that developed seizures, and enhanced animal survival, and decreased neurodegeneration	**(30)**
Daidzin	- Improves antioxidant level - Decreased MDA and nitrate	prevented epileptogenesis and reversed histopathological changes in the hippocampus, prevented protein damage.	**(31)**
SMM-189	CB2 selective inverse agonist	Prevent microglia mediated inflammation, seizure-induced cytokine storm, neuronal death in the hippocampus, and behavioral deficits, and has neuroprotection effect	**(32)**
celecoxib	COX - 2 inhibitor	Decrease frequency and duration, enhance phenytoin delivery	**(34)**
TNF-α	Activation of TNFR2 and TNFR1	Reduced seizures by activation of TNFR2, while it enhances seizures by activation of TNFR1	**(35)**
PMX53 PMX53	C5ar1 antagonist	Reduced seizure power, mortality and neurodegeneration in hippocampus	**(35)**

II. Immunomodulatory Drugs

Some researchers have proven functional disturbances of both humoral and cell-mediated immunity, frequently among people with epilepsy than in general population. Also, a number of abnormalities in cytokine production have been found in epileptic patients.[36] These inflammatory processes lead to the secretion of pro-inflammatory cytokines (brain and serum IL-1ß, IL6, prostaglandin E2 (PGE2), transforming growth factor-beta 2 (TGF-β2), interferon gamma (IFNγ) and heat shock proteins (HSP70)) which is a chaperone protein responsible for BBB disruption and involvement of resident immune cells in the inflammation pathway. It has been demonstrated that IL-1β intracellular signaling cascade is able to modify the neuronal excitability without cell loss.[37] Immune mechanisms might play a role in the pathogenesis of epilepsy, for example, a patient with Rasmussen's encephalitis (a chronic inflammation of the brain, with infiltration of T-lymphocytes) developed focal seizures due to the disease. The findings of an immunological basis may offer new modalities for the treatment of selected cases of intractable partial epilepsies.[38]

a. Mesenchymal Stem Cells Autologous

Mesenchymal Stem Cells (MSC) is a mature fibroblast that had chemotactic characteristics similar to other immune cells that respond to sites of inflammation and injury with the ability to differentiate into tissues of mesodermal origin.[39] A total of 22 patients with refractory epilepsy, included 12 patients in the control group and 10 patients in the MSC therapy group, found that 3 of 10 patients who took MSC treatment for 1 year, didn't have seizure for 1 year and more, and 5 patients from the same group became responsive to antiepileptic drugs. And 70% of the MSC treated patients exhibited a change of their seizure from generalized tonic-clonic seizure to partial seizure (either complex or simple). The patients didn't have any serious side effects.[40] Another study assessed the safety of the bone marrow mesenchymal stem cells derived from CD271-positive cells treatment in pediatric patients, resulted in decreased seizure frequency and disappearance of status epilepticus episodes. There was also improvement in the cognitive function. There were no noticeable side effects.[41] One study used MSCs in 20 patients with symptomatic drug-resistant epilepsy, and found a significant decrease in natural killer cells (NK), CD4+CD8+, CD8+CD25+, CD3+CD95+, and CD3+CD8+, and concluded that cell therapy may be used as a drug of choice in patients with epilepsy that is drug-resistant.[42]

b. Anti- Glutamic Acid Decarboxylase (GAD) Antibody

Anti-glutamic acid decarboxylase (GAD) antibody is one of the most common detected antibodies in patients with idiopathic drug-resistant epilepsy. GAD65-Ab-mediated epilepsy is moderately responsive to steroids and intravenous immunoglobulin/plasma exchange (IVIG/PE) only, but immunosuppressants could be more effective. GAD65-Ab-mediated epilepsy has a poor response to antiepileptic drugs (AEDs) and moderately responsive to immune therapy with steroids, plasma exchange therapy (PET) and long-term treatment with more powerful immunosuppressants as rituximab (RTX), and/or cyclophosphamide or intravenous immunoglobulin (IVIG), is often necessary and could be more effective than current immunosuppressive approaches.[43]

c.MIS416

MIS416 is a modulator for innate immunity that target amplifying myeloid-associated anti-inflammatory/immune surveillance activity, peripheral myeloid cells, and immune regulatory cytokine production.[44] Seizure in a mice were induced by traumatic brain injury (TBI) via Controlled Cortical Impact and it was found that MIS416 treated group had reduction of seizure severity and less neuronal damage.[45]

d.Intravenous Human Immunoglobulin (IVIg)

IVIg was collected from blood plasma of almost 1000 human donors. It's mainly composed of immunoglobulin G (IgG) (95%) and has an immunomodulatory effect of altering IgG- specific receptor (Fcγ R) function and expression, that leads to reduction in the compliment cell mediated damage and interfere in cytokines production. The seizure in experimental mice was induced by pilocarpine injection, 30 minutes after the injection of methylscopolamine. It was found that IVIg decreased the activation of complement system, local glial cell activation and BBB damage, also the treatment reduced the duration and frequency of spontaneous recurrent attacks of seizure.[46]

e.Fingolimod

Sphingolipids is a class of active lipids that have a role in inflammation. They are signaled through sphingosine-1-phosphate receptors (S1PRs) 1-5, which are G-protein coupled receptors. Astrocytes express 1 and 3 S1PRs, which may represent the anti-inflammatory effect. Fingolimod claims to arrest lymphocytes movement from secondary lymphoid tissues, attenuates microgliosis, reduces neuroinflammation, increases oligodendrocyte

differentiation, and potentially neuroprotective.[47] In a study seizure was induced in mice by using either unilateral Supra hippocampal Kainate Acid injection or systemic pilocarpine. It was found that fingolimod decreased chronic seizure frequency, a visible decrease in the first 2 weeks after seizure induction, and even after discontinuation of fingolimod administration in the 3rd and 4th weeks, mice had fewer seizure attacks. There were no side effects observed with its chronic use. Fingolimod had no effect on severity and had no role in the initial acute phase of status epilepsy.[48]

Table 2: Clinical studies using immunomodulatory treatments

Drug	Effect	Reference
MSC autologous	Increase latency, decreased frequency and resistance to antiepileptic drugs, change in seizure pattern from generalized tonic-clonic seizure to partial seizure	**(40)**
MIS416	Reduction of seizure severity and less neuronal damage	**(45)**
IVIg	Reduce the duration and frequency of spontaneous recurrent attacks of seizure	**(46)**
Fingolimod	Decreased chronic seizure frequency, and didn't affect the severity and had no role in acute phase of epilepsy	**(48)**

CONCLUSION:

It was proven by several trails with different drugs that anti-inflammatory and immunosuppressive drugs have a positive role in decreasing the bouts of epilepsy and limiting the status epileptics. Interestingly, some antibiotics and herbs were proven to have an anti-inflammatory effect and in trails was found that it can reduced the neuronal loss, frequency and severity of spontaneous recurrent attacks of seizures also with combination with other drugs they can give a new evolution in epileptic treatment. Considering adding anti-inflammatory or immunosuppressive drugs in the treatment of epilepsy is a promising step especially in the refractory cases of epilepsy.

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