Review Article
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Can the pharmaceutical drug keppra (levetiracetam) be used as a therapeutic agent for patients with butterfly glioblastoma?

Abstract

Keppra (Levetiracetam, LEV) represents a new class of antiepileptic drugs (AED) that modulates seizure-activity in epilepsy. Serving as an option for brain tumor patients suffering from seizures, LEV can be used to treat symptoms in patients with brain tumors and increase the sensitivity of Glioblastoma tumors to the chemotherapy drug, Temozolomide (TMZ). Aggressive treatments of TMZ chemotherapy present benefits toward butterfly glioblastoma (bGBM) patients. Patients diagnosed with bGBM, contain a high grade astrocytoma that crosses the midline via the corpus callosum and is considered to have a dismal prognosis that leads to no attempt of a curative resection. We predict that if LEV has the ability to sensitize glioblastoma behavior toward TMZ chemotherapy treatment, then LEV can serve as a chemotherapeutic agent in order to reach a differential diagnosis to cure bGBM patients. In this review, we discussed whether LEV can be used as a therapeutic agent for patients with bGBM, if so what are the pros and cons of this specific gene therapy and are we able to assess if there is a cross relationship between TMZ and LEV, which in turn provides potential benefits. Overall, it is evident that in connection to TMZ, LEV increases TMZ induced cytotoxicity in patients with bGBM, thus causing a sensitizing effect that provides advantageous and disadvantageous options for LEV as a therapeutic agent in bGBM patients.

Keywords: levetiracetam, temozolomide, butterfly glioblastoma, keppra

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Abbreviations: LEV, levetiracetam; AED, antiepileptic drug; TMZ, temozolomide; GBM, glioblastoma; multiform; bGBM, butterfly glioblastoma; SV2A, synaptic vesicle protein 2A; GABA, gamma-amino butyric acid; ABTA, american brain tumor association; DNA, deoxyribonucleic acid; AGT, alkyltransferase; MGMT, methyltransferase; mmr: mismatch repair; MGMT, o6-methyl guanine-dna methyl transferase; HDAC1, histone deacetylase 1; mRNA, messenger ribonucleic acid; QT-PCR, quantitative real-time polymerase chain reaction; USA, united state of america; EMA, european medicines agency; TPM, topiramate; FDA, food & drug administration

Introduction

Epilepsy

As a common chronic disorder, epilepsy has been appointed as a disease that requires anti-epileptic drug treatment on a long-term basis. During this disorder, permanent changes in the brain cause excitability or irritability that triggers the brain to send out abnormal signals. As a result, unpredictable seizures, dementia, brain tumors and many other injuries to the brain occur. Several symptoms vary from person to person, in which some may have simple staring spells, while others have violent shaking and loss of alertness. Because there are multiple types of seizures, each is distinguished based on the part of the brain that is affected and the cause of epilepsy. It has been proven that the occurrence of a seizure is variably similar to the one that has occurred in past.[1,2] The after effects of a seizure may consist of sensations that may cause tingling, smelling an odor that is not actually there, or emotional changes. This is called an aura. In diagnosing seizures, they can be classified based on their severity and expression. These categories are, the absence (petit mal) seizures, generalized tonic-clonic (grand mal) seizures and partial (focal) seizures. The absence (petit mal) seizures consist of staring spells, while the generalized tonic-clonic (grand mal) seizures affect the entire body, and include symptoms of aura, rigid muscles, and loss of alertness. Partial (focal) seizures involve the symptoms of an aura, emotional changes, rigid muscles and a loss of alertness, which depends on the location in the brain at which the seizure begins (Table 1). To go further in depth, partial seizures occur when there is initial activation of one cerebral hemisphere resulting in electrographic and clinical changes. Partial seizures can then be categorized into simple partial, complex partial and partial to then become generalized. In simple partial seizures, responsiveness and awareness are completely preserved, while the complex partial seizures will present as minimal alterations in responsiveness or awareness. Secondarily generalized seizures will begin as a simple partial or complex partial, then progress to the entire brain and manifest toward generalized tonic and clonic activity. If initial clinical changes occur, this will then lead to a strong indication in which, both hemispheres are involved and the diagnosis is that of a generalized seizure.[3]

The clinical background of keppra (levetiracetam, LEV)

What is keppra (Levetiracetam, LEV)?: Originally discovered in 2000 through a random screening of two genetic rat models, Levetiracetam (LEV), pharmaceutical name Keppra, showed a potent ability to serve as the first synaptic vesicle protein 2A (SV2A) ligand for the usage as a antiepileptic drug (AED) for epilepsy. LEV is a

water soluble pyrrolidone derivative ((S)-a-ethyl-2-oxo-pyrrolidine acetamide). The chemical structure of LEV differs from other AEDs. Clinically approved in 2002, LEV is a prominent AED for partial and generalized epilepsy syndromes serving, as sole or add-on medication and has been extremely effective in its efforts.[4–7] However, unlike other AEDs, LEV is less likely to be a substrate for multi-drug transporters.[8,9] Despite the behaviors of multiple antiepileptic drugs (AEDs), LEV inhibits calcium release by binding to a synaptic vesicle protein and modulates seizure-activity with individuals diagnosed with chronic epilepsy.[9]

Table 1 Types and characteristic signs of generalized seizures

Type of seizure	Characteristic signs
Absence (petit-mal)	Staring or eye flickering Some body movements may occur No convulsions or posticta l symptoms
Myoclonic	Symmetric jerking of the extremities
Tonic	Rigidity
Tonic-clonic (grand-mal)	Tonic stiffening (extension) followed by clonic flexion motions May produce labored respirations, cyanosis, incontinence, involuntary tongue biting (sensitive but not specific sign), and postictal confusion, fatigue, or stupor
Atonic	Sudden loss of postural tone

Action Mechanism: Upon Levetiracetam (LEV) binding to the synaptic vesicle protein 2A (SV2A), a modulation of multiple actions occur, resulting in neural excitability. Though considered an anti-epileptic drug (AED), its action mechanism differs from first and second-generation AED's. Most AED's perform by three routes: sodium channel modulation, or direct gamma-amino butyric acid (GABA) facilitation.[10] Lacking anticonvulsant activity in classic acute seizure models used for AED screening, LEV is unable to promote a fully elucidated mechanism of action for the seizure prevention, but it up regulates glutamate transporters, resulting in the possibility of increased neuroprotection.[11] Though increasing neuroprotection, when compared to traditional therapy, LEV does not interact with other anti-epileptics nor is serum drug monitoring required; yet its safety margin is wide.[12] There have been numerous efforts to decipher the role of SV2A in synaptic vesicle release and cycling yet, its function still remains elusive. The reduced SV2A expression was found in the brain tissue obtained from experimental epileptic models and epileptic patients. These observations appear to correlate with the data from SV2A deficient animal, which display increased vulnerability to seizures.[13] Consequently, SV2A is an intricate player in synaptic vesicle function and represents a unique binding site for LEV. In several partial and generalized epileptic models, the affinity-potency correlations display SV2A as a broad spectrum anticonvulsant target, meaning that the anticonvulsant activity of LEV is closely related to the availability and occupancy of SV2A and SV2A deficiency causes an increase in seizure vulnerability and accelerates epileptogenesis. Taken together, existing experimental data prove that SV2A plays a crucial role in mediation of the anticonvulsant action of LEV in vivo.[13] Furthermore, SV2A is an important novel target for AED discovery that led to the contribution of LEV as a unique AED that characteristically is effective clinically in generalized and partial epilepsy syndromes, when used as a medication. Approved in the United State of America (USA), LEV acts as an adjunctive therapy for partial-onset seizures, and has aided recent experimental trial in being used as an adjunctive therapy for primary generalized tonic-clonic seizures and myoclonic seizures of juvenile myoclonic epilepsy.[3]

Keppra (levetiracetam, LEV) and epilepsy: Epilepsy treatment ranges based upon the specific classification of the epileptic syndrome and seizure type. One an AED has been chosen based on the seizure type, it is imperative that the medication is the most beneficial considering the patient's medical background. Studies have shown that approximately, one half of patients failed the initial antiepileptic drug and about 35% are refractory to medical therapy, thus emphasizing the necessity of more effective and better-tolerated drugs.[3] In regards to epileptic treatment, LEV plays a major role in that it is efficient long-term, initially and for early add-on therapy, in diagnosed myoclonic seizures with juvenile myoclonic epilepsy and generalized tonic-clonic seizures in idiopathic generalized epilepsy. Studies prove that LEV increases Temozolomide-induced cytotoxicity in glioblastoma (GBM) patients expressing the MGMT protein along with minute adverse side-effects. Overall, LEV has repeatedly been shown to exhibit a low potential for clinically relevant pharmacokinetics both with other AED drugs or drugs that could possibly be used to treat brain tumors, thus highlighting its ability to represent as a therapeutic agent for patients with bGBM.[2] Keppra (Levetiracetam, LEV) and treatment with Temozolomide (TMZ) in Butterfly Glioblastoma (bGBM): As of 2010, approximately 700,000 individuals in the USA were living with a brain tumor diagnosis. The current incidence of brain tumor related seizures are as high as 70% and has been historically difficult to control.[14] In statistics, the American Brain Tumor Association (ABTA) states that glioblastomas represent 17% of all primary brain tumors, and 54% of all gliomas. Glioblastoma multiform (GBM) is extremely aggressive and has been characterized as the most common diffuse astrocytic tumor in adults. Commonly spreading through direct extension along white matter tracts, it can infiltrate the corpus callosum, sub-ependymal and cerebrospinal fluid. As in the present case, when the corpus callosum is affected, GBM commonly displays a characteristic bi-hemispheric involvement, resulting in the classic butterfly pattern on imaging.[15] Despite multiple lines of therapy, survey and chemotherapy, the GBM continues to persist yielding a survival rate of only 9-12months. Butterfly glioblastoma (bGBM) presents initially as a grade IV astrocytoma with bilaterally contiguous

enhancement and represents the most threatening glioblastoma multiform, additionally its cerebral hemispheres involve the bilateral corona radiata where the tumor crosses the corpus callosum.[16] Among patients with glioblastoma (GBM), those with bGBM, has the worst prognosis. In regards to treatment, TMZ, pharmaceutical name, Temodar, is the most highly recommended form of therapy in patients who have a first relapse of glioblastoma after chemotherapy treatment or who had no prior cytotoxic chemotherapy at the time of initial therapy. Temozolomide (TMZ) is an alkylating agent used for the treatment of Grad IV astrocytoma, which categorizes a GBM. Discovered in 1999, by Malcolm Stevens and his team of researchers at Ashton University, TMZ stands as a pro-drug and imidazotetratizine and a derivative of the alkylating agent dacarbazine. TMZ contains therapeutic benefits in its ability to alkylate/methylate deoxyribonucleic acid (DNA), at the N-7 or O-6 positions of guanine residues. As a result of the methylation activity, the DNA is damaged and apoptosis of tumor cells are triggered. However, several tumor cells have the ability to repair from this type of DNA damage, and thus diminish the therapeutic foundation and accuracy of TMZ. This particular event occurs by the expression of the O6-alkylguanine DNA alkyltransferase (AGT) protein, which is encoded in humans by the O-6-methylguanine-DNA methyltransferase (MGMT) gene. Epigenetic silencing of the MGMT gene in several tumors can prevent the synthesis of this particular enzyme, increasing their sensitivity of killing by TMZ. Conversely, the presence of the AGT protein in brain tumors predicts poor response to TMZ and these patients receive little benefit from chemotherapy with TMZ.[17] Though TMZ has been a standard first line treatment for malignant glioma since 2010, its clinical effectiveness has been constrained due to active DNA mismatch repair (MMR) proteins requirement, and inherent resistance through MGMT activity. MMR mutation results in acquired resistance and thus demonstrates an aggressive TMZ-resistant tumor regrowth following good initial responses.[18] In connection to TMZ, LEV increases TMZ induced cytotoxicity in patients with GBM who do express the MGMT protein while also experiencing little adverse side-effects by inhibit histone deacetylase activity within the tumor through the increase in the transcription of histone deacetylase 1 (HDAC1) which ultimately silences MGMT.[13] Thus, the connection between LEV and TMZ shows that LEV can be used as a therapeutic agent for bGBM patients, in addition to being directed towards seizure treatments in brain tumor patients. There has been evidence that AEDs may have an indirect impact in modulating MGMT, which is a protein that repairs DNA and aids in tumor cell resistance to alkylating agents.[19] As a result, AEDs are used in treating seizures in glioma patients and LEV stands as the most potent MGMT inhibitor among when compared to other AEDs. In vitro, when LEV is used at human therapeutic range concentrations that are present during seizure prophylaxis, MGMT protein and messenger ribonucleic acid (mRNA) expression levels decrease. Chromatin immunoprecipitation analysis reveals that LEV enhances p53 binding on the MGMT promoter by recruiting the mSin3A/histone deacetylase 1 (HDAC1) corepressor complex.[19] Being that brain tumor patients on chemotherapy or other therapeutic drugs suffer from seizures, this induces cytochrome P450, causing significant drug interactions and allowing LEV to serve as an attractive option for brain tumor patients suffering from seizures. Reason being is that, LEV lacks the ability to induce the P450 system and exhibit relevant drug interactions. By enhancing p53-mediated MGMT inhibition, LEV can then inhibit malignant glioma cell proliferation, and sensitize GBM cells to TMZ. Overall, when compared to other conventional AED's, LEV is a safe alternative for brain tumor patients battling seizures.

Therapeutic advantages and disadvantages of keppra (levetiracetam, lev) on epilepsy and butterfly glioblastoma

Epilepsy: Approved by European Medicines Agency (EMA), LEV has been indicated as an adjunctive therapy in partial seizures treatment in patients 4years and older, adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents 12years and older, with juvenile myoclonic epilepsy and primarily generalized tonic-clonic seizures in adults and children 6years of age and older, with idiopathic generalized epilepsy.[20] In regards to the advantages and disadvantages of LEV treatment, initial mono therapy is less clear-cut. It is evident that there is no decline in the cognitive function of patients with partial epilepsy receiving LEV treatment. For example, a study was performed that compared LEV and topiramate (TPM), which is another common AED, using a standardized neuropsychological test battery. During this study, 30 consecutive patients with focal epilepsy were treated with LEV and 21 treated with TPM. While the TPM group worsened in cognitive speed, verbal fluency, and short-term memory, there was no change in the LEV group.[21] This stands as a major advantage being that, this disease inhibits brain function, and LEV treatment does not show any cognitive loss in epileptic patients. Additionally, LEV is advantageous in the event that rapid onset of action occurs, when the drug is initiated at a therapeutic dose, however initiation of a drug at a therapeutic dose is not necessarily a guarantee that onset of action will be rapid, which can also be a disadvantage. Thus, disadvantages vary due to the fact that there is an absence of a USA Food and Drug Administration (FDA) approval, yet there is ample evidence that LEV is widely used in the hospital setting for new onset epilepsy and acute seizures.[22–26] This is considered a disadvantage because no FDA approval shows that there are no outstanding trials that have supported initial monotherapy use in generalized epilepsy. Several symptoms consist of drowsiness, dizziness, headaches and coordination issues. However, the evidence of adjunctive efficacy in juvenile myoclonic epilepsy has prompted use as initial monotherapy in juvenile myoclonic epilepsy.[10] Thus, without comparing it to other AEDs, the use of LEV as an initial monotherapy cannot be strongly supported. Overall, LEV stands as a well-tolerated AED in the realm of therapeutic agency due to the fact that it has a straightforward pharmacokinetic profile in which, it is almost completely eliminated by renal excretion, has a minimal protein binding and consequently has no interaction with other drugs.[27]

Butterfly glioblastoma: In regards to Butterfly Glioblastoma (bGBM), as previously stated LEV sensitizes glioblastoma cells to TMZ, thus providing advantageous and disadvantageous options for LEV usage as a therapeutic agent. These advantages are based on the all-encompassing goal of curing bGBM. Several of these advantages are, the glioma cell proliferation inhibition, decreased MGMT expression, MGMT expression inhibition due to increased p53 binding on the MGMT promoter, and MGMT protein inhibition in glioblastoma cell lines. The basis of these advantages stem from previous studies in which, human glioma cells and human astrocytes were plated and subjected to western blotting, quantitative real-time polymerase chain reaction (QT-PCR), histological studies and statistical analysis. Through this study, it was determined that LEV was the only AED capable of significant MGMT inhibition, which is directly linked to glioblastoma behavior.[19] We further see that the usage of LEV has the advantage in that it can serve as a therapeutic agent for bGBM stems and has the ability to reestablish a more differentiated phenotype feature by MGMT inhibitory activity of the mutated p53 gene being restored and mSin3A/HDAC1 corepressor

system recruitment, which has been reported in other human cancers as a system that causes LEV to have a widespread regulatory effect. Additionally, when exposed to TMZ, LEV exerts a protective role on normal astrocytes, as well as shows a direct correlation between MGMT levels in glioma transitional models and glioma patients. Several disadvantages may be, direct contact with the glioma and LEV can cause mutational defects as well as, ultimately no effect to completely decimating the bGBM. However, more studies will be required in transferring research into the clinical practice realm in regards to therapeutic intervention for seizure and bGBM.[28–30]

Conclusion

In conclusion, Keppra (Levetiracetam, LEV) stands as a profound AED that has been used for add-on therapy purposes in individuals that have suffered from epilepsy, particularly being prescribed as an outpatient choice of treatment. However, based on its drug profile, LEV is useful for treating hospitalized epileptic patients due to its ability to perform productive pharmacologic interactions, tolerance, and fast action mechanisms. Thus, LEV serves as a strong pharmaceutical agent that confirms its short-term safety and effectiveness to control seizures in these patients. Additionally, it stands as a recognizable AED that has the ability to break the barriers of cancer research and go beyond the surface of therapeutic methods. Through its direct connection to TMZ, as being both instrumental therapeutic agents and its usage in chemotherapeutic events, there lies a deep-rooted ability for LEV to be used as a direct agent in curing bGBM, rather than silencing the episodes of seizures of brain tumor patients. This is supported based upon LEV's ability to directly sensitize bGBM to TMZ and aid in the process of chemotherapeutic progression. As a result, the advantages and disadvantages presented weighs heavily on whether or not, LEV should be considered as a therapeutic process within the clinical field. Lending its hand to combination therapy with TMZ, LEV presents an optimistic future to further chemotherapeutic agents in bGBM. Consequently, through further analysis and research, the pharmaceutical brand known as, Keppra has the ability to progress therapy efforts in the field of cancer.

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Conflict of interest

Author declares that there is no conflict of interest.

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