Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Spl Issue [2] 2023: 336-341.

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

Fingolimod Ameliorates Schizophrenia-Like Cognitive Symptoms: An Update

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ABSTRACT
Research has indicated that schizophrenia is a mental disorder that impacts approximately one percent of the population in various communities. Studies have also shown that severe cases of schizophrenia require extended hospitalization and continuous treatment. Furthermore, as studies have already shown that FG act as a sphingosine-1-phosphate receptor modulator thus, the approval of this treatment for relapsing-remitting MS was highly anticipated. So, the main point of our study was to show that FG is a better choice for SZ illness with the help of its mechanism, adverse effects, safety, usefulness, and future scope.
Key words: *Mechanism, Adverse Effects, Safety, Usefulness, Future Scope, MS, SZ, FG*

Received 28.09.2023 Revised 20.10.2023 Accepted 30.11. 2023

INTRODUCTION

Research has shown that schizophrenia (SZ) is a long-lasting mental disorder characterized by a complex genetic and neurobiological basis.[1] Studies also concluded that problems with motivation and thinking are part of this condition that affects the early development of the brain.[1] Furthermore, research also showed a mix of psychotic symptoms like hallucinations and delusions with almost equal frequency in both males and females.[1] Therefore, its management is a must. In this context, researchs have also shown that "Fingolimod (FG) functions as a sphingosine-1-phosphate receptor modulator".[2] It works by trapping lymphocytes in lymph nodes, thus preventing their involvement in an autoimmune reaction. Additionally, studies have shown that it has been reported to "cut the number of relapses in relapsing-remitting MS by around half during a two-year period".[2]
Thus, in our review we were focusing on FG being more acceptable for SZ illness.

HISTORY

S.NO.	YEAR	DISCOVERY
1.	1992	"Yoshitomi Pharmaceuticals originally derived from an immunosuppressive natural product called myriocin (ISP-I) through chemical modification".[3]
2.	September 2010	"The FDA authorized FG as the first oral disease-modifying medicine to minimize relapses and postpone disability development in individuals with relapsing types of multiple sclerosis".[4]
3.	March 2011	"The European Medicines Agency had to approve the drug for sale throughout the European Union".[5]
4.	April 2011	"Novartis claimed, the drug to be accessible in Canadian pharmacies".[6]
5.	2016	"According to a systematic review, the treatment for people with relapsing-remitting MS has been found to be effective in reducing the likelihood of acute inflammatory relapses. However, its impact on disability progression compared to a placebo may be minimal or nonexistent".[7]
7.	December 2019	"A generic FG has been approved in the United States for treating relapsing forms of multiple sclerosis (MS) in adults".[8]

MECHANISM

Researchers have found that FG comes from the myriocin metabolite of fungi and has a structure like sphingosine, which is a key part of cell membranes. Also, research has shown that sphingosine 1-phosphate (S1P) is created when sphingosine kinase phosphorylates sphingosine. S1P is a soluble regulator of many cellular activities. Studies also concluded that a group of five G-protein-coupled SIP receptors collaborates to carry out these functions. Additionally, studies revealed that, there is something called sphingosine kinase that changes fingolimod into fingolimod-phosphate. This compound binds strongly to four out of five S1P receptors. As a medicine, studies have also concluded that FG may have effects on both the immune system and the central nervous system and these effects may involve controlling S1P receptors.[9,10,11,12]Scientists have also discovered that the S1P-type-1 receptor (S1P1) helps lymphocytes leave lymphoid tissues and return to the center of the body. This receptor is widely expressed on lymphocytes, including T cells and B cells. In this case, FG-phosphate makes receptors break down and enter cells by strongly attaching to S1P1 in lymphocytes and decreasing the amount of S1P1 mRNA that is made.[13] Studies also found that lymphocytes stay in secondary lymphoid tissue because they lose S1P1 surface expression. Additionally, this causes functional antagonism and a loss of responsiveness to the S1P gradient that is needed for egress.[9,11,14]

USE

Studies have concluded that "FG is prescribed for the treatment of the relapsing form of multiple sclerosis. Furthermore, research has shown that it can also be utilized in chronic inflammatory demyelinating polyneuropathy".[15]

ADVERSE EFFECT [16,17,18]

1. Cold
2. Headache
3. Increase gamma-glutamyl
4. Diarrhea
5. Nausea
6. Abdominal Pain
7. Fatigue
8. Skin cancer (few cases)
9. Fatal infection
10. Bradycardia
11. Hemorrhaging focal encephalitis
12. Inflammation of brain with bleeding
13. Brain herpes infection
14. Herpes zoster
15. Multifocal leukoencephalopathy
16. Macular edema
17. Decreased vision
18. Slow heart rate
19. Serious infection
20. Risk for swelling & narrowing blood vessel in brain
21. Respiratory problem
22. Liver injury
23. Increase blood pressure

SAFETY [19]

According to studies, "the safety profile of FG is based on the analysis of data from 2,615 individuals who took part in phase II and phase III studies. In the FREEDOMS trial, the occurrence of adverse effects (AEs) associated with a 0.5-mg dosage of FG was similar to that of a placebo. The 1.25-mg dosage of FG in both the FREEDOMS and TRANSFORMS studies was associated with a higher occurrence of adverse events, leading to the discontinuation of the drug. According to many studies, most common side effects of FG included laboratory abnormalities, bradycardia or AV conduction deceleration, retinal edema, increased susceptibility to infections, blood pressure fluctuations, coughing, difficulty breathing, back discomfort, headache, influenza, and diarrhea".[19]

LITERATURE REVIEW

Schultz et al., (2007) conducted a review article with regard to "evaluate & assess SZ. They come to the conclusion that it is a psychologically crippling illness that affects one percent of the population throughout all civilizations. This percentage is consistent across all populations. It affects about the same number of men and women, although the onset of symptoms often takes place considerably later in women than it does in men. Both positive and negative symptoms are characteristics of the mental illness known as schizophrenia. Positive symptoms include hallucinations, voices that communicate with or about the patient, and delusions that are often paranoid. Other symptoms include hearing voices. Positive symptoms also include being able to hear voices. Some of the negative symptoms include a flattened affect, a loss of pleasure, a loss of will or drive, and social isolation. Both of these kinds of symptoms have an effect on the patients' families. As a consequence, it is vital for medical experts to offer counsel and direction to everyone who is afflicted by the disease. There is potential for improvements in outcomes with the use of interventions that center on psychosocial variables and families. Medications have the capability of reducing symptoms; nevertheless, practically all antipsychotics have neurologic or physical adverse effects (such as weight gain, hypercholesterolemia, or diabetes, to name a few examples). Patients who have been diagnosed with schizophrenia have an increased risk of death by suicide during their lifespan, which is ten percent more than the risk for the general population".[20]

Brunkhorst et al., (2014) did a review article to "assess and analyze the use of FG for the treatment of neurological diseases, taking into consideration both the existing state of things and the prospective advances that may occur in the future. They come to the conclusion that the sphingolipid signaling pathway seems to be of considerable relevance in the pathophysiology of a broad variety of various neurological diseases. In the treatment of multiple sclerosis (MS), the versatile sphingosine analog fingolimod, which is also the prodrug of the S1P-modulating fingolimod phosphate, provides advantages that have been scientifically proven to be beneficial. These benefits include a reduction in the relapse rate and an attenuation of the development of the disease. Findings from clinical studies that were carried out on experimental animal models, on the other hand, suggest that fingolimod may have further therapeutic potential in the future. The vast majority of the diseases that were discussed in this article follow a course that, in the end, culminates in death. Although there are therapies available for these diseases, their efficacy is typically only temporary, and this is despite the fact that there are some treatments available for these diseases. In view of the growing body of experience with fingolimod that has been obtained by clinical neurologists and the outstanding safety profile in the indication of multiple sclerosis (MS), there is hope about the potential for a translation of some of these experimental outcomes into clinical practice. Clinical neurologists have to acquire this increasing body of experience with FG". [21]

Chun et al., (2019) did a review to assess the "efficacy of FG both in and out of the treatment of MS and other disorders. Other illnesses were also studied. They come to the revelation that research on FG and LP receptors has synergized to generate new vistas on basic biology, diseases, and therapeutics. This is something that they had not previously considered. It is plainly obvious that a detailed understanding of the specific receptor pathways that are accessible by fingolimod is important to the effective entry of the medication into the medical armamentarium. In addition, such an understanding is necessary for the development of therapeutics for the next generation, which highlights the need to gather this knowledge as soon as possible. Failure in one treatment area does not rule out success in another, as was the case with fingolimod; nonetheless, it may need creative means of assessing and addressing efficacy and safety aspects in order to be successful. The failure of fingolimod in one therapeutic area did not rule out its potential success in another. It is feasible to increase the efficacy as well as the safety of a particular agent by better matching the qualities of the drug with those of the ideal patient, as has been proven here with fingolimod. This information may serve as the basis for the development of new medications that target LP receptors, which might lead to the development of innovative therapeutics for the brain and other organ systems".[22]

Bascuñana et al., (2020) did a review where the authors found that "FG was beneficial in treating several sorts of neurologic diseases in addition to multiple sclerosis (MS). They come to the conclusion that FG has shown neuroprotective effects in a variety of animal models of neurodegenerative diseases. This leads them to conclude that this finding is significant. These effects are associated with an increase in brain-derived neurotrophic factor as well as an improvement in the illness phenotype (cognition and/or motor skills). The treatment proved successful in suppressing lymphocytes as well as having direct effects on astrocytes and microglia. As a result of this, the treatment caused decreases in a variety of neuroinflammatory indicators, which was something that was anticipated to occur as a consequence of what happened. In addition, treatment with fingolimod was shown to have additional effects for some neurodegenerative illnesses. These effects included a decrease in the generation of amyloid-A as well as

antiepileptogenic qualities. Patients who have received the treatment have demonstrated these effects. The neuroprotective effects that fingolimod demonstrated in these preclinical experiments are detailed, and they provide support for the translation of fingolimod into clinical trials as a treatment for neurodegenerative diseases that extend beyond neuroinflammatory conditions (MS)". [23]

Okura et al., (2021) conducted an original research study to look into the possibility of using "FG as a treatment for psoriasis (PS) by using mice that had psoriasiform dermatitis due to the drug imiquimod (IMQ). They found that FG improved the PS dermatitis that was caused by IMQ both clinically and histologically. On day 6, the mRNA expression level of IL-17A was greater in the inguinal lymph nodes of FG-treated mice than in those of PBS-treated mice, while it was lower in the skin of fingolimod-treated mice than in PBS-treated mice. FG was able to prevent Langerhans cells from migrating from the skin to the lymph nodes. They came to the conclusion that FG was effective for IMQ-induced psoriasiform dermatitis. This was accomplished by preventing the migration of IL-17A-producing T cells from the lymph nodes to the skin. This leads them to believe that FG is a good option for the treatment of PS".[24]

Li et al., (2022) conducted original research to provide evidence supporting the possibility of its "usefulness in improving cognitive function in those who have been diagnosed with SZ. For this reason, they used a rat model of PCP-induced SZ in their study to look into how well fingolimod works and how it does what it does. They discovered that FG can restore hippocampal neurogenesis and lessen cognitive deficits in rats that have been treated with PCP. Moreover, the effectiveness of this ability was found to depend on the dose. Thus, the effects of FG were highly dependent on the dosage that was taken. By inhibiting the activation of microglia and the generation of pro-inflammatory cytokines IL-6 and IL-1, the therapy employing fingolimod showed that it might decrease inflammation. During this process, there is an increase in the creation of brain-derived neurotrophic factor protein, as well as the activation of a signaling pathway that is mediated by extracellular signal-regulated kinase (ERK). They come to the conclusion that the immune system has a role in the cognitive alterations that may be detected in schizophrenia. In addition, the possibility of addressing the cognitive deficits associated with schizophrenia by using immunomodulatory strategies was underlined as a viable treatment option".[25]

Yu et al., (2023) conducted a research article in order to gain a better understanding of the "mechanism underlying phencyclidine (PCP)-induced SZ. They carried out a study to assess the efficiency of FG in a rat model of the illness. They found that FG effectively restored hippocampus neurogenesis and improved cognitive function in rats that had been treated with PCP. Thus, the dosage played a significant role in this process. In addition to this, it was found that the treated area had anti-inflammatory effects, which expressed themselves as a decrease in microglial activation as well as the production of pro-inflammatory cytokines IL-6 and IL-1. In other words, the reduction in microglial activation and production of these cytokines showed that the treated region had an anti-inflammatory effect. Henceforth, they come to the conclusion that the immune system has a significant role in the cognitive abnormalities that may be detected in those who suffer from schizophrenia. In addition to this, they highlighted the prospect of using immunomodulatory strategies in order to treat cognitive deficits in those who are affected by SZ". [26]

Zhuo et al., (2023) did a follow-up pilot study to see "what happened to cognitive performance, whole-brain gray-matter volume (GMV), and interleukin-6 (IL-6) levels in drug-naive first-episode schizophrenia patients who took low doses of lithium for a long time along with antipsychotic drugs. The study also aimed to explore the connections between these factors. They found that after 24 weeks of treatment, patients in the lithium group showed significant improvements in working memory, verbal learning, processing speed, reasoning, and problem solving. In contrast, patients in the placebo group only demonstrated improvements in working memory and verbal learning compared to their initial baseline. The MCCB composite score did not vary significantly among the groups. The decrease in whole-brain GMV was significantly less in the lithium group when compared to the placebo group (0.46% vs. 1.03%; P 0.001 for each comparison). Both groups showed a negative correlation between the reduction ratio of GMV and IL-6 ($r = 0.17$, $P = 0.025$). Some changes in the lithium group were linked to better working memory ($r = 0.15$, $P = 0.030$) and faster processing ($r = 0.14$, $P = 0.036$). The ratio of whole-brain GMV reductions was also related to these changes. It was found that the lower ratio of IL-6 was linked to better working memory ($r = 0.21$, $P = 0.043$) and verbal learning ($r = 0.30$, $P = 0.031$) in the lithium group. It was found that the decrease in whole-brain GMV was only linked to the rise in working memory in the placebo group ($r = 0.24$, $P = 0.019$). Moreover, the lower level of IL-6 was linked to better levels of working memory ($r = 0.17$, $P = 0.022$) and verbal learning ($r = 0.15$, $P = 0.011$). It was determined that both therapies used in this trial significantly improved the cognitive performance of men with schizophrenia. They come to the conclusion that, compared to the placebo, the low-dose lithium had slightly more pronounced effects on different cognitive areas. Furthermore, the groups exhibited varying

patterns of connection between GMV reduction, IL-6 reduction, and improvement in cognitive function".[27]

FUTURE SCOPE [19]

Nevertheless, further studies and clinical experience will provide a more detailed understanding of the specific role of FG in the treatment of multiple sclerosis. Examining long-term safety data might alleviate concerns about the possibility of neoplasms, opportunistic infections, and reproductive effects.Oral S1P modulators provide significant potential for both benefit and hazard, so exploring lower dosages of FG and medicines that exhibit more selective binding to S1P receptors may offer valuable insights on how to minimize this trade-off.

CONCLUSION

The development of an oral formulation of FG has presented a significant and useful new therapy option for multiple sclerosis (MS). Lymphocytes have an essential role to play in the process of controlling the circulation of immune cells, which in turn serves to reduce the risk of inflammatory damage. There is a possibility that FG will provide direct advantages to the central nervous system (CNS). In spite of the fact that a large number of clinical trials have established its efficacy, tolerability, and safety, its usage as the main treatment option is likely going to be restricted in the near future due to worries about the possibility of cardiac adverse events and the drug's long-term safety. In the rapidly evolving field of MS therapy, more study will shed more light on the function of FG and bring about greater clarity.

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CITATION OF THIS ARTICLE

P S Salve, Dhairyasheel D. Patil, Ganesh Thorat. Fingolimod Ameliorates Schizophrenia-Like Cognitive Symptoms: An Update. Bull. Env. Pharmacol. Life Sci., Spl Issue [2]: 2023: 336-341.