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REVIEW ARTICLE

Role of fingolimod in acute respiratory distress syndrome.

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ABSTRACT... Objective: Sphingosine 1 Phosphate (S1P) is a key regulator of inflammation, angiogenesis, vessel permeability, and immune processes, acting through S1P receptors. Fingolimod (FTY720), an S1P receptor analog Fingolimod, was initially approved for multiple sclerosis treatment and has shown potential for application in infectious and inflammatory disorders, including COVID-19. **Study Design:** Comprehensive Literature Review. **Setting:** Northwest School of Medicine. **Period:** 1st March 2023 to 3rd July 2023. **Methods:** Examining S1P pathways, S1P receptor analogs, and their potential in treating inflammatory and infectious disorders, particularly COVID-19, utilizing Fingolimod. **Results:** S1P analogs have demonstrated therapeutic benefits in autoimmune diseases. In COVID-19, these analogs modulate the inflammatory response, reduce tissue damage, and promote viral clearance. Fingolimod, in particular, affects S1PR1, S1PR4, and S1PR5, blunting the inflammatory response and mitigating lung tissue injury. Early administration may prevent excessive inflammation without interfering with viral clearance. Potential risks include disturbance of cytokine homeostasis and delayed administration. Limited human studies and concerns about off-target effects need addressing. **Conclusion:** Fingolimod shows promise in treating COVID-19 by reducing inflammation and lung damage. Further research is needed to address limitations and ensure safety for clinical application. Sphingosine 1 Phosphate (S1P) plays a key role in regulating inflammation and immune responses, with Fingolimod being a potential treatment option.

Key words: COVID-19, Fingolimod, Respiratory Distress Syndrome, Sphingosine 1 Phosphate.

INTRODUCTION

Sphingosine 1 Phosphate (S1P) is involved in the regulation of inflammation, angiogenesis, the permeability of vessels, the central nervous system as well as metastatic processes.[1] S1P lipids act via attachment to the G protein-coupled S1P receptors (S1PRs).[2] The immune processes are also controlled through the modulatory changes in the trafficking of T lymphocytes. Analogs of the S1PR have been under study for their application in auto-immune therapeutics. In 2010 FTY720 (Fingolimod) was approved to be used in the relapsing-remitting multiple sclerosis as a first-line drug.[3] Further studies on this group of drugs directed toward their effect on the innate immune system and hence hypothesized their use in infectious and inflammatory disorders. The effect of the S1PR on the innate system can propose its efficacy in the SARS-COVID-19 viral infection as the innate system is the first line of defense following the viral entry. This article is intended to understand and elaborate on the utility of sphingosine 1 phosphate analogs on inflammatory and infectious disorders including COVID-19.

Sphingosine 1 phosphate is a product of sphingosine phosphorylation through the action of sphingosine kinase 1 and 2 (SphK1, SphK2). The activation of the SphK1 receptor plays a central role in the functions of its agonists including hormones, growth factors, lipo-polysaccharides, cytokines, IgE, IgG, and many G protein-coupled receptors. The SphK1 is mainly localized in the cytosol and is also translocated to the cell membrane with the help of mediators such as calcium and integrin-binding protein 1. SphK 2 is primarily present in various compartments intra-cellularly. It is involved in the regulation of transcription of many genes via inhibition

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of histone deacetylation. It also takes part in the mitochondrial oxidase enzyme complex assembly. The activation follows ligands such as EGF and phorbol. These diverse compartment-specific localizations of the SphKs are indicative of the specific microenvironment in which S1P is produced and hence dictate its functions.[4]

The S1P phosphatases regulate the levels of S1P by irreversibly degrading the S1P by removal of the phosphate group. The phosphorylated S1P then binds to its GPCRs which have a varying distribution among different cell types hence exerting different effects on several cellular pathways. In addition, S1P also has the potential to produce certain intra-cellular effects even independent of its extra-cellular receptors.[5]

Fingolimod is a medication used in the treatment of multiple sclerosis (MS). Fingolimod may have potential benefits in RDS by targeting certain pathways involved in lung inflammation and injury. Specifically, fingolimod acts on sphingosine-1-phosphate (S1P) receptors, which play a role in immune cell trafficking and inflammatory responses. By modulating these receptors, fingolimod may help reduce inflammation and promote lung development in premature infants with RDS.

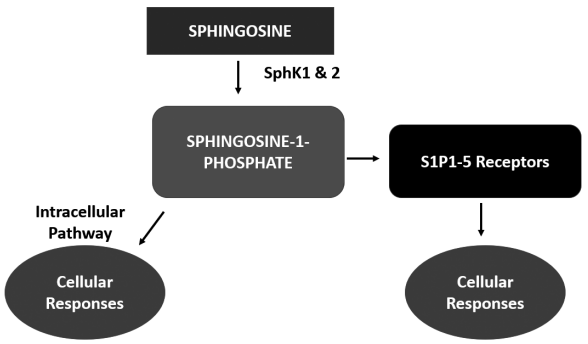

Figure-1. Outline of the sphingosine 1 phosphate pathway

METHODS

A comprehensive review of relevant literature on sphingosine 1 phosphate (S1P) pathways, S1P receptor analogs, and their potential therapeutic applications in inflammatory and infectious disorders, including COVID-19 was carried out in Northwest School of Medicine from 1st March 2023 to 3rd July 2023. Data were collected from existing studies, preclinical research, and clinical trials related to the use of Fingolimod in autoimmune diseases and COVID-19. Experimental data was identified, in vitro and in vivo studies, and clinical observations to evaluate the potential efficacy and safety of Fingolimod. The specific mechanisms by which Fingolimod modulates the S1P pathways and S1P receptor activation, clinical trials or case reports were investigated. Animal models, and experimental setups used to study the effects of Fingolimod on viral infections and inflammatory responses were analyzed.

The collected data was analyzed to evaluate the potential therapeutic outcomes of Fingolimod in COVID-19, considering its effects on inflammation, tissue damage, and viral clearance. The overall efficacy and safety of Fingolimod as a potential treatment for acute respiratory distress syndrome in COVID-19 was assessed. The key findings were summarized from the literature review, data collection, and analysis.

RESULTS

Sphingosine-1-Phosphate Receptors & their Targets

Sphingosine receptors are G protein couple receptors and are of 5 types S1PR1 to S1PR2. These receptors have an affinity for the endothelial differentiation genes (EDG) with the S1PR1 with the S1PR1 (EDG1), S1PR2 (EDG5), S1PR3 (EDG3), S1PR4 (EDG6) and S1PR5 (EDG8).[6] The type 1 receptor (S1PR1) is most widely distributed. G_i and β-arrestin bind to the receptor together leading to its internalization and down-stream pathway activation. The receptor is expressed by the macrophages during an innate immune response. Experimental studies utilizing S1PR1 specific agonist (SEW2871) and antagonist (VPC44116) have shown anti-inflammatory action of the dS1PR1 receptor stimulation. Other data concluded the role of S1R1 in macrophage apoptosis, decreased recruitment of neutrophils and eosinophils, lymphocyte migration, inhibition of the production of alpha interferons following viral infections and it plays a role in immune

responses towards infectious diseases via an effect on the recruitment and trafficking of innate immune cells, polarization of macrophages, and regulation of dendritic cell functions.[7,8]

S1PR2 signals via different alpha subunits of G_i and G_q receptors. This receptor mainly opposes the action of S1PR1. In addition, it is involved in the antibody phagocytosis that is dependent on opsonin, and release of anti-microbial peptides. S1PR2 also increases the phagocytosis of fungi mediated by antibodies and inhibits the bacterial phagocytosis in the macrophages of the alveoli hence interfering with the triggering of mast cells following viral infection.[9,10] S1PR3 binds to G_i and G_q and increases the migration of mature dendritic cells and endocytosis. It also functions in the maturation process of the dendritic cells and responses of the helper T cells. There is activation of macrophage chemotaxis and the generation of reactive oxygen species driving the killing of the bacteria. There is up-regulation of the S1PR3 in the neutrophils and eosinophils following bacterial infections hence enhancing the chemotaxis and recruitment. S1PR3 is expressed in the endothelial cells where it is responsible for the leukocyte activation via up-regulation of the P selectins on the membrane. Thus, S1PR3 plays a role in immune regulation through the induction of maturation of the dendritic cells, chemotaxis of macrophages, and recruitment of eosinophils as well as basophils.[11]

S1PR4 mostly signals via G_i. The receptor is involved in the activation of Rho Kinase and regulation of re-arrangement of the cytoskeletal proteins. The activated Rho kinases also induce apoptosis in the myoblasts and regulate cell metabolism, autophagy, and the cell cycle. S1PR4 restricts the differentiation of the dendritic cells and restricts the release of alpha interferons. The receptor is also linked to proliferation as well as migration of neutrophils and macrophages.[12] S1PR5 has a role in the regulation of oligodendrocytes, natural killer cells, and monocytes. The receptor manages monocyte trafficking independent of the gradients of sphingosine 1 Phosphate, hence indicating that S1PR5 follows so different downstream mechanism that remains unclear.[13]

Potential Therapeutic Outcomes of S1P Analogs in Corona Virus Disease

S1P analogs have been studied previously for their efficacy in auto-immune diseases, especially multiple sclerosis, and be of therapeutic benefit. We are going to apply the pharmacology of the sphingosine 1 phosphate analogs in viral infections regarding their potential utility in coronavirus disease. The analogues of sphingosine 1 receptor have a blunting effect on the inflammatory response following viral entry which may lead to decreased tissue damage following the inflammatory mediator activation. The reduction in the release of inflammatory mediators especially cytokines including interferons alpha, 6, and gamma decreases the tissue injury to the soft tissues of the lungs.

Receptor Type	Associated G Proteins	Associated Endothelial Differentiation Genes (EDG)	Main Functions
S1PR1	G_i	EDG1	Macrophage apoptosis, decreased recruitment of neutrophils and eosinophils, lymphocyte migration, inhibition of the production of alpha interferons, polarization of macrophages, and regulation of dendritic cell functions.
S1PR2	G_i, Gq	EDG5	Opposes S1PR1, opsonin dependent antibody phagocytosis
S1PR3	G_i, Gq	EDG3	Induction of dendritic cell maturation, chemotaxis of macrophages, recruitment of eosinophils & basophils.
S1PR4	G_i	EDG6	Rho Kinase activation and cytoskeletal re-arrangement
S1PR5	G_i	EDG8	Regulation of oligodendrocytes, natural killer cells and monocytes

Table-I. S1P receptors & their main mechanisms

Although the viral load may not be reduced following this reduction of the inflammatory response the ability of the host to clear this viral load is also not impaired.

Needless to say, the S1PR analogs will reduce the damage associated with viral infections improve the patient survival rate, and reduce morbidity. Experimental data show that the analogues reduce the natural killer cell and CD8 type T cell infiltration hence leading to a decrease in the production of the tumor necrosis factor alpha (TNF Alpha) and interleukins. The pattern of the SARS-COVID infection includes lung damage following infiltration of the CD 8 type T cells as well as the natural killer cells. The question however arises here that the T cells are also involved in the clearance of the viral infection, so a decrease in the CD8 cells should theoretically decrease the viral clearance by the host. But this is not the case in regards to coronavirus infection as the clearance of the viral load occurs mediated by the CD4 type of T cells instead of the CD8 cells which are mostly involved in the soft tissue damage. Therefore, the S1P analogs are capable of minimizing lung damage while maintaining the ability of the T cells to clear the virus.

The analogs have been studied to regulate the mitogen-activated protein kinases (MAPK) as well as the kappa B enhancer nuclear factor (NF-kB) via reduction in the MAPK phosphorylation hence inactivating the production of cytokines. The evidence also suggests that there is degradation of the alpha interferon receptors and de-activation of signal transducers, hence reducing the effect of interferons.

Role of Fingolimod in COVID-19 Therapy

From the discussion so far, an ideal candidate for the prevention of tissue damage following a viral infection would be a drug that agonizes the S1P receptors 1, 4, and 5 and either blocks or does not activate the S1P receptors 2 and 3. Fingolimod is an S1P receptor analog that has previously been studied for its efficacy in auto-immune multiple sclerosis relapses. It is an agonist at S1PR1, S1PR4, and S1PR5 and does not affect the S1PR2. Fingolimod is known to be a partial agonist at S1PR3 and hence in vivo, it can in a way antagonize the inflammatory effects of S1P through S1PR3 activation. The drug causes significant inhibition of interleukin production, downregulation of alpha tumor necrosis factor, and neutralizes the cytotoxic T cells. There is a decrease in the levels of cytokines and interferons.[14,15]

One of the prominent factors producing lung tissue injury during the coronavirus disease is the disruption of the vascular-endothelial cell barrier. Fingolimod maintains the endothelial cell barrier hence alleviating lung tissue injury to a great extent. The outcomes of the fingolimod therapy hence include minimal lung damage, inhibition of the inflammatory response, and a profound decrease in the overall disease severity.[16]

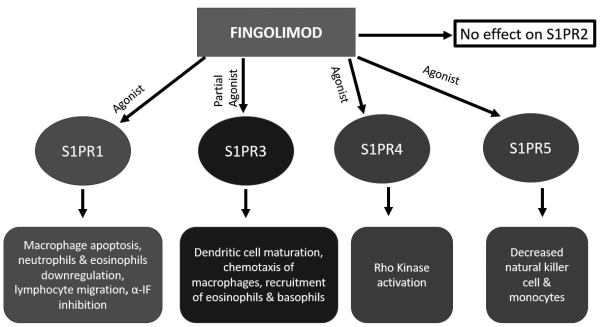

Figure-2. Mechanism of action of Sphingosine 1 Phosphate Analogue, Fingolimod

Considering the pharmacodynamic data of the mechanism of fingolimod action, it may be beneficial to commence with fingolimod therapy during the early phases of the viral infection. The drug will be able to prevent the inflammatory response that usually quickly follows the viral entry in the body. The blockade of the inflammatory response early on in the infection will play a preventive role and mitigate tissue inflammation leading to damage while not interfering with the clearance of the viral load by the body.

The efficacy of the S1P analog in viral lung diseases may be potentiated by the addition of anti-viral agents as it will enhance the viral clearance process in addition to influencing inflammatory signaling. The response may also be potentiated by the addition of a blocker

of S1PR2 that in a way opposes some of the effects of S1PR1 receptor activation and hence might interfere with the protective response of fingolimod administration.

Limitations of the Fingolimod Therapy in COVID-19

The S1P analogs do promise a good therapeutic benefit in the treatment of the coronavirus-associated lung disease however, the risk associated with the therapy also needs to be considered before moving forth with their clinical application. Although theoretically, the therapy does not interfere with the clearance of the virus by the host, the process may still be impaired as the cytokine homeostasis gets disturbed by the administration of these drugs. The addition of anti-viral drugs may be beneficial for the avoidance of interference with the viral clearance if any. The analogs also might have a low or no therapeutic benefit if started late following the infection by which time lung damage has already taken place and decreasing the inflammatory response at this stage cannot reverse the damage already done. The most important reservation to the use of fingolimod in the lung disease following COVID-19 infection is that no human studies have been conducted so far and most of the clinical data available is related to the efficacy of this drug in multiple sclerosis. Moreover, it is unclear whether this drug will produce any off-target effects as their specificity for the target receptors is not fully understood.

CONCLUSION

Fingolimod has a potential therapeutic benefit for the treatment of coronavirus disease as it decreases the inflammatory response following the viral entry via its effect on the sphingosine receptors 1, 3, 4, and 5. It decreases soft tissue injury and brings about better therapeutic outcomes. However further work needs to be done before these drugs can be used therapeutically owing to certain limitations including the lack of target specificity, a decrease in the viral load clearance, and probable off-target effects. If these limitations are dealt with, fingolimod can prove to be an efficacious therapy for corona-associated lung disease.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
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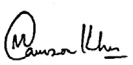
2	Manzoor Khan	Conception and Planning of the research, Active participation in active methodology, Interpretation, analysis and discussion.	
3	Salman Zahir	Conception and Planning of the research, Interpretation, analysis and discussion.	
4	Khansa Khan	Active participation in active methodology, Interpretation, analysis and discussion.	
5	Sarah Saleem	Active participation in active methodology, Interpretation, analysis and discussion.