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CALCINEURIN - A NEW ERA OF IMMUNITY

Oral Pathology

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ABSTRACT

Calcineurin is a calcium/calmodulin dependent serine/threonine protein phosphatase which plays a significant role in regulating cellular responses and is also responsible for organ development. Calcineurin inhibitors (CNIs) such as cyclosporine, tacrolimus, pimecrolimus, and voclosporin, are immunosuppressant drugs primarily used in prevention of organ rejection in transplantation and managing autoimmune disorders. These agents act by inhibiting the transcription of cytokines, thereby disrupting T-cell proliferation and differentiation. In the context of oral health, topical CNIs have emerged as effective treatments for autoimmune conditions like oral lichen planus (OLP), they act as an alternative for patients who don't respond to traditional corticosteroids. Cyclosporine and tacrolimus have demonstrated significant efficacy in managing OLP, with tacrolimus being particularly noted for its effectiveness in recalcitrant cases. While both CNIs and corticosteroids have their respective advantages and disadvantages, CNIs may be preferred for long-term management due to their favorable safety profile and reduced systemic side effects. In addition, further research is necessary to assess the long-term efficacy and safety of CNIs in diverse patient populations, emphasizing the need for ongoing monitoring and individualized treatment strategies.

KEYWORDS

INTRODUCTION:

Calcineurin is a protein phosphatase which plays a prominent role in cellular processes. It is a heterodimeric protein which consists of a catalytic subunit - Calcineurin A and a regulatory subunit (calcium binding subunit) - Calcineurin B. Calcineurin is present in almost all eukaryotes but is absent in higher plants. Calcineurin plays a major role in modulating cellular responses which includes immune response, stress response and organ development.

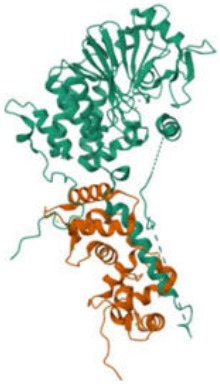

Image 1- Human structure of Calcineurin
(Image from RCSB PDB RCSB.orghttps://doi.org/10.2210/pdb4OR9/pdb)

Calcineurin inhibitors (CNIs) are immunosuppressant drugs used in prevention of organ rejection after transplantation. These agents target the immune system by inhibiting the activation of T-cells. Two prominent CNIs, cyclosporine and tacrolimus, have revolutionized transplantation outcomes, significantly reducing the incidence of graft rejection.Calcineurin inhibitors (CNIs) play a significant role in managing immunologically mediated oral conditions, particularly oral lichen planus (OLP). Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus are an alternative treatment option for patients who do not respond well to traditional corticosteroids.

Calcineurin Inhibitors:

Calcineurin inhibitors (CNIs) are immunosuppressant drugs used to manage autoimmune disorders (e.g., lupus nephritis, idiopathic inflammatory myositis) and in organ transplantation. They bind to cytoplasmic receptors such as cyclophilin, FK-binding proteins (FKBP-12) resulting in inhibition of calcineurin. This intercepts transcription of interleukin-2(IL-2) and other cytokines of T lymphocytes and thus results in inhibition of T cell activation and proliferation. Calcineurin inhibitors primarily affect the T-helper cells, and also along with that it inhibits the T suppressor and cytotoxic cells. Cyclosporine, tacrolimus, pimecrolimus, voclosporin are calcineurin inhibitors.

Cyclosporine is an immunosuppressant drug generally used in treating organ rejection, post transplantation cases and is also used in inflammatory conditions such as Rheumatoid arthritis, Crohn's disease and autoimmune conditions.

Tacrolimus is an immunosuppressive agent used in treating atopic dermatitis (moderate to severe) and also plays an essential role in preventing organ rejection.

Voclosporin is a immunosuppressant that suppresses the immune system thus controlling lupus nephritis (LN), which is a manifestation of autoimmune disease - systemic lupus erythematosus.

Pimecrolimus, a calcineurin inhibitor, is a prescription medication. Available as a topical cream which is used in treating mild-moderate eczema, oral lichen planus, psoriasis etc,. They are usually used in patients who failed to respond to other therapy.

Pharmacokinetics:

Calcineurin inhibitors (CNIs) are immunosuppressants with complex pharmacokinetics. Oral bioavailability can vary significantly; for example, cyclosporine has a bioavailability of 20-50%, while tacrolimus is around 25-30%. The presence of food can affect the absorption of these drugs. Patients are advised to avoid grapefruits as it can cause impact on the drug's metabolism and may cause high blood

levels. Similarly cyclosporine is better absorbed when taken with a high-fat meal.These drugs are distributed in various tissues, including the liver, kidneys, and lymphoid tissues and thus responsible for immunosuppressive effect.The half-life of CNIs varies, tacrolimus has a half-life of about 12 hours, while cyclosporine can range from 8 to 12 hours.CNIs are extensively metabolized in the liver by CYP3A4 and CYP3A5 enzymes. CNIs are primarily excreted in bile and feces; renal excretion of the unchanged drug is minimal. High plasma levels are associated with nephrotoxicity, neurotoxicity, hypertension, and metabolic disturbances. Dosage depends on individual patient characteristics, drug interactions, and genetic factors.

Mechanism Of Action Of Calcineurin Inhibitors:

Calcineurin plays a significant role in dephosphorylation of NFAT (nuclear factor of activated T-cells), a transcription factor which is involved in expression of the cytokines essential for T-cell activation, such as IL-2, IL-4, and CD40L. Calcineurin inhibitors (CNIs) binds with the cytoplasmic receptors called immunophilins - Cyclophilin, FK-binding proteins (FKBP-12) forming a drug- receptor complex that inhibits the phosphatase activity of calcineurin involved in T-cell activation. When calcineurin is inhibited, it prevents transcription of the key cytokine genes(e.g., IL-2, TNF-α) essential for nuclear translocation in T-cell and thus disrupts the activation, proliferation, and differentiation of T-cells (Matsuda & Koyasu, 2000). CNIs primarily affect the T-helper cells but also play a role in inhibiting T suppressor and cytotoxic cells. Additionally, CNIs have protective effects on podocytes, improving their viability and reducing migratory activity.

Image 2 - Mechanism of action of Calcineurin inhibitors

Role of CNIs In Oral Health:

Studies have shown that topical CNIs like Cyclosporine, tacrolimus are effective in treating OLP, providing similar efficacy to topical corticosteroids (TCS). It also has certain disadvantages, generally well-tolerated. Tacrolimus, in particular, has been highlighted as a first-line treatment for recalcitrant cases of OLP (Sotoodian et al., 2015). In some cases, CNIs may be used in conjunction with other treatments to enhance efficacy and manage symptoms more effectively.

Cyclosporine:

Cyclosporine is an potent immunosuppressive agent approved by FDA for various medical applications, primarily in the context of organ transplantation and autoimmune diseases. Cyclosporine is used in managing severe refractory cases of oral lichen planus when conventional therapies fail. It helps reduce the immune-mediated inflammatory response responsible for the symptoms. Cyclosporine is available as a mouthwash or gel, which is applied 3-4 times daily. The most frequent side effects involve local irritation or burning sensation when used topically, systematic side effects include nephrotoxicity, gastrointestinal disturbance, hypertension and gingival hyperplasia. When used topically there is a limited absorption into the bloodstream and thus minimizing the risk of systemic side effects. This is also used in managing graft-versus-host disease (GVHD). It is commonly used with agents like methotrexate to reduce the incidence of GVHD and to improve patient outcomes. This also helps in management of mild to moderate conditions of GVHD often with corticosteroids, and is also utilized in chronic GVHD cases requiring long-term immunosuppression.

Tacrolimus:

Tacrolimus is also an FDA approved immunosuppressive medication primarily used to prevent organ transplant rejection. It is derived from the bacterium Streptomyces tsukubaensis. Tacrolimus plays a significant role in oral health by treating conditions like oral lichen planus (OLP) and managing oral lesions associated with graft-versus-host disease (GVHD).Topical tacrolimus (0.1%) has been used as a second-line treatment for OLP. Studies indicate that approximately 80% of patients experience significant improvement in symptoms and lesions after 8 weeks of treatment also histopathological evaluations show moderate to strong regression of OLP. Side effects include tremors, headache, diarrhea, nausea, increased thirst, tingling sensation,itching, kidney issues, and may increase the risk of infection.

Limitations:

The most common side effects of using cyclosporine and tacrolimus are almost similar. There will be an acute elevation of creatinine levels in plasma levels leading to nephrotoxicity which can further lead to chronic kidney disease, due to renal dysfunction and sodium retention that may lead to high blood pressure. They also cause hepatotoxicity, glucose intolerance, other metabolic disturbances and chances of getting infected is high due to the suppression of the immune system. These systemic side effects can be widely controlled by using topically since there is reduced systemic absorption thus avoiding most of the abovementioned side effects.

CONCLUSION:

Calcineurin inhibitors act as a therapeutic agent for managing oral health conditions, particularly those with an immunological basis like oral lichen planus. Their ability to modulate the immune response while minimizing systemic side effects makes them an good alternative option for patients requiring long-term management of chronic oral conditions. Further research is necessary for establishment of their long-term efficacy and safety profiles in diverse patient populations.Both corticosteroid and CNIs have their advantages and disadvantages.CNIs may be preferred for long-term management due to their favorable safety profile, while corticosteroids remain effective for immediate relief of inflammation.Ongoing monitoring and patient-specific considerations are essential for calcineurin inhibitors.

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