CALCINEURIN INHIBITORS

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Introduction

Calcineurin Inhibitors (CINs) are immunosuppressants, that, alongside corticosteroids, are the standard for transplant maintenance. As a group the CINs decrease cell-mediated immune response by suppressing Interleukin 2 (IL2) production through their inhibition of calcineurin. [1,2]

CINs may be useful in patients with COVID-19 by their activity as immunomodulators, in the treatment of hyperinflammation/cytokine storm, as well as the potential for viral suppression.

a. CYCLOSPORINE

Introduction

Cyclosporine-A (CsA) is a fungus derived molecule discovered in 1970 and is used in high as well as low doses.[1]

High dose CsA is widely used to prevent primary rejection in solid organ transplantation. It is also indicated for preventive or curative treatment of graft-vs.-host disease (GVHD) and treatment of inflammatory disorders such as psoriasis, atopic dermatitis, nephrotic syndromes, or rheumatoid arthritis. Low dose CsA has been used for immunomodulation, graft vs. host disease (GVHD) and cancer therapy.[1]

Mechanism of Action

In high doses CsA binds with cyclophilins, forming a drug-receptor complex which competitively binds to calcineurin decreasing the transcription of Interleukin 2 (IL2) and several immunologically important factors including IL-3, IL-4, tumor necrosis factor alpha (TNF-α) and interferon-gamma (IFN-γ). In low doses a paradoxical immunomodulation occurs, increased auto-immunity and anti-cancer immunity.[1]

In vitro studies show the potential to inhibit viral growth and replication of SARS-CoV1 and MERS-CoV in low non-cytotoxic doses. [3]

Cyclosporine has been used to treat cytokine storm related syndromes in JRA, hematologic disorders and SLE.[4,5,6,7]

Clinical Studies

A case study of a renal transplant patient on Cyclosporine who survived COVID-19 adds to the possibility of its use as therapy, although no conclusions can be derived from a single case. [8] There are a few articles have proposed that CINs may have a role in the treatment of COVID-19[1,9] As of September 20, 2020, there are 4 studies, in the recruiting stage, that propose to use Cyclosporine as intervention for COVID-19. (Appendix 8)

Recommended Dose

Still to be established but a low, non-cytotoxic dose: ≤ 3 mg/kg, may be preferred to high Dose: ≥ 4-5mg/kg/dose[1]

Adverse Effects

The principal adverse reactions to cyclosporine therapy are nephrotoxicity and hypertension. Tremors, hirsutism, hyperlipidemia, and gum hyperplasia also are frequently encountered. Hypertension occurs in about 50% of renal transplant and almost all cardiac transplant patients. Hyperuricemia may lead to worsening of gout, increased P-glycoprotein activity, and hypercholesterolemia. [2]

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b. TACROLIMUS

Introduction

Tacrolimus (FK506) is an immunosuppressive drug discovered in 1984, chemically known as a macrolide. Its main use is in the prevention of primary rejection in solid organ transplant. It inhibits T-lymphocyte signal transduction in a similar mechanism as Cyclosporin.[1,2]

Mechanism of Action

Tacrolimus binds to the immunophilin FKBP-12 (FK506 binding protein) creating a complex that inhibits T-lymphocyte signal transduction and IL-2 transcription. Inhibition of other cells also occur and there is evidence for its use in immunomodulation in cytokine storm syndromes. Authors draw a parallel between the excessive pro-inflammatory cytokine release in conditions like hemophagocytic lymphohistiocytosis (HLH)[3] and Macrophage Activation Syndrome (MAS)[4] with COVID-19 and propose the possible use of Tacrolimus in the later.

In vitro studies shows that Tacrolimus inhibits viral growth and replication for coronavirus.[5,6]

Clinical Studies

In a case report of COVID-19 in 7 kidney transplant patients, the authors draw no conclusion on the immunomodulatory effect of Tacrolimus maintenance on outcomes.[7] Another case report on COVID-19 in 3 long term liver transplant patients (one on Tacrolimus) can draw no conclusion.[8] However, both authors voice out the need for evidence Tacrolimus' effect on cytokine storm and inflammation vs. possible immunosuppression and transplant rejection.

A "Clinical Trial to Evaluate Methylprednisolone Pulses and Tacrolimus in Patients With COVID-19 Lung Injury" started in April 1, 2020. Still in its recruiting stage, it is a randomized parallel study using Tacrolimus at doses necessary to obtain blood levels of 8-10 ng/ml alongside 3 days of Methylprednisolone pulses. (Appendix 8)

Recommended dose

Dose for COVID-19 therapy is still to be determined but the ongoing study suggests the dose necessary to obtain trough blood levels of 8-10 ng/ml. (Appendix 8)

Adverse Effects

Commonly seen adverse effects include the following: nephrotoxicity, neurotoxicity (e.g., tremors, headache, motor disturbances, seizures), GI

complaints, hypertension, hyperkalemia, hyperglycemia, and diabetes. As with other immunosuppressive agents, there is an increased risk of secondary tumors and opportunistic infections.[2]

Conclusion

While there is a potential for use, there is limited evidence to evaluate the efficacy and safety of the Calcineurin Inhibitors (Cyclosporine and Tacrolimus) in patients with COVID-19.[9]

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