MYCOPHENOLATE MOFETIL

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Introduction

Mycophenolate mofetil (MMF) is derived from mycophenolic acid (MPA), an antineoplastic antibiotic isolated from different species of *Penicillium* fungi.[1] It is used mainly for its immunosuppressive properties in solid organ transplant patients to prevent or treat allograft rejection.[2] Other indications for its use are autoimmune disorders (e.g. lupus nephritis, myositis syndromes, or Crohn's disease), small or large vessel vasculitides, or various skin conditions.[3]

In-vitro studies have shown antiviral activity of MPA against both Middle East respiratory syndrome coronavirus (MERS-CoV)[4,5,6] and SARS-CoV-2.[7] Clinical studies to support these findings, however, are lacking.

Mechanism of Action

Mycophenolic acid (MPA), the active component of MMF, acts as an immunosuppresant by targeting cell-mediated and humoral immune responses. Aside from preventing human B and T lymphocyte proliferation by inhibiting conversion of inosine monophosphate to guanosine monophosphate,[8] it has also been found to affect lymphocyte function through various mechanisms. In vitro studies have shown MPA downregulating cell adhesion molecules of T lymphocytes, inhibiting T cell proliferation in response to mitogens, and inhibiting expression of interferon gamma in murine T cells.[8,9,10] Similarly, MPA blocked human plasma cell differentiation, and antibody production by human B lymphocytes.[11]

In addition to its immunomodulating properties, antiviral activity has been demonstrated by MPA against MERS-CoV.[4,6] A proposed mechanism for this is the inhibition of an enzyme found in coronaviruses. Papain-like protease (PI^{pro}) is an enzyme necessary for viral maturation and survival against the host's interferon reponse. MPA has been found to inhibit MERS-CoV PI^{pro} activity. However, the same study demonstrated that MPA had no effect on SARS-CoV PI^{pro}.[6] An in vitro study years later on SARS-CoV-2 showed that MPA did not prevent viral growth by the cytopathic effect method. SARS-CoV-2 replication, however, was inhibited 100-fold at low effective concetrations.[7]

Clinical Studies

No human studies have been done to determine whether MPA's immunomodulatory or antiviral properties have an effect on SARS-CoV-2 or COVID-19.

A related study done was a retrospective cohort of 51 patients with MERS-CoV infection. Survival was associated with treatment with mycophenolate mofetil.[12] Important to note, however, that mycophenolate mofetil was given to

less severely ill patients, and was given in combination with interferon beta, another immunomodulator, in 7 out of 8 patients.

Adverse Effects

Mycophenolate mofetil is associated with nausea, diarrhea, abdominal pain, anemia, headache, hypertension, leukopenia, thrombocytopenia, or a predisposition to developing infections.[2] It is also less commonly associated with hepatotoxicity, which is in most cases mild and self-limited.[2,13]

Conclusion

While a few in vitro studies may have demonstrated the antiviral activity of MMF against MERS-CoV and SARS-CoV-2, there is insufficient clinical evidence to determine its efficacy and safety against COVID-19. More high quality researches are needed to establish the role of MMF in treating COVID-19.

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