Evaluation of the Role of Itraconazole and Posaconazole in Viral Infection as Immunomodulatory Drugs

The widespread therapeutic use of azole-based pharmaceutical drugs has given rise to multiple interests, and their research and development has become a very fast creation of a successful spotlight of infinite space.[1,2] Itraconazole (ITZ) and posaconazole (POS) belong to triazole that have a broad-spectrum antifungal agent. They commonly used to prevent and treat several fungal infections that cause superfiial, subcutaneous, and systemic infections.[3] These drugs have few side effects compared with other drugs.[4-6]

Since antifungal drugs are commonly used in patients who are to some extent immunocompromised, it is important to assess the potential effects of these therapies on the immune system.[7-9] It has been proposed that the efficacy of some antifungal agents may be related to their capacity to induce cytokine production. This also confirmed that some antifungal drugs increase chemokine levels in the supernatants of human mononuclear cell cultures such as CCL3 and CCL4.[10]

From invasive fungal infection that treated with POS are chromoblastomycosis, mucormycosis, candidiasis, fusariosis, mycetoma, cryptococcosis, aspergillosis, and coccidioidomycosis. Furthermore, ITZ drug has a broad range activity on fungal infections in humans, with rare resistance compared with other antibiotics.[11-15] Besides the antifungal role of POS and ITZ, they have antiviral efficacy against some viruses by different mechanisms of actions.[16]

As shown by both *in vitro* and *in vivo* studies, some drugs, especially antibiotics, have direct modulating effects on the immune system, in addition to their antimicrobial acts such as certain antifungal on the activities of animal and human macrophages, monocytes, and neutrophils.[17]

It is also found that ITZ can exert a marked immunomodulatory effect at a serum level of 1 μg/mL (therapeutically achievable concentration), followed by a slight pulmonary immunosuppressive tendency in healthy male BALB/c mice, which suggests an alternative, but unexplored, mechanism of ITZ-mediated immunomodulation.[18]

This lipophilic antifungal drug of POS is absorbed within human cell membranes, including neutrophils and other leukocytes.[19] It concentrates inside dHL-60 cells to high levels.[20] After touch, these cells are capable of transferring POS to *Aspergillus fumigatus* hyphae and exhibit well antifungal activity to *A. fumigatus in vitro*.

In an invasive pulmonary aspergillosis neutropenic mouse model, treatment with POS-charged dHL-60 cells resulted in decreased pulmonary fungal burden and even removal of some mice infections. These findings indicate that neutrophils could be an effective mechanism for POS delivery.[21]

A combination of antiviral drugs also has a role in the inhibition of replication of certain viruses such as dengue virus, flvivirus, and Zika virus by reducing the viral single strand RNA replication.[22]

Regarding enteroviruses (which are nonenveloped icosahedral RNA viruses), ITZ identified as an effective inhibitor of EV71 replication in the low micromolar range and also inhibited other enteroviruses including coxsackievirus B3, coxsackievirus A16, enterovirus 68, and poliovirus 1. The mechanism of action by targeting a step involved in RNA replication or polyprotein processing. ITZ and POS may target a specific site(s) in the viral genome.[23]

There are different concentrations of POS found in the plasma. The intracellular absorption of the azoles tends to be passive and dependents on the composition of the extracellular media. Therefore, the intracellular and, consequently, the extracellular concentrations would automatically adjust upon reaching multiple body compartments with distinct extracellular media compositions. The intracellular concentration of POS in mononuclear peripheral blood cells and polymorphonuclear neutrophils has been shown to have greatly increased compared to the plasma concentration.[24] High intracellular POS loading may assist the competent phagocytes in their pathogen killing tasks.[25] ITZ and POS may be promised antiviral therapy to treat some viral infections including those that have no antiviral drugs yet.[26-28]

In conclusion, from previous studies, ITZ and POS could be an effective drug against many RNA viral infections in multiple mechanisms, including inhibitions of NAADP-stimulated lysosomal calcium release, NPC1 protein function, increase cholesterol level, acidic PH, and stimulating interferon. Because viral infections are common in the world, which is difficult to control, especially RNA viruses with constantly changing, so some studies have conducted a series of experiments on some of the treatments available for reuse to treatment or prevention of viruses.

As it is known, in viral infection immune system plays a crucial role in viral elimination and body defending, so using an antibiotic that has the ability to enhance immune response, activate innate immunity, and stimulate pro-inflammatory responses such as ITZ and POS may be very important to protect from viral invasion. It has strong immunomodulatory characteristics by triggering pro-inflammatory responses; this effect has been associated with protective effects. ITZ and

POS act during infection not only on the pathogen but also on the host. This issue is of particular interest because patients affected by viral infections may be immunocompromised.

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Conflicts of interest

There are no conflicts of interest.

Falah Hasan Obayes Al-Khikani

Department of Microbiology, Al-Shomali General Hospital, Babil, Iraq

Address for correspondence: Dr. Falah Hasan Obayes Al-Khikani, Department of Microbiology, Al-Shomali General Hospital, Babil, Iraq.
E-mail: falahgh38@gmail.com

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