Immunological Prospects of Tamoxifen as Modern Antiviral Therapy

Sir,

Tamoxifen (TAM) is a nonsteroidal SERM of the triphenylethylene family and was structurally derived from diethylstilbestrol-like estrogens and anti-estrogens.[1] It was primarily discovered in 1962, by the scientist in chemistry, Dora Richardson.[2] Besides the effectiveness of TAM on malignant cells as breast cancer, it has other effects on numerous microbes including parasite and fungi. Recently, some studies focused on the potential antimicrobial action of TAM against some enveloped and nonenveloped viruses such as Ebola virus[3] and human immunodeficiency virus (HIV).[4] Furthermore, a recent study suggested using TAM to treat COVID-19 viral infection due to its unique properties as well as its immunomodulatory effect on immune responses by different mechanisms that may help the body to fight viral diseases.[5] Also, other drugs such as AmB[6] and ITZ.[7] have immunomodulatory effect suggested as antiviral drugs.

Viruses are considered the most numerous type of biological entity, and are found in almost every ecosystem on the earth.[8] There are difficult to treat viral infections, and some viruses have no specific therapy such as COVID 19.[9-11] Nearly 5000 species of viruses have been identified in detail, of the millions of virus types in the world.[8]

TAM, an anti-estrogen that competes for the estrogen receptor, modulates natural killer (NK) cell activity *in vivo*. It has been demonstrated that TAM can enhance murine NK activity *in vivo* and can enhance human NK activity *in vitro*.[12] Another study demonstrated that cytotoxic T lymphocyte-mediated, NK cell-mediated, and lymphokine-activated killer cell-mediated target cell lyses were amplified by TAM.[13] Most common drugs have adverse effect.[14-18] Also, some side effects associated with TAM.

NK cells are a type of innate immune cell, which responds immediately to new pathogens. It is the host's first line of defense against tumors and viral infection. NK cells kill cancerous or virally infected cells by recognizing certain molecules. In human lungs, NK cells are located in the parenchyma and are not detected outside the parenchyma, accounting for about 10%–20% of the lymphocytes.[19]

Numerous studies have described the effects of female sex hormones (steroid hormones estrogen) on NK cell activity. It is well established that sustained estrogen (β-estradiol) treatment of mice leads to a reduction in *in vivo* NK cell activity.[20] However, as TAM does not reduce estrogen levels in postmenopausal patients,[21] the enhancement of NK by TAM could not be ascribed to the reduction in serum estrogens.

A variety of DNA and RNA viruses have been shown to stimulate prostaglandin E2 (PGE2) production through cyclooxygenase (COX)-2 expression,[22] resulting in negative feedback in the regulation of macrophages and NK cells through inhibitory effects on interleukin-12 (IL-12) production and the expression of IL-12 receptors,[23] inhibiting interferon (IFN)-γ.[24] In NK cells, PGE2 functions by suppressing the responsiveness of IL-12 and IL-15, which suppresses the cytolytic effects of NK cells.[25] PGE2 abrogates the NK cell "helper" function by inhibiting the ability of NK cells to produce IFN-γ. Indeed, this documented ability of TAM to reduce PGE production may be the mechanism that resulted in the positive modulation of NK activity in both the *in vivo* and *in vitro* settings.[26]

Furthermore, PGE2 can play a role in viral infection directly by increasing the production and release of virions and stimulating viral gene expression. Because TAM decreased the PGE2 production,[27] targeted PGE2 may reduce viral replication and enhance antiviral immunity [Figure 1].

The activity of TAM toward herpes simplex virus type 1 (HSV-1) has been evaluated by one study which revealed that pretreatment or treatment with TAM and 5-nitro-2-(3-phenylpropylamino) benzoic acid at various time points during HSV-1 infection, suppressed viral RNA synthesis as well as expression of protein and virus production. A chloride channel inhibitory activity of TAM is thought to block HSV 1 fusion preventing viral binding, penetration, and nuclear translocation.[28]

Further studies have shown that TAM and other SERMs (raloxifene (RLX), the CLMs stereoisomers enclomiphene and zuclomiphene are also active against Ebola Virus, emerging treatment options for Ebola Virus Disease different strategies have been followed to target the virus and blocking viral entry.[29]

The *in vitro* antiviral activity of TAM on the replication of HIV, hepatitis C virus , and HSV-1 had been evaluated. The effect of TAM on viral infection caused by vesicular stomatitis virus is by suppression viral RNA replication.[30]

One study which reviewed different therapeutic groups such as ER antagonists, kinase signaling inhibitors, protein-processing inhibitors, inhibitors of lipid or sterol metabolism and inhibitors of DNA synthesis or pair, and neurotransmitter inhibitors, suggested that TAM citrate and toremifene citrate *in vitro* have antiviral effects on MERS-CoV at 10.11 μM and 12.91 μM, respectively, and 92.88 μM and 11.96 μM on SARS-CoV, respectively.[31] Some drugs have potential immunomodulatory properties that may enhance antiviral effects.[32-35]

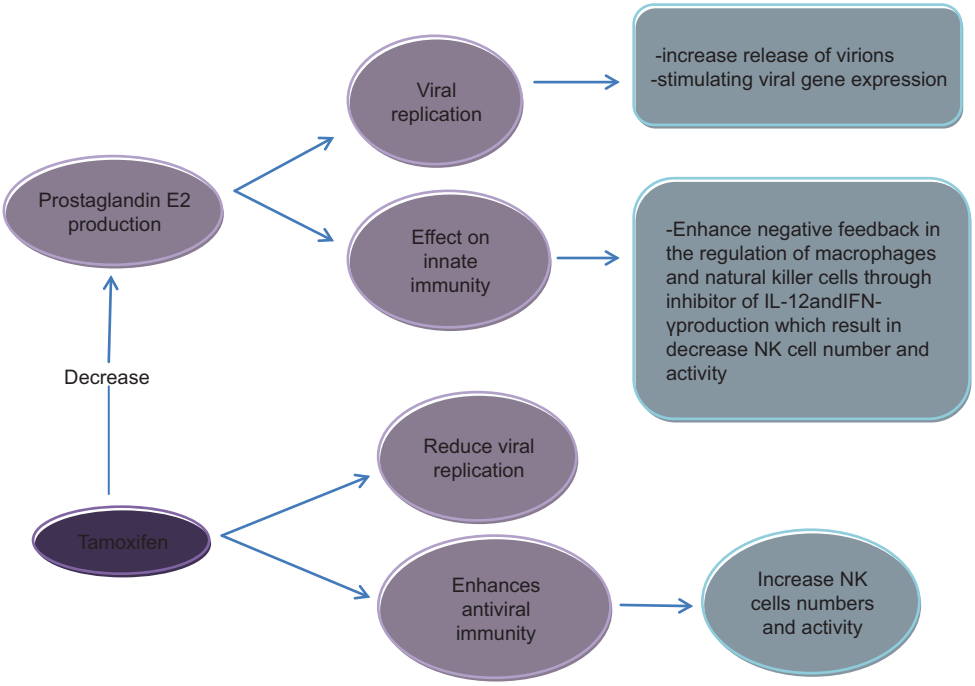

Figure 1: The effect of tamoxifen on immune response

In conclusion, TAM can be used as antiviral therapy against some viral infections due to its ability to positive modulation of NK cells activity in both the in vivo and in vitro settings, reducing viral replication by decreasing PGE2 production as well as the unique properties of TAM to treat a viral infection.

As known, in viral infection immune system plays a crucial role in viral elimination, so using an antibiotic that has the ability to enhance immune response, activating innate immunity, and stimulate pro inflmmatory responses; like TAM may be very important to protect from some viral invasion. This effect has been associated with protective effects. TAM acts 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. Consequently, TAM can be used as a potential antiviral drug particularly in immunocompromised patients by acting as an antiviral drug and enhancing immune responses by activating the positive immune modulation.

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Conflicts of interest
There are no conflicts of interest.

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