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REGULAR ARTICLE

Combination of IMOD™ and Arbidol to increase their immunomodulatory effects as a novel medicine to prevent and cure influenza and some other infectious diseases



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Abstract Viral diseases such as influenza, which are easily transferable from person to person or even country to country, pose one of the biggest threats to health today. Viruses such as avian influenza viruses (N1H5 and H9N1) have been reported to spread in the present decade and, very recently, the novel coronavirus that has caused many life-threatening illnesses and deaths all around the world has received much attention.

To prevent these highly contagious viral infections, we have proposed the combination of IMOD™ and Arbidol to increase their immunomodulatory effects as a novel medicine to prevent and cure influenza and some other infectious diseases such as hepatitis B and C. On the one hand, IMOD™ within the last few years has been proven to safely and effectively increase the life expectancy for human immunodeficiency virus (HIV)-infected individuals by increasing CD4 lymphocytes. On the other hand, Arbidol, an antiviral agent has been used safely and effectively in the past two decades to prevent and cure all types of influenza and flu. Therefore, the combination of both in a single dosage to further increase CD4 lymphocytes and interferon gamma (IFN-γ) could be a better choice for treatment of viral infections. This proposal tries to provide enough support and background for approval of a randomized clinical trial by a relevant team of investigators.

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Introduction

IMOD™ (Immuno-Modulator Drug), which is a patented herbal drug that improves the immune system, is formulated from three herbal extracts of *Tanacetum vulgare*, *Urtica dioica*, and *Rosa canina*, which is then enriched with selenium [1]. This drug is used for the treatment of human immunodeficiency virus (HIV) infection by increasing CD4 lymphocytes [2]. These cells are measured in the blood as CD4 and CD8 counts [3]. The CD4 count is a reflection of immune system efficiency: the lower the CD4 count, the weaker the immune system will be. If the CD4 count is <200 in a microliter of blood, the person is considered to be infected and is involved with AIDS [4]. In fact, patients with a CD4 count of <400 showed a significant increase in their CD4 counts following treatment with IMOD™ for 3 months in comparison to those in a control group who were not treated with IMOD™ [5]. Therefore, this viral infection disease can be treated with an increasing number of CD4 lymphocytes in the blood [6]. In addition, the presence of selenium as an immune booster and the presence of flavonoids such as chlorogenic acid, caffeic acid, kaempferol, esculetin, apigenin, luteolin, rutin, ferulic acid, etc., which have antioxidant effects, help to remove free radicals and improve the immune system as well.

On the other hand, Arbidol, which is a synthetic broad-spectrum antiviral agent [7], has immunomodulating effects and is an interferon-inducing agent. Therefore, the agent can improve CD4 counts [8] as well. Arbidol inhibits the fusion of influenza A and B (N1H1, N2H2, N2H3, and avian influenza viruses of N1H5 and H9N1) and has the same effect on severe acute respiratory syndrome (SARS) viruses that interact with cell membranes. Additionally, the agent inhibits acute and chronic hepatitis C virus infection [8,9]. Furthermore, Arbidol has antioxidant properties and is in the category of the least toxic drugs (LD50 > 4 g/kg) which does not have adverse effects on the human body when taken orally at the recommended dosages [9].

The hypothesis

We propose that the combination of effects from both natural and synthetic medicines as described above in a single oral capsule could result in a stronger medicine. In addition, it was shown in different studies that IMOD™ can increase interferon release from host cells significantly [2]. One such interferon is interferon gamma (IFN- γ) which is crucial for innate and adaptive immunity. This is also the case with Arbidol, which shows interferonogenic activity as well [8]. Therefore, this provides strong evidence to indicate that IMOD™ can increase the efficacy of Arbidol further in the treatment of patients. Consequently, this new idea will produce a novel medicine that increases CD4 cell numbers, boosts the immune system further, and thus will be a better choice to prevent and cure viral infectious diseases.

Evaluation of hypothesis

The hypothesis will be tested as follows:

1. Initial animal toxicity tests have shown that the drug is practically nontoxic (unpublished data). Thus, a human clinical trial will be carried out in randomized

large gathering groups. Such a clinical test could be carried out on individuals who will be participating in the *Hajj* pilgrimage to Mecca, where millions of people could be infected and carry a broad range of different viruses, should the authorities' permission become available to the research team of investigators.

2. A battery of genotoxicity and pharmacokinetic studies including drug interaction tests for such a novel medicine will be explored deeply.
3. If the above results are satisfactory, then mass production will be organized.

Discussion

After a clinical study for Arbidol in a sample of 50 patients, it was concluded that all five doses of 50, 100, 200, 500, and 1000 mg were well tolerated [10]. The same result was achieved in another similar clinical trial on 66 patients [11]. Therefore, Arbidol is effective and safe for patients with the above-cited influenza types including acute viral upper respiratory infection (URI). The properties of IMOD™, concerning its safety and efficacy, have been the subject of several studies [2,3] and review articles [12,13] in animals and humans. In addition, it is a bonus to indicate the positive function of IMOD™ through its antioxidant activity in aged mice [14]. In this study, it was concluded that IMOD™ prevents superoxide anion and free radicals through its total antioxidant power. All these aforementioned effects from IMOD™ can be used in the treatment of immunologic disorders. The same results in the safety and efficacy are expected for the novel medicine; however, it is anticipated to have a stronger action.

At present, the mixture of IMOD™ and Arbidol at a laboratory scale has been formulated in a single 500-mg capsule and a pilot scale is in progress. In this formulation, 120 mg of IMOD™, as an active herbal mixed dried extract, and 100 mg of Arbidol raw material were combined with suitable common excipients (15 mg talc, 85 mg starch, and 180 mg lactose). The toxicology studies of this novel medicine was carried out by the investigators in mice and showed practically zero toxicity for doses ranging from 2 to up to 4 g/kg (unpublished data). Based on Arbidol itself, a course of 12 capsules twice a day should be prescribed. Accordingly, the dosage in this study would be two capsules a day, 6 days per week.

Today, with the discovery of new viruses such as the deadly "Middle East respiratory syndrome coronavirus" (MERS-CoV) [15,16] in Saudi Arabia, which could potentially spread all around the world, the importance of such a new hypothesis becomes much more clear.

Conclusion

In this context, we proposed a novel idea to prevent and treat viral infections such as influenza diseases. As discussed above, IMOD™ has been used successfully within the last few years, resulting in increased CD4 lymphocyte counts and consequent improvement of the immune system. Similarly, Arbidol also by itself has proven within the last two decades to be a safe and effective drug for the prevention and treatment of flu and influenza. Therefore, with the advantage of both medicines, a stronger choice to prevent and cure not only flu but also some other

infectious diseases such as acute hepatitis B and C can also be targeted. In a large sample of gatherings such as the *Hajj* pilgrimage where millions of Muslims are in close contact while performing their religious obligations, the viruses can be transferred with ease by sneezing and coughing. Testing the idea in several groups of attendees could prove the safety and the efficacy of the above combination in a clinical trial. Such results will be published and the whole society can benefit, especially during the flu seasons of the year. This strategy will also help to stop the spreading of such viruses to other countries. Moreover, the mass production of such a beneficial medicine in different forms such as capsules, tablets, and probably ampoules are proposed if biological tests prove promising.

Overview box

First question: What do we already know about the subject?

1. IMOD™ safely and effectively increases the life expectancy for the human immunodeficiency virus (HIV)-infected individuals by increasing the CD4 lymphocytes.
2. Arbidol, as an antiviral agent, prevents and cures all types of influenza and flu, and has been used safely and effectively in the past two decades.

Second question: What does your proposed theory add to the current knowledge available, and what benefit does it have?

This hypothesis examines the combination of IMOD™ and Arbidol to increase their immunomodulatory effects as a novel medicine to prevent and cure influenza and some other infectious diseases in vitro, in animal preclinical trials, and in human clinical trials. Consequently, in this combination, the weakness of the agents will be improved by advantages of both medicines as discussed. Eventually, CD4 cell numbers will increase further to obtain a better choice to prevent and cure viral infectious diseases. This could be achieved by the addition of interferon-inducing activity, broad-spectrum antiviral efficiency, antioxidant activity, and inhibition of the fusion of influenza viruses interacting with cell membranes. Today, because of severe deadly “Middle East respiratory syndrome coronavirus” (MERS-CoV) that has caused many life-threatening infections in Saudi Arabia and can cause a global epidemic, the importance of this hypothesis becomes much clearer.

The mixture of Arbidol and IMOD™ is formulated in single 500-mg capsules (120 mg of active ingredients of IMOD™ and 100 mg Arbidol) and demonstrated to be practically nontoxic in mice with an LD₅₀ > 4 g/kg.

Third question: Among numerous available studies, what special further study is proposed for testing the idea?

The hypothesis will be tested first in T cells and B cells in vitro, before testing in animals and then humans who will be participating in the *Hajj* pilgrimage to Mecca, where millions of people could be infected and carry a broad range of different viruses, should the authorities' permission become available.

Conflict of interest

There is no conflict of interest.

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