Imiquimod as a potential treatment for COVID-19

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SARS-CoV-2 and COVID-19

Coronaviruses are a large family of viruses that can cause illness ranging from the common cold to more severe diseases, like Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome. The 2019 novel coronavirus, called 'SARS-CoV-2' is a new strain that causes Corona Virus Disease 2019 (COVID-19), for which no effective treatment has been found until now. The outbreak of SARS-CoV-2, that first emerged in Wuhan in December 2019, has rapidly spread throughout the world (1, 2). Considering the ongoing outbreak in China and fast worldwide spread of COVID-19, infected by SARS-CoV-2, it has led to the declaration of Public Health Emergency of International Concern by the World Health Organization (WHO) on 30 January 2020 (3). As of Mar 25, 2020, a total of 440000 laboratory-confirmed cases, has been identified in the world.

IMMUNOLOGICAL DATA

According to numerous publications the patients tended to have lymphopenia, higher infection-related biomarkers and several elevated inflammatory cytokines (i.e. tumor necrosis factor (TNF)-α, interleukin IL-2R and IL-6). The total number of B cells, T cells and NK cells significantly decreased in patients with COVID-19 and more evident in the severe cases, compared to the non-severe group. T cells were shown to be more affected by SARS-CoV-2 as T cell count was nearly half the lower reference limit. The function of CD4+, CD8+ T cells, and NK cells was within normal range and no significant difference was found between severe cases and non-severe ones (4). Higher serum levels of pro-inflammatory cytokines (TNF-α, IL-1 and IL-6) and chemokines (IL-8) were found in patients with severe COVID-19 compared to individuals with mild disease (4).

A rapid and well-coordinated innate immune response is the first line of defense against viral infections, however, when immune response is dysregulated, it will result in an excessive inflammation, even cause death (5). Qin et al demonstrated pronounced lymphopenia and low counts of CD3+ and CD4+ cells in COVID-19 cases (4).

It is well known that the innate immune system is important in early life, when the adaptive functions are underdeveloped. The innate immune response signalling cascade starts with the recognition of pathogen-associated molecular patterns by pattern recognition receptors (PRRs) (6). For RNA viruses in the lungs, the Toll-like receptors (TLRs) 3, 7 and 8, are important PRRs (7). The innate immune system senses foreign material that is possibly pathogenic, and

this triggers downstream signalling to ultimately induce transcription factors in the nucleus which in turn stimulate expression of types I and III IFNs and other proinflammatory cytokines.

A second round of autocrine and paracrine signalling subsequently ensures that infected, and the surrounding uninfected cells, express a myriad of interferon stimulated genes that establish a so-called antiviral state (8). The strict distinction between innate and adaptive responses is probably not accurate. In the respiratory tract, several cell types and mechanisms that integrate aspects from both branches of human immunity are thought to be very important for the defence against respiratory infections. NKs, T cells, mucosal-associated invariant T cells, and neutrophils, form a bridge between the innate and adaptive machineries and play very important roles during the clearance of respiratory viruses (8).

IMIQUIMOD AS AN IMMUNOSTIMULATOR

Imiquimod is a synthetic molecule which enhances both the innate and acquired immune response, in particular the cell-mediated pathways (9). It has shown antiviral and antitumor properties in animal models. Imiquimod acts as a potent immune response modifier through its ability to induce the production of cytokines, which in turn stimulate T cells, thereby enhancing innate and acquired cellular immunity (10).

Imiquimod effects on the innate immune response, in particular its ability to induce IFNa and other cytokines, are largely responsible for its acute antiviral and antitumor effects. Induction of the cytokines IFNa, IL-6 and IL-12 and TNFa by Imiquimod has been observed in many studies. Imiquimod also stimulates other aspects of the innate response in animal models: NK cell activity is stimulated, macrophages are activated to secrete both cytokines and nitric oxide, and B lymphocytes are induced to proliferate and differentiate (11). The action of Imiquimod to stimulate innate immunity indicates its potential to treat viral infections. The cellular arm of the two pathways in the acquired immune response is induced by Imiquimod, although this is not a direct effect.

Imiquimod indirectly stimulates the production of the T-helper type 1 (Th1) cytokine IFNc. Imiquimod also acts to suppress the humoral arm of acquired immunity by inhibiting the production of the Th2 cytokines, IL4 and IL5. IFNa is believed to play a major role in this inhibition by Imiquimod (11). An additional effect of Imiquimod on the immune response is the activation of Langerhans' cells (10). Imiquimod enhances the migration of these cells to the regional lymph node potentially enhancing antigen presentation to T cells. In animal models, it has been shown that Imiquimod acts through TLR7 and stimulates rapid synthesis and release of cytokines from monocyte, macrophage and dendritic cells. Imiquimod is the first small molecule disclosed to act through TLR activation, especially TLR7 (9).

Topical imiquimod as a 5% cream (Aldara) is approved for the treatment of genital/perianal warts. Imiquimod is listed as a Category C drug, as for safety. When applied topically the half-life is approximately 30 hours. Imiquimod is well accepted (when applied locally), safe and with limited adverse effects (12). We have clear evidence that Imiquimod is able to offer satisfactory stimulation of innate and acquired immunity, helping the elimination of SARS-CoV-2, at least during the early phases of infection.

We propose the trial of Imiquimod as a potential anti-SARS-CoV-2 drug, by compounding Aldara creams to suppositories (see Appendix).

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APPENDIX

A suppository is a solid molded medication that is inserted rectally or vaginally. The medication is delivered once the suppository dissolves inside the body. It will then be absorbed locally and systemically. Types of suppositories include: Rectal Suppositories, Vaginal Suppositories, Rectal Enemas and Vaginal Creams. By using a suppository, we are able:

- To bypass liver metabolism (first-pass metabolism).
- To ease delivery for those who have trouble swallowing pills.
- To bypass gastrointestinal degradation from stomach acid.
- To bypass gastrointestinal sensitivity.
- To bypass oral ingestion for those with vomiting tendency.