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Alternative management of Covid-19 infection

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Abstract

Cytokine storm is a life-threatening complication of Covid-19 infection. Excessive cytokines are the products of hyperactive immune inflammatory response mounted by the host against the virus. There is no agreed treatment for cytokine storm. Three therapeutic agents with proven immune-modulatory properties in regular use in a wide range of inflammatory disorders (high dose intravenous immunoglobulin, Rituximab and thalidomide) are proposed for the treatment of cytokine storm. Safety and efficacy of the proposed treatment should be assessed by randomised controlled clinical trials. The use of the proposed treatment is expected to reduce the mortality rate and alter the overall management of the pandemic.

Keywords

Covid-19 infection, cytokine storm, high dose intravenous immunoglobulin, Rituximab, thalidomide

Introduction

The official Covid-19 deaths recorded in the UK is in excess of 38000, in the USA is more than 100000 and in the world is greater than 360000. Excess death rate is widely acknowledged as the most accurate measure of mortality in the current Covid-19 pandemic even more so than the cumulative daily count of Covid-19 deaths. With the UK excess death rate has already exceeded 64000, is it appropriate to persevere with existing management of Covid-19 infection without considering an alternative management?

Treatment of patients with Covid-19 infection is mainly supportive. A proportion of patients also receive investigational treatment of one form or another with varying degrees of success. Specific treatments are generally of two types. Type I treatment is aimed at the virus either directly such as anti-viral Favipiravir, Oseltamivir, Umifenovir, Remdesivir and others or indirectly by other mechanisms such as Chloroquine, Hydroxychloroquine, Azithromycin and others. Type II treatment is aimed at altering the immune status of patients either through conferring passive immunity by plasma rich in Covid-19 antibody from patients who have recovered from Covid-19 infection or by drug-induced immune modulation/regulation. The rationale for using immune modulation is the "cytokine storm"[1,2] detected in patients with severe Covid-19 infection. It is believed that excessive cytokines are the products of hyperactive immune inflammatory response mounted by the host against the virus. Such dysregulated immune reaction akin to autoimmunity is thought to lead to the observed lung injury and correlated with grim clinical outcome.

In order to counteract the "cytokine storm", specific (targeted) and nonspecific immune regulatory therapies have been tried or at least suggested as follows:

Specific immune regulatory investigational therapies include interlukin-1 inhibitor (Anakinra), interlukin-6 inhibitors (Sarilumab, Siltuximab and Tocilizumab), Janus Kinase Inhibitor (Baricitinib) and AXL kinase inhibitor (Bemcentinib).

Nonspecific immune regulatory investigational therapies include Corticosteroids (including Methylprednisolone), Colchicine and Interferon Alpha and Beta.

A host of miscellaneous drugs have also been tried or suggested including: Bevacizumab, EIDD-2801,

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Fingolimod, Ivermectin, Leronlimab, Lopinavir/Ritonavir and Tocilizumab.

The multiplicity of therapeutic agents considered as possible investigational treatment highlights the fact that none so far proved to be optimally safe and effective. This may be due to our limited understanding at present of the mechanism(s) of development of the "cytokine storm" in terms of steps involved and sequence of events so that what is observed and presumed to be a cause and effect may indeed be epiphenomena rather than causally-related. This can explain the apparent failure of even the most specific and directed form of therapies mentioned earlier.

Proposal

The purpose of this contribution is to draw attention to the potential of certain therapeutic agents for treatment of the severe inflammatory complications of Covid-19 infection which are believed to be the cause of respiratory failure and death of a significant number of patients rather than the viral infection per se. These agents are widely used in Haematology as well as in other specialities. However, it would appear they have been overlooked in the treatment of Covid-19 complications.

High dose intravenous immunoglobulin (HD IV Ig)

HD IV Ig is an established form of treatment for Immune Thrombocytopenic Purpura (ITP). The mechanism of action is believed to be down regulation of the immune response.[3] After the impressive success of this therapy as a definitive treatment of ITP but mainly for the control of this condition to bring about a rapid increase in the platelet count whenever needed, it was tried in other autoimmune conditions and proved to be highly effective and well-tolerated. At present HD IV Ig is used for the treatment of Kawasaki disease, Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy and in a number of autoimmune dermatological conditions. Since the severity of Covid-19 infection is correlated with the development of severe immune (autoimmune) inflammatory reaction, the "cytokine storm", it is logical to expect HD IV Ig also to be useful in this situation thanks to its immunomodulatory properties. Indeed, there has been a published report from China of beneficial effect of HD IV Ig in three patients with Covid-19 infection.[4] The emergence of Kawasaki like syndrome in association with Covid-19 infection in children responsive to HD IV Ig lends further support to treating "cytokine storm" of Covid-19 infection with HD IV Ig as it is recognised that Kawasaki like syndrome is the paediatric form of the "cytokine storm" seen in adult patients infected with Covid-19.

Rituximab

This is a chimeric mouse-human IgG1 monoclonal antibody that targets CD20, a transmembrane protein expressed in B cells. Rituximab is primarily used in conjunction with chemotherapy to treat haematological malignancies such as large diffuse non-Hodgkin lymphoma and chronic lymphocytic leukaemia.[5] Following the discovery that concomitant autoimmune disorders such as rheumatoid arthritis improved following Rituximab treatment for haematological malignancies, Rituximab is now also used to treat an expanding range of autoimmune diseases including rheumatoid arthritis,[6] autoimmune haemolytic anaemia, pure red cell aplasia, ITP, Evans syndrome,[7] vasculitis (granulomatosis with angiitis), bullous skin disorders pemphigus, systemic lupus erythematosus, multiple sclerosis, chronic inflammatory demyelinating polyneuropathy to name but a few. The rationale for the use of Rituximab in Covid-19 infection to prevent and/or treat the "cytokine storm" depends on the multifaceted mode of action of Rituximab in down-regulating the immune responses by at least three major independent mechanisms (antibody dependent cellular cytotoxicity, complement mediated cytotoxicity and apoptosis).[8] Based on these mechanisms Rituximab has been successfully used to treat a wide range of immune/autoimmune disorders and for this reason it is expected to be useful for the treatment of "cytokine storm" because it involves hyperactive immune reaction. However, since we do not fully understand at this stage the precise mechanism of development of "cytokine storm" and whether it involves B or T cell or both, we cannot be certain without a clinical trial that Rituximab use in this setting can be definitely efficacious. Furthermore, the use of Rituximab can be associated with severe reactions which are avoidable with certain precautions known by those familiar with its use. To my knowledge Rituximab has not been reported to have been used or suggested for use in the context of Covid-19 infection.

Thalidomide and analogues

Thalidomide was promoted in the late 1950s for anxiety, sleep disturbance and morning sickness. It was realised in 1961 that thalidomide use was associated with birth defects mainly because of its anti-angiogenic property.[9] Thalidomide was not available for therapeutic use for nearly forty years until its anti-tumour effect in multiple myeloma was discovered

in the late 1990s. Since then its use has gained popularity as a first line treatment for multiple myeloma in combination with other chemotherapy,[10] in some forms of leprosy (Erythema Nodosum Leprosum)[11] and TB (tuberculous meningitis),[12] as a second line treatment of graft versus host disease,[13] in Crohn's Disease, rheumatic disorders and in some dermatological conditions.[14] Thalidomide is known as an anti-inflammatory and a modulator of the immune responses through its effects on cytokines interlukin-1, 6, 10 and 12 but more importantly it selectively inhibits the production of human monocyte tumour necrosis factor (TNF)-alpha through enhanced degradation of TNF-alpha m-RNA.[15,16] Through these complicated reactions it is highly likely that thalidomide will effectively dampen down the "cytokine storm" which in addition to causing lung injury, may well be the trigger of the state of hypercoagulability observed in Covid-19 patients. Tissue injury is a potent stimulator of thrombin generation and clot formation. It follows that treatment of "cytokine storm" would probably prevent and/or treat both lung injury as well as hypercoagulability. However, thalidomide has its own set of undesirable side effects including peripheral neuropathy, thrombocytopenia, anaemia and paradoxically venous thromboembolism. Patients requiring treatment for the "cytokine storm" probably only need treatment in the short term whereas the side effects of thalidomide treatment, apart from sleepiness, are likely to appear after a relatively prolonged use. Nevertheless, it would be prudent to add low molecular weight heparin in the prophylactic dose to the treatment protocol. To my knowledge thalidomide or its analogues have not been reported to have been used or suggested for use in the context of Covid-19 infection.

Discussion

Of the three investigational drugs I have proposed, thalidomide is the easiest to use because it is taken orally whereas the other two are administered intravenously. If proven safe and effective in a randomised controlled clinical trial, thalidomide is likely to become the drug of choice to treat and/or prevent "cytokine storm" fatal complication of Covid-19 infection but the main drawback is the teratogenic effect of thalidomide if and when taken during pregnancy.

All three proposed investigational treatments should only be administered to patients in the context of randomised controlled clinical trials in order to derive the maximum benefit from their use to guide the treatment of other patients in the future. Timing of treatment is crucial for the success. Since the proposed treatment is not meant to be for the viral infection but aimed at treatment for its severe inflammatory complication, treatment should be reserved in the first instance for patients whose conditions have deteriorated after hospital admission. Success is measured in terms of recovery and prevention of the need for treatment in an Intensive Care Unit (ICU) and/or recovery and reduction of stay in an ICU. Since recovery can happen spontaneously with best supportive care, the proposed trials should have sufficient discerning statistical power in terms of patient numbers to demonstrate whether each of these three investigational remedies when used in conjunction with best supportive care either as single agents or in combination are superior to the control arm of best supportive care only. If and when such superiority has been demonstrated, the investigation may be progressed to administer the medicine(s) with proven anti "cytokine storm" activity on admission of patients with Covid-19 infection to hospital in further randomised controlled trails with the aim of preventing rather than treating "cytokine storms". Alternatively, early treatment for prevention of complications on admission to hospital versus late treatment for cases of diagnosed "cytokine storm" complication may be conducted as different arms of the same trails in one stage rather than in two stages to save patients' lives, time and effort.

The differences between the current management of Covid-19 infection and the alternative management is that we are aiming actively in the latter at reduction of the development of "cytokine storm" complication of Covid-19 infections, reduction of the need for ICU admission, and most importantly, reduction of the mortality rate. Consequently, more patients will recover clinically and return to the community. They may develop sufficient protective immunity (likely to be more than conferred by vaccination) or may continue as virus carriers but this may not be such a bad thing because the infection is spreading in the community anyway unabated all the time in a silent manner as most infections are not symptomatic. Infections symptomatic or otherwise are all contributing to the build-up of active protective immunity in the community at large the "herd immunity".

To ease and eventually end the current lockdown safely without risking a second and subsequent waves of Covid-19 infection, humanity is pinning its hopes on the development of a safe and effective vaccine which may or may not materialise, even in the long term, because the indications are, the immune response may not confer sufficient protection or is short-lived. Virus mutation is another worrying consideration. The development of a safe and effective anti-viral therapy to Covid-19 does not seem, at present, to be a brighter prospect either. I have presented a third approach: to

take the sting out of the deadly Covid-19 and convert it to a "tame" infection.

When we deprive Covid-19 of its "cytokine storm", we downgrade it to behave just like any other form of influenza. Furthermore, the availability of safe and effective remedies proven by randomised controlled clinical trials for the deadly and most feared complication of Covid-19 infection the "cytokine storm" is likely to make the decision to ease and eventually to lift the lockdown acceptable particularly in parts of the United Kingdom and parts of the world in which there has been reluctance to ease the lockdown.

Declaration of Conflicting Interests

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