Japan Journal of Research

Short Communication

Trials of arsenic trioxide therapy should be envisioned for severely respiratory distress syndrome related to a cytokine storm in COVID-19 patients

François Rieger*

CEO, Medsenic SAS, 204 Avenue de Colmar, 67 100 Strasbourg, France

Correspondence

François Rieger

Medsenic SAS, 204 Avenue de Colmar, 67 100 Strasbourg, France

- Received Date: 27 June 2020;
- Accepted Date: 09 July 2020;
- Publication Date: 27 Feb 2021.

It is becoming more and more obvious, and even consensual, that the Coronavirus Disease 2019 (COVID-19) is composed of two distinct phases. The first one is the early episode of infection by the highly contagious SARS-CoV-2 virus. The virus gains access to the type-2 surfactant secreting alveolar cells of the host lungs via the angiotensin converting enzyme 2 (corresponding gene: ACE2) as a main membrane receptor [1]. It then enters the cells thanks to Janus kinases (JAKs)-mediated endocytosis process, as discussed by Stebbing et al., 2020 or Favalli et al., 2020) [2,3] and starts replicating. The second one is clearly related to an excessive release of immune mediators, cytokines or chemokines, which are very recently thought to lead to some 15-20 % of the COVID 19 patients, who develop life threathening severe respiratory distress syndrome [4-6]. However, the treatment of these patients is particularly difficult, as no specific drug therapy is currently recommended.

Thus, one should distinguish between a) therapeutic interventions aimed at protecting against the viral infection, the viral replication and the direct viral damage caused to the lungs and possibly other organs, and b) therapies intended to decrease the intensity of the secondary innate immune response and hyperinflammation. Indeed, the immune response may become overwhelmingly too strong, provoking a life-threathening severe pneumonia [4].

However, an immediate difficulty is that the precise timing and intensity of an immunosuppressive intervention must be weighed against possible deleterious effects on prolonged replication and delayed clearance of the virus. Numerous attempts of immunosuppressive therapies are trying to guess the best tradeoff between the clearance of the virus and the modulation of the immune response, as this latter may end up in increased viral replication or even bacterial or fungal infections. This was highlighted early in studies showing an increase in viral replication under corticosteroid treatment: it is well-known that corticosteroid immunosuppression significantly reduces the induction of the type 1 interferon- mediated antiviral response to a wide range of respiratory viruses [7,8].

More selective immunosuppressive therapies, such as those targeted to the JAK/STAT pathway (which is important for the production of antiviral type 1 interferon), should also be tested, but with great caution: it has been found that tofacitinib, a JAK inhibitor, inhibits interferon-1 production in vitro [9]. The same has been found for baricitinib, an inhibitor of both JAK1 and JAK2 enzymes [3], as well as for other more specific inhibitors of JAK1, upadacitinib and filgotinib [10]. Therefore, it is clear that a strategy aiming at lessening the cytokine storm in COVID-19 patients should carefully avoid a too early inactivation of the powerful innate immune response (which is largely interferon-mediated), naturally preventing the replication of the virus. It is at least clear that the interferon-activated JAK/STAT signalling pathway, leading to the upregulation of many interferon-controlled genes, quickly kills viruses in infected cells and should be carefully preserved in the first stages of the disease. This particular aspect makes it difficult to find ways to control the overall cytokine response in due time. It indeed requires a specific inhibition of various key cytokines, as some of them could turn out to be double-edge swords, at the same time controlling the replication of the virus, but potentially damaging cells, in the long run. This occurs if some proinflammatory cytokines are expressed at too high levels – leading to cell death and impairment of critical physiological functions, such as respiratory activity.

The challenge is thus to find a good balance between the replication activity of the virus and the inhibition of the cytokine storm. This is why we think that it should be helpful to find drugs and treatment opportunities which would not lead to a global, non-specific, immunosuppression, but to a more selective immunosuppression or immunomodulation. Sustained non-specific immunosuppression is harmful to any kind of immune cells. This is the case of the immunosuppressive strategies mentioned above, such as corticotherapy. Other non-specific immunosuppression could be harmful to too many types or subsets of immune cells, whether quiescent or active. This type of limited, still non-specific immunosuppression is observed when certain cell surface antigens are targeted by monoclonal antibodies and could damage "good" as well as "bad" coexistent immune responses. As a matter of fact, one would prefer drugs that are active only on very specific reactive and pathogenic cell subsets of the immune system. Such drugs would interfere with very specific proteins or cellular pathways

Citation: Rieger F. Trials of arsenic trioxide therapy should be envisioned for severely respiratory distress syndrome related to a cytokine storm in COVID-19 patients. Japan J Res. 2021;2(1):1-2.

directly involved in a given pathological molecular process, therefore displaying more specific actions. Thalidomide, which is useful to alleviate the symptoms of some autoimmune diseases, could be one of these drugs.

Indeed it is known to interact with a large protein complex known as DDB1-CRBN, which is part of a major protein complex, including E3 ubiquitin ligases [11]. Thalidomide is presently undergoing clinical trial in a cohort of critically ill COVID-19 patients (ClinicalTrials.gov Identifier: NCT0427358).

Such drugs would thus, ideally, fit the aim of controlling the pathogenic cells, (i.e. those producing too high levels of pro-inflammatory cytokines, once they have contributed to limit the viral replication and decrease the viral load), without damaging other sets of useful immune cells. The danger of suppressing any other useful, critical immune protection against infection would be thus drastically lowered.

To us, a typical drug of this kind, characterised by selective immunomodulatory properties, may well be arsenic trioxide. In our hands, two small Phase II trials aimed at evaluating the use of arsenic trioxide in two characteristic autoimmune diseases (ClinicalTrials.gov identifiers: NCT01738360 in Lupus and NCT02966301 in GvHDc) , show that arsenic trioxide is safe and gives promising preliminary results in controlling the immune system, with no increased rate of infectious events in treated autoimmune patients. Preclinical work has already given important clues on the specificity of the immunomodulation which is observed under arsenic trioxide treatment: activated immune cells are returned to a normal, quiescent, differentiation state. They are thought to be eliminated through cell stress-induced cell death; but, importantly, there is no apparent effect on the otherwise unreactive cells of the diseased immune system. These observations suggest that the still normal components of the immune system are not altered in a detectable way, and that they would still be active when necessary, for example in the event of infections. The first studies on such a specific immunosuppression phenomenon led researchers using arsenic trioxide in animal models of systemic lupus erythematosus [12,13] and Crohn's disease [14] to postulate that they were witnessing a new, rather subtle immunomodulation. This immunomodulation process would ignore normal cells and would bring back to normal, and possibly cure, an otherwise abnormal immune system [9,12]. More than that, subsequent work on animal models for scleroderma and chronic GvHD suggested that arsenic trioxide would target certain cell types, such as plasmacytoid dendritic cells [15,16]. Plasmacytoid dendritic cells are known for their role in cytokines release under specific stimuli, such as viruses or lipopolysaccharide motives present on bacteria. Recent in vitro studies show that healthy human peripheral blood mononuclear cells (PBMCs) stimulated through Toll Like 9 receptors demonstrate a change in cytokine production, without being induced to cell death (Rieger F. unpublished results). These observations suggest that arsenic trioxide is a true immunomodulator of a new kind, which may positively act on the exagereted cytokine production of immune cells activated by the attack of a virus such as SARS-CoV-2. This could be of help in other related respiratory diseases of viral origin, without interfering with other immune functions. Finally, a recent paper gives direct proof to the fact that arsenic trioxide is a powerful anti-inflammatory agent: indeed Li et al. reported the regulation of proinflammatory cytokine levels in patients with rheumatoid arthritis, with the inhibition of various cytokines such as IL17A,IL6, IL23 and TNFalpha [17]. Some of these cytokines are found related to COVID-19 lung pathology, as reported recently by Chinese authors [18].

Our proposition, in these times of catastrophic emergence and rapid propagation of COVID-19, is that it could be advisable to try arsenic trioxide as an inhibitor of the cytokine storm occuring in this disease, at a time chosen before full blown immune storm. This would hopefully lead to the decreased potential to damage the cytokine-target organs, such as the lung, thus aborting the too often fatal respiratory distress, related to the out-of-control cytokine storm.

In conclusion, we strongly believe that arsenic trioxide should be tried to inhibit the cytokine storm that is responsible for the respiratory distress in COVID 19. Other severe respiratory or non-respiratory diseases, characterised by the occurrence of exacerbations of immune inflammatory reactions, could also benefit of arsenic trioxide.

Declaration of interests

FR is the CEO of Medsenic SAS, a private company holding exclusive patent rights on the use of arsenic salts in autoimmune diseases and GvHDc, with no actual involvement in respiratory diseases or viral affections. FR declares no direct competing interests.

References

1. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbiol. 2020;5(4):562-569.
2. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis. 2020;20(4):400-402.
3. Favalli EG, Biggioggero M, Maioli G, Caporali R. Baricitinib for COVID-19: a suitable treatment? [published online ahead of print, 2020 Apr 3]. Lancet Infect Dis. 2020;S1473-3099(20)30262-0.
4. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-733.
5. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-1034.
6. Feldmann M, Maini RN, Woody JN, et al. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. Lancet. 2020;395(10234):1407-1409.
7. Singanayagam A, Glanville N, Girkin JL, et al. Corticosteroid suppression of antiviral immunity increases bacterial loads and mucus production in COPD exacerbations. Nat Commun. 2018;9(1):2229.
8. Thomas BJ, Porritt RA, Hertzog PJ, Bardin PG, Tate MD. Glucocorticosteroids enhance replication of respiratory viruses: effect of adjuvant interferon. Sci Rep. 2014;4:7176.
9. Boor PPC, de Ruiter PE, Asmawidjaja PS, Lubberts E, van der Laan LJW, Kwekkeboom J. JAK-inhibitor tofacitinib suppresses interferon alfa production by plasmacytoid dendritic cells and inhibits arthrogenic and antiviral effects of interferon alfa. Transl Res. 2017;188:67-79.
10. Biggioggero M, Becciolini A, Crotti C, Agape E, Favalli EG. Upadacitinib and filgotinib: the role of JAK1 selective inhibition in the treatment of rheumatoid arthritis. Drugs Context. 2019;8:212595.
11. Fischer ES, Böhm K, Lydeard JR, et al. Structure of the DDB1-CRBN E3 ubiquitin ligase in complex with thalidomide. Nature. 2014;512(7512):49-53.
12. Pistoia V. Poisoning autoimmunity. Blood 2006;108(13):3964-65
13. Bobé P, Bonardelle D, Benihoud K, Opolon P, Chelbi-Alix MK. Arsenic trioxide: A promising novel therapeutic agent for lymphoproliferative and autoimmune syndromes in MRL/lpr mice. Blood. 2006;108(13):3967-3975.
14. Singer M, Trugnan G, Chelbi-Alix MK. Arsenic trioxide reduces 2,4,6-trinitrobenzene sulfonic acid-induced murine colitis via nuclear factor-κB down-regulation and caspase-3 activation. Innate Immun. 2011;17(4):365-374.
15. Kavian N, Marut W, Servettaz A, et al. Reactive oxygen species-mediated killing of activated fibroblasts by arsenic trioxide ameliorates fibrosis in a murine model of systemic sclerosis. Arthritis Rheum. 2012;64(10):3430-3440.
16. Kavian N, Marut W, Servettaz A, et al. Arsenic trioxide prevents murine sclerodermatous graft-versus-host disease. J Immunol. 2012;188(10):5142-5149.
17. Li C, Zhang J, Wang W, Wang H, Zhang Y, Zhang Z. Arsenic trioxide improves Treg and Th17 balance by modulating STAT3 in treatment-naïve rheumatoid arthritis patients. Int Immunopharmacol. 2019;73:539-551.
18. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.