Received: 17 July 2020 | Revised: 11 August 2020 | Accepted: 30 August 2020

DOI: 10.1111/sji.12972

DISCUSSION FORUM

Scandinavian Journal of Immunology WILEY

Oromucosal immunomodulation as clinical spectrum mitigating factor in SARS-CoV-2 infection

Francisco Rodríguez-Argente[1] | **María Alba-Domínguez**[2] | **Elena Ortiz-Muñoz**[3] | **Ángel Ortega-González**[4]

[1]Department of Pediatrics, Emergency Department, Department of Pneumology, Hospital Universitario Nuestra Señora del Prado, Talavera de la Reina, Spain

[2]HistoBioMol Lab, Lugo, Spain

[3]Emergency Department, Hospital Universitario Nuestra Señora del Prado, Talavera de la Reina, Spain

[4]Pneumology Department, Hospital Universitario Nuestra Señora del Prado, Talavera de la Reina, Spain

Correspondence
Francisco Rodríguez, Pediatric Immunology Unit, Department of Pediatrics, Hospital Nuestra Señora del Prado, 45600, Ctra. de Madrid, Talavera de la Reina. Spain.
Email: frodrigueza@sescam.jccm.es

Abstract

Mounting evidence supports the importance of mucosal immunity in the immune response to SARS-CoV-2. Active virus replication in the upper respiratory tract for the first days of infection opens a new perspective in immunological strategies to counteract viral pathogenicity. An effective mucosal innate immune response to SARS-CoV-2 paves the way to an also effective adaptive immune response. A strong local immune response seems to be crucial in the initial contention of the virus by the organism and for triggering the production of the necessary neutralizing antibodies in sera and mucosal secretions. However, if the innate immune response fails to overcome the immune evasion mechanisms displayed by the virus, the infection will progress and the lack of an adaptive immune response will take the patient to an overreactive but ineffective innate immune response. To revert this scenario, an immune strategy based on enhancement of immunity in the first days of infection would be theoretically well come. But serious concerns about cytokine response syndrome prevent us to do so. Fortunately, it is possible to enhance immune system response without causing inflammation through immunomodulation. Immunomodulation of local immune response at the oropharyngeal mucosa could hypothetically activate our mucosal immunity, which could send an early an effective warning to the adaptive immune system. There are studies on immunotherapeutic management of upper respiratory tract infections in children that can place us in the right path to design an immune strategy able to mitigate COVID-19 symptoms and reduce clinical progression.

1 | INTRODUCTION

Common cold is the most frequent human illness, in children and adults, leading to millions of days of work and school absence, physician visits and inappropriate antibiotic use.[1] Coronaviruses—229E, OC43, NL63 and HKU1—are known to be frequent cause of common cold in nearly twenty per cent of all cases.[2] Paediatricians and general physicians are

Summary: This study enquires about the immunopathogenic and clinical basis of immunomodulation of oropharyngeal mucosa immune response to SARS-CoV-2 as an effective immunotherapeutic strategy able to mitigate COVID-19 symptoms and reduce clinical progression

quite used to deal with common cold symptoms: the clinical spectrum varies from the complete absence of symptoms or mild respiratory ones to a severe acute disease in selected population groups (immune-suppressive therapy or patients with chronic diseases).[3] This is how it was at least until the outbreak at the beginning of the 21st century of two new strands of coronaviruses responsible of the so-called acute respiratory syndrome (SARS-CoV) and the middle east respiratory syndrome (MERS-CoV), both linked to sometime fatal illness with a higher morbimortality than the previous known four species. Both threats, SARS and MERS, were barely staved off.[4] Unfortunately, it did not stop there, and the sudden outbreak of a seventh new coronavirus responsible of the acute respiratory syndrome pandemic initiated at Wuhan, China, in December 2019 (SARS-CoV-2) is currently causing a considerable number of deaths due to the lack of specific immunity in the entire world population.[5] Although the paediatric population seems to experience less severe COVID-19 than adults, presenting good prognosis and recovering within several weeks after disease onset, in the course of hospitalization some children with coexisting conditions can require intensive care support and mechanical ventilation.[6] Besides the illness itself, children are suffering all the different consequences of the present pandemic in a special dramatic way.

2 | RESPONSES TO COVID-19 PANDEMIC. WAITING FOR A SAFE VACCINE

Efficient responses to this lethal pandemic have been looked for. In first place, epidemiological measures, quarantines and social distancing initiated at the city of Wuhan have demonstrated their efficacy even with a high economic and social cost. Secondly, many experts think that collective immunity could protect us but at least half of the population would have to develop immunity through getting sick. Finally, most of our hopes rely on the development of a safe vaccine, but this will take at least twelve to eighteen months.[7]

Could we do anything else while we wait for the development of a safe vaccine? There are studies on immunotherapeutic management of upper respiratory tract infections in children that show what we consider some interesting aspects on this issue.

3 | IMMUNE RESPONSE TO SARS-COV-19 AND OTHER CORONAVIRUSES

We know by the research work done by the Common Cold Unit of Harvard Hospital at Salisbury, England, in the second half of the 20th century that: 'Immunological changes during and after coronaviruses infections, are in some respects like those which follow other respiratory infections such as rhinovirus infections'.[8] Although the exact mechanisms of the immune response to SARS-CoV-2 infection and its immune evasion strategies remain unknown, we can figure out the main picture helped by what we know about the immune response to MERS-CoV, SARS-CoV and the old known four coronaviruses.

The immune response induced by different coronaviruses goes through quite similar clinical phases. During the incubation and first stages, the innate immune response stops viral invasion and helps to build a specific adaptive immune response. This adaptive immune response is needed to eliminate the virus and to avoid disease progression to severe stages.[9]

SARS-CoV-2 tropism for upper respiratory mucosas is being recently demonstrated stating the role of these tissues as portal of entry in coronavirus disease. Mechanism of cell infection by coronavirus depends on the binding of the spike protein to angiotensin-converting enzyme 2 cellular receptor (ACE-2). Interestingly, viral entry-associated genes are co-expressed in nasal epithelial cells with genes related to innate immunity, what spotlights the importance of the upper respiratory tract mucosa innate immune response in the first immunopathogenic stages of coronavirus invasion.[10]

Mucosal immune response is initiated at inductive sites in mucosa-associated lymphoid tissues in upper respiratory tract (nasopharyngeal lymphoid-associated tissue (NLAT)). Activated antigen-presenting cells (APCs) go from peripheral tissues to lymphoid tissues, where T and B cell response mature; APCs are important components of innate immunity and can trigger the production of large quantities of cytokines and chemokines.[11] Thus, APCs connect innate and adaptive immunity. Subsequently, both T cells and B cells of the adaptive immune response are stimulated for a specific response: virus-specific T and B cells enter the blood, and finally, a good proportion of them go back to a very precise place, the lamina propria of upper respiratory tract mucosas, where they act as effectors: high specific IgA- and IgG-producing plasma cells and activated T lymphocytes.[12]

Coronaviruses like rhinoviruses and other respiratory infection viruses have different ways to evade immune response by manipulating innate immunity and preventing interferon (IFN) production.[13] As it happens in infections with rhinovirus, influenza and SARS-CoV, we know that lymphocytopenia occurs in the early stages of infection of SARS-CoV-2.[8,14]

Viruses try to silence APCs blocking their activation by downregulating IFN production and other cytokines. Inactivation of APCs means that APCs main functions, antigen presentation to lymphocytes and creation of an adequate cytokine atmosphere for immune activation are disrupted. If the host immune system is able to overcome the immunosuppression caused by the virus, the adaptive immune response can go

ahead successfully with the activation of T lymphocytes and the production of highly specific viral neutralizing antibodies, IgG and IgA in sera and oropharyngeal secretions by plasma cells. 'Both local and circulating antibodies have been shown to be associated with protection from infection and disease due to coronaviruses and other respiratory tract infection viruses'.[8,12,13]

However when a protective immune response is impaired, when our antigen-presenting cells are inactivated by SARS-CoV-2 evasion mechanisms and innate immunity fail to raise the alarm, virus will propagate and massive destruction of the affected tissues will occur, especially in lungs and in organs that have high ACE-2 expression, such as intestine and kidney.[9] 'The damaged cells induce innate inflammation in the lungs that is largely mediated by proinflammatory macrophages and granulocytes. Lung inflammation is the main cause of life-threatening respiratory disorders at the severe stage'.[15]

4 | IMMUNOSENESCENCE, IMMUNODEFICIENCY, TRANSIENT IMMUNE FUNCTION DECLINE

Importance of immunosenescence and immunodeficiency as risk factors in the pathogeny of COVID-19 is well known. Immunosenescence affects mainly the innate immune response and IgA secretion, and this might partly explain why children experience a less severe COVID-19 than aged people..[16] We know that patients who deteriorate in course of SARS-CoV-2 infection due to the inhibition and suppression of the immune system by the virus itself are not able to stop viral replication so were not patients infected by MERS-CoV and SARS-CoV neither.[12] However, many children and many severely ill adults with COVID-19 do not have any recognizable immunodeficiencies or other pathologies, but some of these healthy children and young adults, beside other possible causes, may have mild problems in selected immune components that can be an expression of transient immune decline.[17]

5 | CYTOKINE STORM SYNDROME

Concerns arising on cytokine storm syndrome in severe ill patients of COVID-19 can lead one to think wrongly that immune system is the final culprit of the disease. Cytokine storms are common complications not only of COVID-19 but of other respiratory diseases caused by coronaviruses such as SARS and MERS. Cytokine storm syndrome happens at the late stages of the disease when the immune system is overwhelmed by the infection.[6,12] We should not blame immune system for the disease but its dysregulation. 'Furthermore, an effective adaptive immune response is needed for suppressing overzealous early innate response and minimizing collateral damage caused by inflammation'.[18]

6 | IMPORTANCE OF MUCOSAL IMMUNITY IN SARS-COV-2 INFECTION

Mounting evidence supports the importance of mucosal immunity in the immune response to SARS-CoV-2 as happens in other upper respiratory tract infections. Active virus replication in the upper respiratory tract for the first days of infection adds a new perspective in immunological strategies to counteract viral pathogenicity. 'Pharyngeal virus shedding is extremely high during the first week of symptoms'.[19] A strong local immune response seems to be crucial in the initial contention of the virus by the organism and for triggering the production of the necessary neutralizing antibodies in sera and mucosal secretions.[10,11]

Mucosal innate immune response plays the same role the sacred geese played in the siege of the Capitoline hill by the Gauls in ancient times. The city of Rome was sacked and spoiled by the Gauls but a few roman soldiers were able to refugee at the Capitoline hill. Gauls tried to storm by surprise the roman fortress at the top of the Capitolium climbing the walls by night, no sentinel nor dog was able to advert the invaders but the sacred geese did and warned the Romans that were successful in repelling the attack.[20]

7 | IMMUNOMODULATION OF MUCOSAL IMMUNE RESPONSE, A FEASIBLE IMMUNOTHERAPEUTIC STRATEGY FOR MITIGATING THE CLINICAL SPECTRUM OF CORONAVIRUS INFECTION DISEASE 2019

An effective mucosal innate immune response to SARS-CoV-2 paves the way to an also effective adaptive immune response. An immune strategy based on enhancement of immunity in the first days of infection would be theoretically well come. But serious concerns about cytokine response syndrome prevent us to do so. Fortunately, it is possible to enhance immune system response without causing inflammation through immunomodulation.[21] Immunomodulation of local immune response at the oropharyngeal mucosa could hypothetically help our mucosal immunity to send an early an effective warning to the adaptive immune system.

Immunomodulation is an immunotherapeutic strategy able to restore homeostasis in a disbalance immune system without producing inflammation. As stated by the American

Committee on New directions in the study of Antimicrobial therapeutics: 'Treatment regimens that modulate the immune response have the potential to revolutionize how infectious diseases are treated […]. However, it should be remembered that history shows that it is possible to develop immunomodulatory strategies without understanding the full complexity of immunology, as evidenced by early vaccines and serum therapy. Hence, the complexity of the host-microorganism interaction and the fact that we do not yet fully understand it need not prevent us from pursuing the development of immunomodulating therapeutics'.[20,21]

8 | BIOLOGICALLY ACTIVE POLYSACCHARIDES AND POLYPHENOLS IN PREVENTION AND TREATMENT OF RESPIRATORY TRACT INFECTIONS IN CHILDREN

Many natural compounds and medications have immunomodulatory properties, but only few also possess a consistent clinical and immunopathogenic basis. Among these substances, we find biologically active polysaccharides (BAPs), the most important BAPS are beta-glucans. Given the similarity of beta-glucans to bacterial wall and yeast components, it is assumed that they must have a stimulating effect on innate immunity particularly on macrophage activation and antigen presentation. An extensive review by Milos Jesenak and coworkers from Comenius University at Bratislava of a series of studies about the immunomodulating action of enteral administrated BAPs shows a decrease of the number of respiratory tract infections in the children studied, reaching in some cases nearly fifty per cent.[22]

Polyphenols are also well-known, pharmacologically active compounds with immunomodulatory activity. Polyphenols produce an increasement in nitric oxide production by macrophages, enhancing their functional activity. Vaughan Sommerville and coworkers from Auckland University, New Zeeland, investigated the effect of oleuropein and hydroxytyrosol on upper respiratory tract infection incidence and duration in school athletes. The study showed that polyphenols had no significant effect on incidence but significantly reduced the number of sick days by twenty-eight per cent.[23]

In our opinion, these studies on enteral immunomodulation with beta-glucans and polyphenols in children with upper respiratory tract infections give a consistent clinical basis to suggest that immunomodulation of immune response to SARS-CoV-2 infection has the potential to mitigate clinical symptoms of COVID-19.

All these studies are based on immunomodulation of gut-associated lymphoid tissue (GALT), using an enteral route. On the contrary, we would like to clarify why we think that immunomodulation of lingual tonsils (NALT), using an oromucosal route, would obtain better results.

9 | IMMUNOPATHOGENIC AND CLINICAL BASIS OF OROMUCOSAL IMMUNOMODULATION. IMPORTANCE OF PLASMA CELLS MUCOSA HOMING PROFILE

At this point, we should consider again how mucosal immunity works. According to Per Bradtzaeg from the Centre for Immune Regulation of the Laboratory for Immunohistochemistry and Immunopathology of Oslo University Hospital: 'Gut associated lymphoid tissue (GALT) and nasopharynx associated lymphoid tissue (NALT) do not contribute equally to the pool of memory/effector B cells differentiating to mucosal plasma cells (PCs) throughout the body. Thus, enteric immunostimulation may not be the best way to activate the production of salivary IgA antibodies although the level of specific secretory IgA in saliva may still reflect an intestinal immune response after enteric immunization. Parotid secretory IgA could more consistently be linked to immune induction in palatine tonsils/adenoid (human NALT) and cervical lymph nodes as suggested by the homing molecule profile observed after immune induction at these sites'.[24]

The route of administration of immunomodulatory substances should attend the portal of entry of the infectious microorganism. In SARS-CoV-2 infection, as reviewed above with other upper respiratory tract infections, high specific viral IgA- and IgG-secreting plasma cells must home to oronasopharynx mucosas in order to obtain high avidity IgA and IgG with viral neutralizing activity and opsonization among other protective antibody functions,[25] just at the place where they are more needed, the upper respiratory tract mucosa barrier.

There are not previous studies of specific local oromucosal immunomodulation with beta-glucans and polyphenols in respiratory tract infections. Interestingly, there is clinical experience in a similar immunotherapeutic strategy consisting in sublingual administration of interferon in children and adults in the same clinical setting. Studies of sublingual administration of low doses of interferon alfa in children with upper respiratory tract infections, as reviewed by Mandred W. Beihazr and coworkers from the University of Western Australia, show the feasibility and clinical effectiveness of using an oromucosal route to overcome viral suppression of mucosa innate host defences..[26] Unfortunately, even administration of IFN alfa at low doses seems to have a good safety profile, we do not know whether IFN can be as safe as immunomodulatory

substances as beta-glucans and polyphenols, a question far beyond the scope of this report.

10 | DISCUSSION

Importance of mucosal innate immune response to SARS-CoV-2 should not be neglected. There is enough scientific background to support the key role of mucosal immunity in early warning the immune system in respiratory tract infection by SARS-CoV-2. Mucosal innate immune response does not only consist in a simple barrier of mucous membranes full of macrophages, but innate defence factors are paramount for the development of an adaptive humoral and cell immunity mediated by antibodies and activated T cells. Common cold symptoms, coughing, having a runny nose, fever and myalgias, are very annoying but all together are a good price to pay for not having a pneumonia. A strong mucosal innate immune response gives you more possibilities to have COVID-19 as a common cold rather than a pneumonia or an acute respiratory syndrome.

Oromucosal immunomodulation with beta-glucans and polyphenols if effective should not be considered a magical cure but it is not a puerile phantasy neither. We could hypothesize that people who were having oromucosal immunomodulation with beta-glucans and polyphenols and were infected by SARS-CoV-2 would have more possibilities to have less severe symptoms and a better outcome.

11 | CONCLUSIONS

It is a truism to say that COVID-19 pandemic must be managed with well thought global and local strategies by the scientific community and health authorities. This means that all well-known effective measures from quarantines, face mask wearing, hand washing and evolving effective medical treatments should be strictly followed by all of us. There are no easy solutions to this pandemic. In our humble opinion, oromucosal immunomodulation with a diary sublingual low dose of both beta-glucans and polyphenols has the potential to be a good additional protection.

In view of the present world pandemic situation, it does not seem premature to recommend that a clinical trial should be started to look more closely the operative mechanisms of the immunomodulation of mucosal immune response with beta-glucans and polyphenols as mitigating factors in COVID-19.

CONFLICT OF INTERESTS

None of the authors has ant potential conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Dr Rodríguez conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Ms Alba-Dominguez conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Dr Ortiz and Dr Ortega helped to design the study, reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Francisco Rodríguez-Argente https://orcid.org/0000-0002-8682-9279

REFERENCES

1. Greenberg SB. Update on rhinovirus and coronavirus infections. *Semin Respir Crit Care Med*. 2011;32(4):433-446.
2. American Academy of Pediatrics. Coronaviruses, including SARS and MERS. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:297-301.
3. De la Flor i Bui J. Infecciones de las vías respiratorias altas-1: el resfriado común. *Pediatr Integral*. 2017;XXI(6):377-398.
4. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol*. 2016;14(8):523-534.
5. 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.
6. Castagnoli R, Votto M, Licari A, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review [published online ahead of print, 2020 Apr 22]. *JAMA Pediatr*. 2020;174(9):882.
7. Instituto de Salud Global de Barcelona. Instituto de Salud Global Barcelona. COVID-19: Lecciones y recomendaciones, 2018. Disponible en: https://www.isglobal.org/coronavirus-lecciones-y-recomendaciones. 2020/05/24
8. Callow KA, Parry HF, Sergeant M, Tyrrell DA. The time course of the immune response to experimental coronavirus infection of man. *Epidemiol Infect*. 1990;105(2):435-446.
9. Shi Y, Wang Y, Shao C, et al. COVID-19 infection: the perspectives on immune responses. *Cell Death Differ*. 2020;27(5):1451-1454.
10. Sungnak W, Huang N, Bécavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat Med*. 2020;26:681-687.
11. Murphy K, Weaver C. The mucosal immune system. In: Murphy K, Weaver C, eds. *Janeway`s Immunobiology: The Immune System in Health and Disease*. New York, NY: Garland Science, Taylor & Francis Group, LLC; 2017:493-531.
12. Crespo HJ, Lau JT, Videira PA. Dendritic cells: a spot on sialic Acid. *Front Immunol*. 2013;4:491.

13. Mubarak A, Alturaiki W, Hemida MG. Middle East Respiratory Syndrome Coronavirus (MERS-CoV): infection, immunological response, and vaccine development. *J Immunol Res*. 2019;2019:6491738.
14. Channappanavar R, Zhao J, Perlman S. T cell-mediated immune response to respiratory coronaviruses. *Immunol Res*. 2014;59(1–3):118-128.
15. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome [published correction appears in Lancet Respir Med. 2020 Feb 25]. *Lancet Respir Med*. 2020;8(4):420-422.
16. Ginaldi L, Loreto MF, Corsi MP, Modesti M, De Martinis M. Immunosenescence and infectious diseases. *Microbes Infect*. 2001;3(10):851-857.
17. Mackinnon LT. Exercise and resistance to infectious illness. In: Mackinnon LT, ed. *Advances in Exercise and Immunology*. Champaign, ILHuman Kinetics; 1999:1-26.
18. Palm NW, Medzhitov R. Not so fast: adaptive suppression of innate immunity. *Nat Med*. 2007;13(10):1142-1144.
19. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019 [published online ahead of print, 2020 Apr 1]. *Nature*. 2020;581(7809):465-469.
20. Livy. *Ab urbe condita*. Cambridge, MAHarvard University Press; 1922.
21. Committee on New Directions in the Study of Antimicrobial Therapeutics: Immunomodulation. *Promising Approaches to the Development of Immunomodulation for the Treatment of Infectious Diseases: Report of a Workshop*. Washington, DCNational Academies Press, 2006. Available from: https://www.ncbi.nlm.nih.gov/books/NBK19846
22. Jesenak M, Urbancikova I, Banovcin P. Respiratory tract infections and the role of biologically active polysaccharides in their management and prevention. *Nutrients*. 2017;9(7):779.
23. Somerville V, Moore R, Braakhuis A. The effect of olive leaf extract on upper respiratory illness in high school athletes: a randomised control trial. *Nutrients*. 2019;11(2):358.
24. Brandtzaeg P. Secretory immunity with special reference to the oral cavity. *J Oral Microbiol*. 2013;5(1):20401.
25. French MA, Moodley Y. The role of SARS-CoV-2 antibodies in COVID-19: healing in most, harm at times. *Respirology*. 2020;25:680-682.
26. Beilharz MW, Cummins MJ, Bennett AL, Cummins JM. Oromucosal administration of interferon to humans. *Pharmaceuticals*. 2010;3(2):323-344.

How to cite this article: Rodríguez F, Alba-Domínguez M, Ortíz E, Ortega Á. Oromucosal immunomodulation as clinical spectrum mitigating factor in SARS-CoV-2 infection. *Scand J Immunol*. 2021;93:e12972. https://doi.org/10.1111/sji.12972