Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Medical Hypotheses 154 (2021) 110661

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Supportive therapy during COVID-19: The proposed mechanism of short-chain fatty acids to prevent cytokine storm and multi-organ failure

M. Jardou, R. Lawson *

INSERM, Univ. Limoges, Pharmacology & Transplantation, U1248, F-87000 Limoges, France

ARTICLE INFO

Keywords:
COVID-19
Cytokine storm
Multi-organ failure
Intestinal dysbiosis
Short-chain fatty acids
Butyrate

ABSTRACT

The world is currently facing the COVID-19 pandemic that is taking a heavy toll on several countries. While many infected patients have a good prognosis, in some cases the progression can be serious and even lead to death. The commonly seen complications are a cytokine storm and multi-organ failure that require intensive care. The mortality of critically ill patients depends on age, sex, immune state or co-morbidities. There is an urgent need to discover a biomarker to identify early on patients at risk of developing serious complications and to find an effective treatment that could prevent disease progression and critical states. Recent investigations have pointed to the possible contribution of intestinal dysbiosis to the pathophysiology of COVID-19. Herein, we hypothesize that butyrate, a short-chain fatty acid initially produced by the gut microbiota, could be administered as supportive therapy to prevent immune system activation and disease progression.

Background

The coronavirus disease (COVID-19) pandemic for which the first case was reported in December 2019 in Wuhan (China), is a highly contagious and life-threatening viral infection. For the period from December 2019 to June 2021, it has already affected more than 176 million people and caused more than 3.8 million deaths worldwide according to the World Health Organization [1].

Clinical presentation

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is responsible for COVID-19 is a new member of the *Coronaviridae* family. Transmission mostly occurs via respiratory droplets and aerosols from person-to-person. Once in the respiratory tract, the virus attaches to its specific receptor site, the angiotensin I converting enzyme 2 (ACE-2) and its entry into cells then requires transmembrane protease serine 2 (TMPRSS2) expressed by pulmonary epithelial cells. The virus penetrates host cells for replication followed by viral particles assembling and release of the new virions [2].

The clinical spectrum of COVID-19 ranges from asymptomatic, moderate, severe illnesses, up to critical states. The most frequent symptoms are fever, dry cough, dyspnea and fatigue that can be associated to myalgia, rhinorrhea, vomiting and cephalgia. Most of the infected patients have a good prognosis but in some cases, progression can become severe, possibly leading to death. The commonly seen complications in critically ill patients are acute respiratory distress syndrome (ARDS), sepsis, disseminated intravascular coagulation, acute liver or kidney injuries and pulmonary embolism. In rare cases, multisystem inflammatory syndrome, rhabdomyolysis, autoimmune hemolytic anemia and neurological complications have been observed [3,4]. The mortality of critically ill patients depends on age (more than 65 years old), sex (male), co-morbidities (e.g., metabolic syndrome, diabetes, cerebrovascular, cardiac or pulmonary diseases) and immune state [5,6]. Furthermore, SARS-CoV-2 associated risk is increased with respect to seasonal influenza since its transmission rate is nearly three times higher [7,8]. Fortunately, influenza vaccine is associated with a better clinical outcomes and presents no harmful effect on COVID-19 susceptibility [9].

Severe prognosis is correlated to the so-called “cytokine storm” which is frequently observed in critically ill patients. Such an event is defined by a huge increase of pro-inflammatory cytokines (namely interleukin (IL)-1β, IL-6, IL-12, interferon (IFN)-α/β, tumor necrosis factor (TNF)-α) and chemokines (namely C–C motif chemokine ligand (CCL)2, CCL3, CCL5). A well-coordinated innate immune response is the first line of defense against pathogens and plays a crucial role in the

* Corresponding author at: Centre de Biologie et Recherche en Santé (CBRS), Faculty of Pharmacy, University of Limoges, 2, av. Martin Luther King, 87042 Limoges Cedex, France.
E-mail address: roland.lawson@unilim.fr (R. Lawson).

https://doi.org/10.1016/j.mehy.2021.110661
Received 12 February 2021; Received in revised form 23 July 2021; Accepted 25 July 2021
Available online 5 August 2021

prevention of SARS-CoV-2 spreading [10]. However, dysregulated and/or excessive immune responses have been shown to fail at clearing the virus and in turn, can even contribute to the pathogenesis of ARDS as well as multi-organ failure [3]. The excessive production of cytokines results in tissular infiltration of inflammatory cells (e.g., macrophages and neutrophils); which favors (i) the alteration of the alveolar-capillary barrier, (ii) lung tissue damage (vascular leakage, alveolar oedema) and (iii) hypoxia associated with ARDS [11]. The cytokine storm also plays a central role in extrapulmonary multi-organ failure (heart, kidney and liver) [12]. Moreover, decrease in natural killer (NK) and T cell populations ascribed to lymphocytopenia have been also observed and correlated to disease severity [13,14]. The cytokine storm promotes tissue homing of immune cells and thrombosis. Moreover, a post-COVID syndrome leading to multi-organ sequelae is associated to immunologic aberrations and inflammatory damages. This syndrome encompass a spectrum of pulmonary, hematologic, cardiovascular, neuropsychiatric, renal, endocrine, dermatologic and gastrointestinal injuries.

Current pharmacological treatment of the cytokine storm

Since the beginning of the pandemic, many antiviral agents have been used or are still under clinical evaluation for COVID-19 (e.g., lopinavir-ritonavir or darunavir-cobicistat combinations, remdesivir, favipiravir, camostat mesylate-nafamostat) [15]. However, once immunologic complications occur, the use of standalone antiviral treatment is not sufficient. It should be combined with anti-inflammatory treatments to manage the cytokine storm as well as anti-coagulative drugs. Regarding the cytokine storm mechanism, the current therapeutic approaches consist in: (i) supplementing with IFN-λ to potentiate innate immunity, (ii) using immunomodulators (e.g., corticosteroids, intravenous immunoglobulins) to restore immune balance, (iii) inhibiting cytokine productions (*e.g.*, IL-1 or IL-6 antagonists, TNF blockers, IFN-α/β inhibitors, ulinastatin, oxidase phospholipids, sphingosine-1-phosphate receptor 1 agonists and stem cell therapy), (iv) scavenging cytokines (hemofiltration), (v) inhibiting mononuclear macrophage recruitment and action (toll-like receptor (TLR) 7 antagonist and C–C motif chemokine receptor type (CCR) 2 blockers), and/or (vi) strengthening the vascular barrier by activating the endothelial Slit-Robot4 signal pathway [12,15,16].

The period of treatment administration for SARS-CoV-2 is crucial. Indeed, an early exposure of the aforementioned strategies may inhibit the onset of the host's immune response, for example if drugs are administered too early. However, the best strategy is to act before the production of pro-inflammatory cytokines. For instance, montelukast commonly used in the treatment of persistent asthma has recently been proposed for COVID-19 treatment in an intensive care unit [17]. Montelukast can inhibit cytokine production through the inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, which down-regulates pro-inflammatory mediators. This approach seems promising since the blockade of cytokine production might be efficient in preventing pro-inflammatory consequences.

The hypothesis

In the present article, we aim to propose a new strategy dedicated to block the immune system overactivation. It is worth mentioning that after virus recognition, macrophages polarize towards the pro-inflammatory M1 phenotype. M1 macrophages actively produce pro-inflammatory cytokines which in turn drive viral replication and facilitate spreading of pathogens in the patient and tissue damage [18]. Therefore, a very promising therapeutic alternative could be to modulate the differentiation of macrophages in order to orient them towards the anti-inflammatory M2 phenotype.

Indirect proof of macrophages M1/M2 ratio skewing in critically ill COVID-19 patients

Macrophages are major regulators of inflammatory response and also play a central role in host defense [19]. They are featured by an important cell heterogeneity and plasticity. Indeed, in reaction to microenvironmental stimuli, macrophages can adopt different functional programs. Macrophages can either differentiate through a pro-inflammatory (M1) or anti-inflammatory (M2) phenotype [18]. M1 macrophage polarization is mediated by IFN-γ, TNF-α or lipopolysaccharides stimulation. M1 transformation hallmarks are both the inducible nitric oxide synthase (iNOS) expression and the pro-inflammatory cytokines IL-1β, IL-6, IL-12, IFN-γ, TNF-α and chemokines CCL2, CCL3, CCL4, CCL5, CCL8 production. This leads to pathogens destruction for which the time-window of inflammatory processes usually ranges from hours to days, but it has been shown that it can last for months or years, resulting in non-resolving inflammation. On the other hand, M2 macrophage polarization involves other interleukins stimulation (namely IL-4 and IL-13) and promotes up-regulation of genes associated to tissue repair and remodeling (e.g., *arginase 1* (*arg1*)) [18]. M2 macrophages exert their anti-inflammatory response *via* some specific cytokines like IL-1, IL-13, tumor growth factor (TGF)-β and chemokines CCL1, CCL2, CCL13 [18]. Therefore, M1 and M2 macrophages can easily be distinguished by their cytokine profiles as well as the expression of cell surface markers.

M1/M2 macrophages balance is finely regulated by specific signaling pathways. NF-κB and signal transducer and activator of transcription (STAT) 1 signaling pathways lead to M1 phenotype, while STAT3, STAT6 and PPARγ signaling pathways favor the M2 phenotype [19]. An imbalance between these two phenotypes has been already observed in chronic inflammatory diseases such as asthma, chronic obstructive pulmonary disease or atherosclerosis [20,21].

According to cytokines and chemokines profiles at the systemic level of critically ill patients (e.g., IL-1β, IL-6, IL-12, TNF-α and CCL5), it has been suggested that macrophages involved in the cytokine storm have the pro-inflammatory M1 phenotype [22]. However, such an observation still needs to be validated in clinical samples.

Intestinal dysbiosis, macrophages polarization and arguments for supportive therapy with short-chain fatty acids

Clinical characteristics of patients who develop severe forms of COVID-19 consistently suggest the contribution of intestinal dysbiosis. These patients are those with specific risk factors in relation to unhealthy gut microbiome status [23]. Moreover, COVID-19 infection itself is associated to the alteration of the gut microbiome characterized by an enrichment of opportunistic organisms and depletion of beneficial commensals [24,25]. Therefore, there is a link between gut microbiota alterations and the pathophysiology of COVID-19. Maintaining a healthy microbiome status is a possible strategy to tame COVID-19 severity. Gut microbiota is known as a key factor of host immune system homeostasis and its composition has been found depleted with bacteria associated to immunomodulatory effects in some COVID-19 patients [24]. Furthermore, intestinal dysbiosis has been linked to the decrease of main pro-resolving mediators. *Faecalibacterium prausnitzii*, a butyrate-producing bacteria, has been found depleted in critically ill patients [26]. This has also been associated to a pro-inflammatory state featured by (i) a decrease of regulatory T cells and (ii) polarization of macrophages into the M1 phenotype [27].

Short-chain fatty acids (SCFAs) belong to the pro-resolving mediators that participate in the dynamic host-microbiome network to regulate immune response. SCFAs are produced by the gut microbiota from the anaerobic fermentation of indigestible polysaccharides such as dietary fibers and resistant starches. Acetate, propionate and butyrate are key since they ensure the communication between the host and the microbiome, playing an important role in host homeostasis [28]. SCFAs

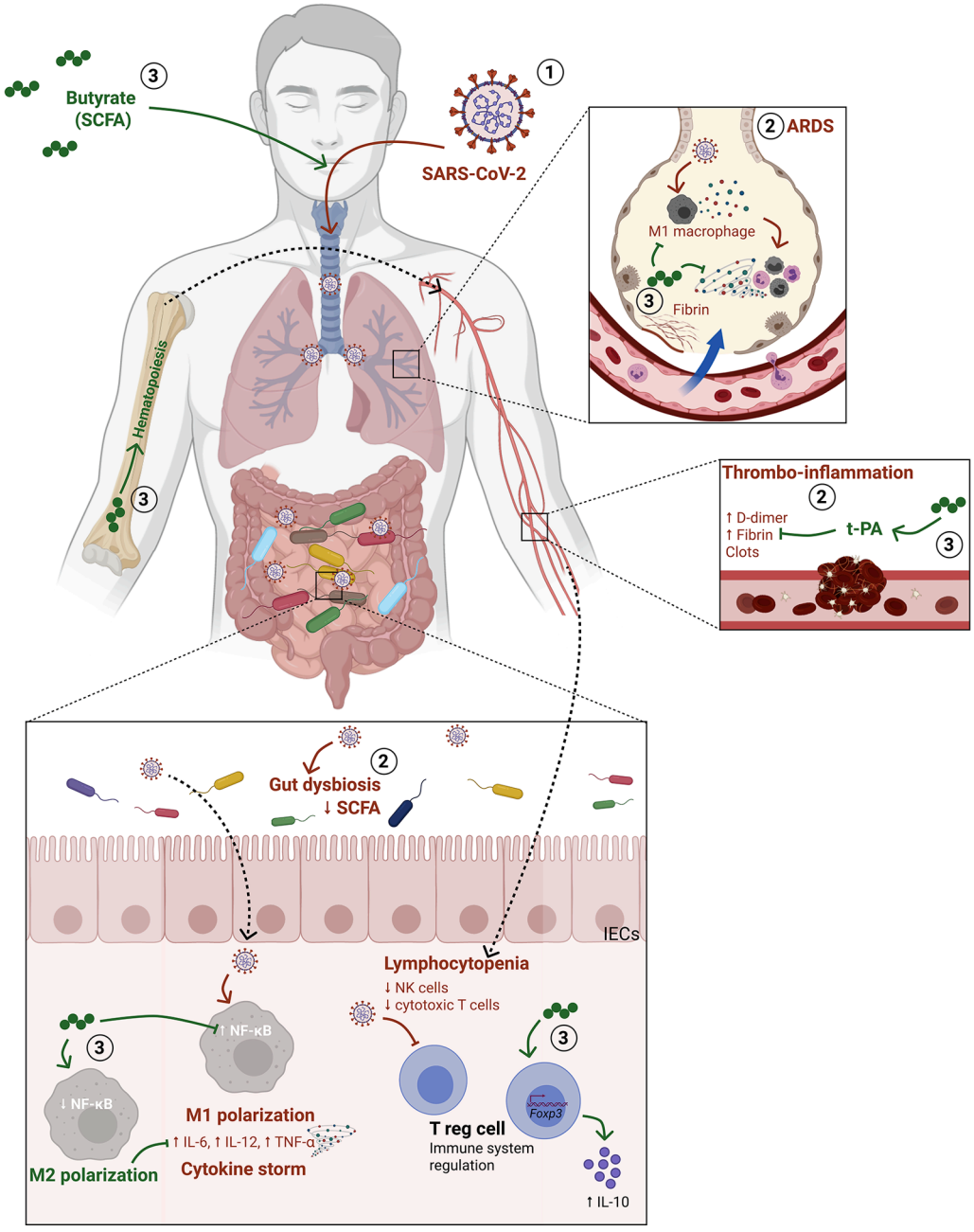

Fig. 1. The proposed mechanism of short-chain fatty acids to prevent cytokine storm and multi-organ failure. (1) SARS-CoV-2 enters and colonizes the host organism mainly through the airways. (2) Intestinal dysbiosis is found in patients with severe forms of COVID-19. Lymphocytopenia is also observed and SARS-CoV-2 inhibits regulatory T cells and leads to activation of the NF-κB signalling pathway which promotes the cytokine storm. (3) Supplementation with butyrate could help to limit the cytokine storm through the inhibition of the NF-κB pathway and promotion of anti-inflammatory M2 macrophages. Moreover, butyrate could restrain the thrombo-inflammation phenomenon by activating the t-PA. Created with Biorender.com.

can act on various immune cells in the gut to inhibit inflammation through multiple mechanisms. For instance, they modulate the differentiation of regulatory T cells or inhibit histone deacetylase (HDAC). They can also specifically activate some G protein-coupled receptors (GPCRs, *e.g.*, FFAR2, FFAR3) in order to enhance the intestinal barrier function and to modulate the immune system. Moreover, butyrate mainly triggers the metabolic shift in macrophages towards anti-inflammatory M2 phenotype *via* the inhibition of HDAC3 [28]. In other words, SCFAs may provide a better control of the inflammatory response, suggesting that their therapeutic properties are worth exploring.

Focus on the systemic anti-inflammatory effects of butyrate

SCFAs are first absorbed by intestinal epithelial cells and are then metabolized in the liver. Only a small fraction reaches the systemic circulation. However, it has been suggested that systemic SCFAs are protective against allergic asthma [29]. Butyrate can inhibit adhesion of eosinophils to the endothelium and is known to improve allergen-induced inflammation in mice [29]. Moreover, HDAC inhibitors are protective against vascular inflammation and atherosclerosis by modulating the endothelial function and production of pro-inflammatory cytokines, particularly with butyrate. SCFAs also improve kidney function after acute kidney injury induced by ischemia–reperfusion [28]. Butyrate has been thoroughly evaluated as HDAC inhibitor and pointed as the most pharmacologically active of SCFA [30]. HDAC inhibition by butyrate promotes the inhibition of lipopolysaccharide-induced production of nitric oxide (*via* iNOS) and pro-inflammatory cytokines (IL-6, IL-12) release [30]. More interestingly, butyrate has shown inhibition of NF-kB signaling pathway and facilitates the expression of anti-inflammatory cytokines such as IL-10 in mononuclear cells and neutrophils [31]. Recently, it has been shown in gut epithelial organoids and in some gastric cells lines that butyrate can downregulate genes essential for SARS-CoV-2 infection (*Ace2*, *Tmprss2*) and can also

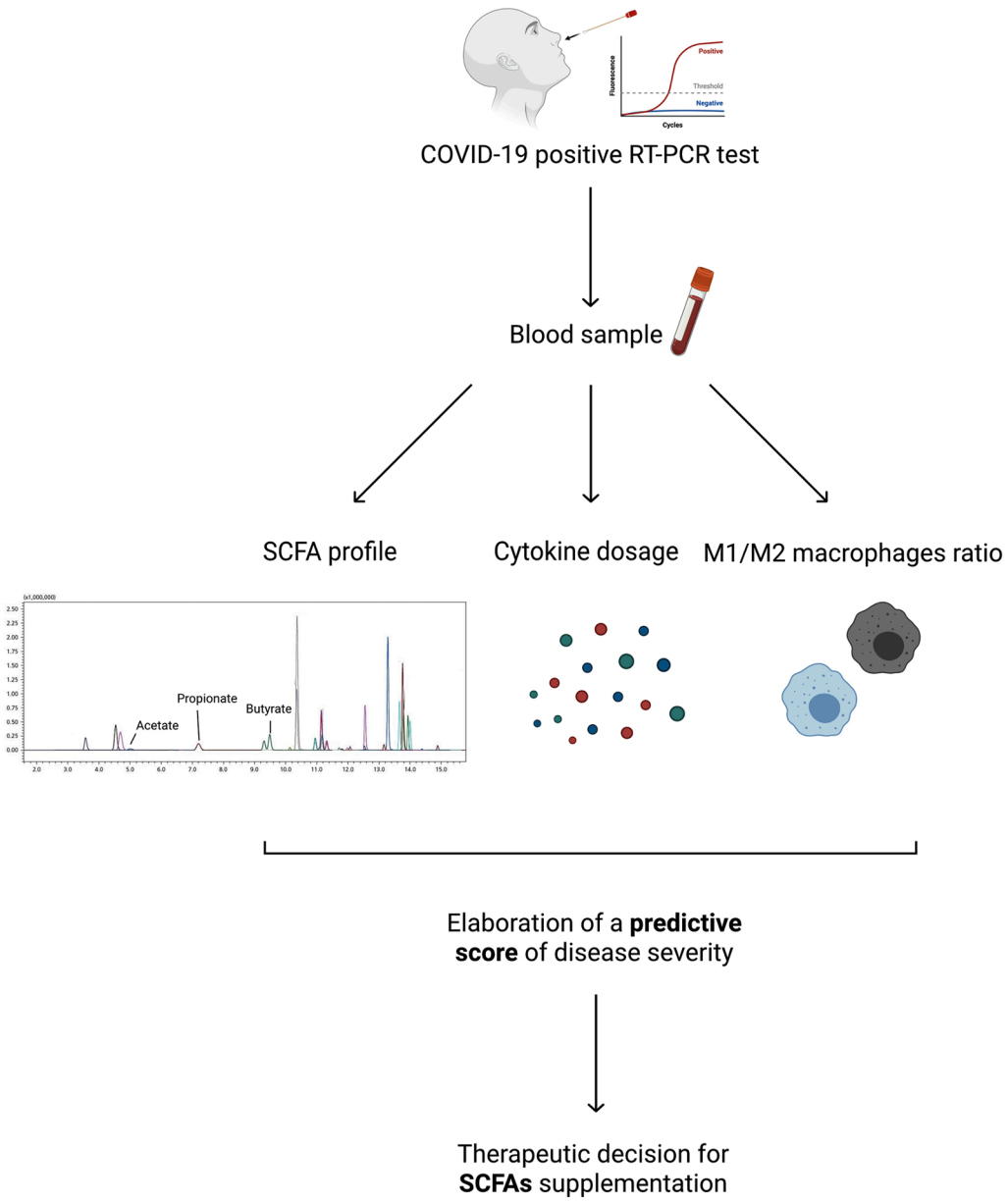

Fig. 2. Path for the decision of supportive therapy with SCFA. From the blood sample of a person tested positive for COVID-19, we propose to perform plasma SCFA profiling, relevant cytokine dosage and M1/M2 macrophages ratio at early stages of the disease. These data will serve as inputs to build a predictive score of disease severity or progression and to decide SCFAs supplementation.

upregulated other antiviral pathways [32,33]. Altogether, all these studies provide strong evidence that SCFA and especially butyrate exhibit a worth-investigating anti-inflammatory action that might be used to prevent or alter the course of cytokine storm in critically ill COVID-19 patients.

Butyrate supplementation for preventing the cytokine storm

Similar to the observations made on experimental models of viral infection (e.g., Influenza A), we propose that the inflammatory response during COVID-19 involves an increased M1/M2 macrophage phenotype ratio [34]. The M1 phenotype is likely to be associated to the activation of the NF-κB pathway and the pro-inflammatory cytokine production (e.g., IL-6, IL-12, TNF-α). This could at least partially explain the observed excessive cytokine release. Therefore, a relevant alternative is to restore the M1/M2 balance ratio by favoring M2 macrophage differentiation. Butyrate supplementation is expected to help polarize macrophages into M2 phenotype, which in turn might decrease pro-inflammatory cytokine production. Butyrate is proposed to inhibit the NF-κB pathway by preventing proteasomal degradation of the NF-κB inhibitor, namely IκB. Ji et al. elegantly demonstrated that butyrate facilitates M2 macrophage polarization by HDAC inhibition and STAT6 signaling pathway activation. Furthermore, they observed an upregulation of M2 markers such as *arg1* and *found in inflammatory zone 1* (*fizz1*) [35]. Furthermore, butyrate is known to prevent excessive neutrophil recruitment into the airways via a GPCR-dependent receptor and by an alteration of the CXCL1 synthesis, which is a neutrophil chemoattractant produced by macrophages [34]. In other words, butyrate supplementation could also limit inflammatory cell infiltration in the airways, which in turn might reduce tissue and vascular disruption. In addition, butyrate also stimulates hematopoiesis by favoring the development of macrophage progenitors with the M2 phenotype [36]. Through the expression of the transcription factor *forkhead box protein P3* (*foxp3*) butyrate also promotes regulatory T cells, which modulate the immune system and secrete anti-

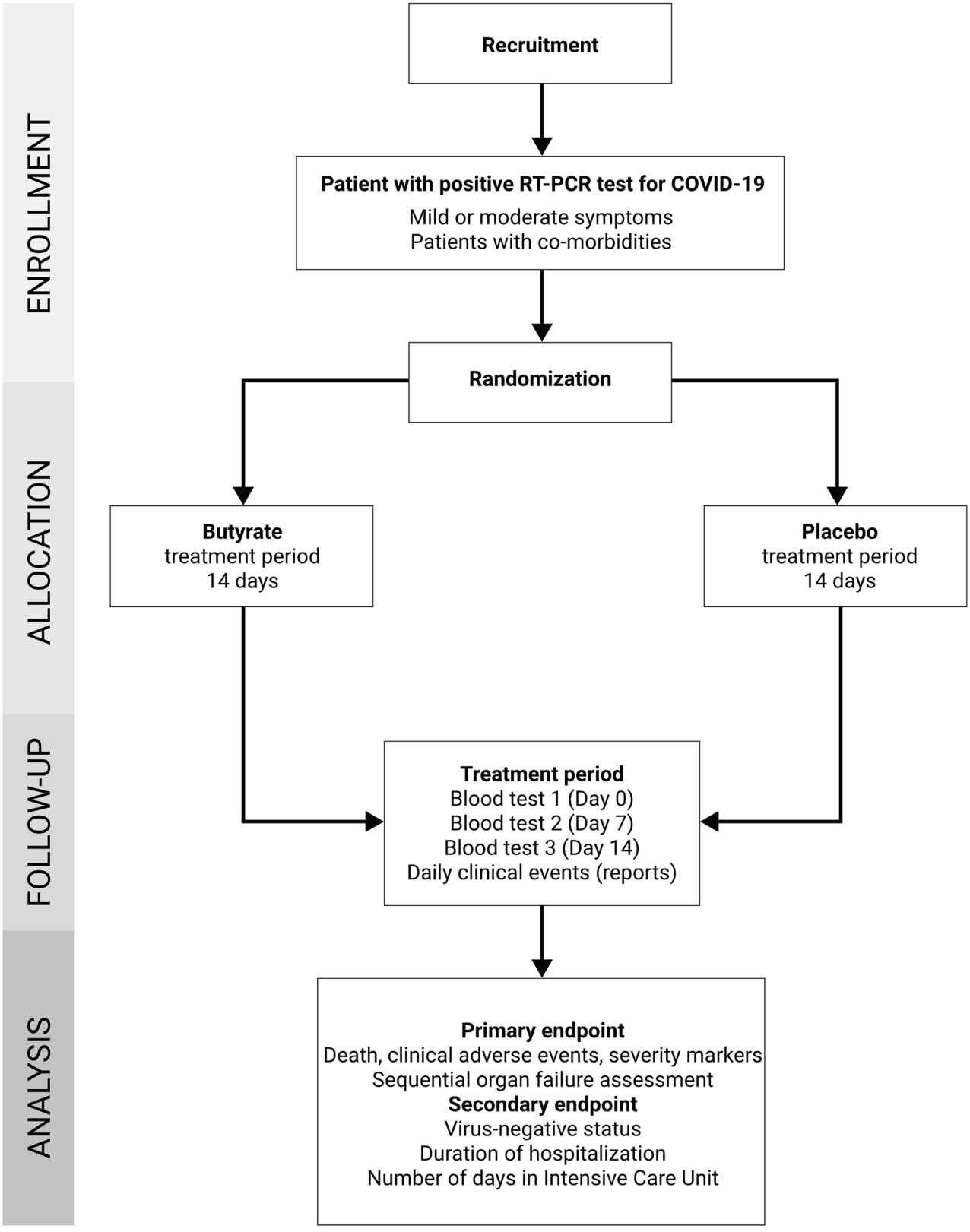

Fig. 3. Flowchart of the proposed clinical trial. This clinical trial will enrol patients positive for COVID-19 (RT-PCR test) at mild to moderate stage who have co-morbidities. After randomization, blood samples will be collected at different endpoints for SCFA profile and cytokine dosage. The primary endpoint could combine clinical adverse events, disease severity markers, sequential organ failure assessment, the need and duration of hospitalization, time until virus negativation or death due to SARS-CoV-2 infection.

inflammatory cytokines (IL-10). Butyrate is also known to limit the thrombo-inflammation phenomenon by activating the tissue-plasminogen activator (t-PA), thus likely to play a role in anti-coagulation COVID-19 strategies (Fig. 1).

Evaluation of the hypothesis

Supportive therapeutic strategy with SCFA

The cytokine storm plays a critical role in COVID-19 pathophysiology depending on macrophage activation. Supplementation with SCFAs and especially butyrate could help to modulate the immune system activation early on. Our idea is to systematically associate SCFAs serum profiling, cytokine dosage and/or M1/M2 macrophages ratio determination in each patient positive for COVID-19 at the early stages of the disease. In face of the absence of validated borderlines of these tests in specific cohort of COVID-19 patients, investigations will be performed according to limits routinely applied for other pathologies. This might help to detect intestinal dysbiosis and identify patients at risk of developing severe immune complications that could benefit from this supportive therapy. In addition to clinical characteristics, these parameters could also serve to elaborate a strong predictive score of COVID-19 progression and to initiate early butyrate supplementation as a supportive treatment in such detected vulnerable patients (Fig. 2).

Preclinical proof-of-concept of butyrate as supportive therapy

Recently, butyrate treatment shows beneficial effects in influenza-induced mice by preventing excessive neutrophil recruitment into the airways [34]. These results have driven the hypothesis that butyrate could serve as a supportive therapy during COVID-19 infection. Preclinical investigations performed with gut epithelial organoids or gastric cell lines have shown down-regulation of SARS-CoV-2 entry genes under butyrate treatment [32,33]. Another level of proof-of-concept could be reached by investigating the effects of butyrate supplementation in a relevant mouse model of SARS-CoV-2 infection. This could be achieved with mice expressing human ACE2 enzyme, inoculated with SARS-CoV-2 that develop ARDS within five days [37].

Clinical trial design

Our hypothesis could be tested through a randomized double-blind prospective trial. This trial would enroll patients tested positive for SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR) and who are at risk of progressing to severe COVID-19 (older patients with confirmed co-morbidities like heart disease, hypertension, chronic respiratory disease, obesity, diabetes). After signing the informed consent, patients would be randomized to either “butyrate” or “placebo” groups. Patients would be proposed either butyrate capsules or placebo on a daily basis and for a fortnight. A remote telehealth monitoring service for clinical events would be performed from diagnosis to the final outcome. This would include the use of validated specific and general health questionnaires to document disease progression. Blood samples would be collected before treatment initiation and at 7 and 14 days after, for SCFA profiles and cytokine dosage. The primary endpoint could be a combined score aggregating clinical adverse events, severity markers, sequential organ failure assessment, the need and duration of hospitalization, time until virus negativation or death due to SARS-CoV-2 infection (Fig. 3).

Conclusion

The cytokine storm acts as a critical factor in the occurrence of severe-to-death patients with COVID-19. This event is mostly defined by the unbalanced increase of circulating pro-inflammatory cytokines, which in turn may lead to multi-organ failure. To counterpoise this phenomenon, we propose an early identification of patients at risk by investigating macrophages polarization. The decision to supplement with butyrate will be made on the basis of SCFA profiles, cytokine dosage and M1/M2 macrophage ratio. SCFAs and mainly butyrate can be considered as pro-resolving mediators due to their already known role in the immune response modulation. It is important to note that pro-resolving mediators have the major advantage of not blocking the initial immune response but rather downregulating the process to resolve inflammation, which is crucial during COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to acknowledge Ms. Karen Poole for manuscript editing and all the INSERM U1248 members for their valuable inputs and discussions during the preparation of this manuscript.

Funding source.

The authors received no specific funding for this work.

Consent statement/Ethical approval

Not required.

References

[1] WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data [Internet]. [cited 2021 Jun 21]. Available from: https://covid19.who.int/.
[2] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181(2):271–280.e8.
[3] Grasselli G, Tonetti T, Protti A, Langer T, Girardis M, Bellani G, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med 2020;8(12):1201–8.
[4] Parasher A. COVID-19: Current understanding of its Pathophysiology, Clinical presentation and Treatment. Postgrad Med J 2021;97(1147):312–20.
[5] McGurnaghan SJ, Weir A, Bishop J, Kennedy S, Blackbourn LAK, McAllister DA, et al. Risks of and risk factors for COVID-19 disease in people with diabetes: a cohort study of the total population of Scotland. Lancet Diabetes Endocrinol 2021;9(2):82–93.
[6] Alizadehsani R, Alizadeh Sani Z, Behjati M, Roshanzamir Z, Hussain S, Abedini N, et al. Risk factors prediction, clinical outcomes, and mortality in COVID-19 patients. J Med Virol 2021;93(4):2307–20.
[7] Piroth L, Cottenet J, Mariet A-S, Bonniaud P, Blot M, Tubert-Bitter P, et al. Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study. Lancet Respir Med. 2021;9(3):251–9.
[8] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475–81.
[9] Conlon A, Ashur C, Washer L, Eagle KA, Hofmann Bowman MA. Impact of the influenza vaccine on COVID-19 infection rates and severity. Am J Infect Control 2021;49(6):694–700.
[10] Catanzaro M, Fagiani F, Racchi M, Corsini E, Govoni S, Lanni C. Immune response in COVID-19: addressing a pharmacological challenge by targeting pathways triggered by SARS-CoV-2. Vol. 5, Signal Transduction and Targeted Therapy. Springer Nature; 2020.
[11] Rendeiro AF, Ravichandran H, Bram Y, Chandar V, Kim J, Meydan C, et al. The spatial landscape of lung pathology during COVID-19 progression Pathophysiology of lungs in patients with COVID-19. Nature 2021;593(7860):564–9.
[12] Ye Q, Wang B, Mao J. The pathogenesis and treatment of the ‘Cytokine Storm’’ in COVID-19’. J Infect 2020;80(6):607–13.
[13] Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science (80-). 2020 Aug 7;369(6504):718–24.
[14] Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020;383(2):120–8.

[15] Scavone C, Brusco S, Bertini M, Sportiello L, Rafaniello C, Zoccoli A, et al. Current pharmacological treatments for COVID-19: What's next? Br J Pharmacol 2020;177(21):4813–24.
[16] Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol 2020;39(7):2085–94.
[17] Sanghai N, Tranmer GK. Taming the cytokine storm: repurposing montelukast for the attenuation and prophylaxis of severe COVID-19 symptoms. Drug Discov Today. 2020;25(12):2076–9.
[18] Atri C, Guerfali F, Laouini D. Role of human macrophage polarization in inflammation during infectious diseases. Int J Mol Sci 2018;19(6):1801. https://doi.org/10.3390/ijms19061801.
[19] Sica A, Mantovani A. Macrophage plasticity and polarization: In vivo veritas. J Clin Invest. 2012;122(3):787–95.
[20] Liu Y-C, Zou X-B, Chai Y-F, Yao Y-M. Macrophage polarization in inflammatory diseases. Int J Biol Sci. 2014;10(5):520–9.
[21] Girodet P-O, Nguyen D, Mancini JD, Hundal M, Zhou X, Israel E, et al. Alternative macrophage activation is increased in asthma. Am J Respir Cell Mol Biol 2016;55(4):467–75.
[22] Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20(6):355–62.
[23] Donati Zeppa S, Agostini D, Piccoli G, Stocchi V, Sestili P. Gut Microbiota Status in COVID-19: An Unrecognized Player? Vol. 10, Frontiers in Cellular and Infection Microbiology. Frontiers Media S.A.; 2020. p. 742.
[24] Yeoh YK, Zuo T, Lui G-Y, Zhang F, Liu Q, Li AYL, et al. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. Gut 2021;70(4):698–706.
[25] Tang L, Gu S, Gong Y, Li Bo, Lu H, Li Q, et al. Clinical Significance of the Correlation between Changes in the Major Intestinal Bacteria Species and COVID-19 Severity. Engineering. 2020;6(10):1178–84.
[26] Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nature Med Nature Res 2021;27(4):601–15.
[27] Sousa LP, Pinho V, Teixeira MM. Harnessing inflammation resolving-based therapeutic agents to treat pulmonary viral infections: what can the future offer to COVID-19? Br J Pharmacol 2020;177(17):3898–904.
[28] Zhang Z, Tang H, Chen P, Xie H, Tao Y. Demystifying the manipulation of host immunity, metabolism, and extraintestinal tumors by the gut microbiome. Signal Transduct Target Ther. 2019;4(1):1–34.
[29] Theiler A, Bärnthaler T, Platzer W, Richtig G, Peinhaupt M, Rittchen S, et al. Butyrate ameliorates allergic airway inflammation by limiting eosinophil trafficking and survival. J Allergy Clin Immunol 2019;144(3):764–76.
[30] He J, Zhang P, Shen L, Niu L, Tan Ya, Chen L, et al. Short-chain fatty acids and their association with signalling pathways in inflammation, glucose and lipid metabolism. Int J Mol Sci 2020;21(17):6356. https://doi.org/10.3390/ijms21176356.
[31] Chang PV, Hao L, Offermanns S, Medzhitov R. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. Proc Natl Acad Sci U S A. 2014;111(6):2247–52.
[32] Li J, Richards EM, Handberg EM, Pepine CJ, Raizada MK. Butyrate regulates COVID-19-relevant genes in gut epithelial organoids from normotensive rats. Hypertension 2021;77(2). https://doi.org/10.1161/HYPERTENSIONAHA.120.16647.
[33] Takahashi Y, Hayakawa A, Sano R, Fukuda H, Harada M, Kubo R, et al. Histone deacetylase inhibitors suppress ACE2 and ABO simultaneously, suggesting a preventive potential against COVID-19. Sci Rep 2021;11(1). https://doi.org/10.1038/s41598-021-82970-2.
[34] Trompette A, Gollwitzer ES, Pattaroni C, Lopez-Mejia IC, Riva E, Pernot J, et al. Dietary fiber confers protection against flu by shaping Ly6c− patrolling monocyte hematopoiesis and CD8+ T cell metabolism. Immunity 2018;48(5):992–1005.e8.
[35] Ji J, Shu D, Zheng M, Wang J, Luo C, Wang Y, et al. Microbial metabolite butyrate facilitates M2 macrophage polarization and function. Sci Rep 2016;6(1). https://doi.org/10.1038/srep24838.
[36] Dang AT, Marsland BJ. Microbes, metabolites, and the gut–lung axis. Mucosal Immunol 2019;12(4):843–50.
[37] Hong W, Yang J, Bi Z, He C, Lei H, Yu W, et al. A mouse model for SARS-CoV-2-induced acute respiratory distress syndrome. Signal Transduct Target Ther. 2021;6(1). https://doi.org/10.1038/s41392-020-00451-w.