

NARRATIVE REVIEW

A New Perspective on Covid-19 Treatment: When a Paradigm Changes in Infectiology Become Necessary against an Emerging Virus as the SARS-Cov2

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Abstract: Background & Aims: The covid19 is a world changing challenge. Furthermore, this disease challenges our capacities to change our point of view in the domain of infectiology, immunology and global public health. Many trials try some drug such as antiviral (lopinavir, remdesivir) interferon, and the chloroquine. Unfortunately, all approach is not really convincing at this time. We are proposing another approach on this issue. In infectiology there are two protagonists: the host and its immune system versus pathogens and its virulence. Our approach focuses on an intervention on the host's immune system and how stimulate and modulate its reactions. Methods: We searched on PubMed and Google Scholar databases for French and English-language studies, without a limit of date of publications, for randomized clinical trials, meta-analyses, reviews, systematic reviews, observational studies, case report. We performed a review on the field of immunology enhancements by nutrients use. Results: We identified groups of vitamins (D and C), oligo-elements (magnesium, zinc, selenium) and nutrition advice which enhance immune system response. Indeed, these supplements have some proved properties in modulating and stimulating the immune system. For example, a recent study demonstrates that vitamin D deficiency is linked with the severity of covid19. Majority of the population has a deficiency in these elements. According to this, we propose a therapeutic protocol using these elements to reach an efficient therapy against covid19 by enhancing host's immune system. Conclusion: Due to this serious pandemic, any solutions must not be disregarded. The nutrition way is an entire part of the solution.

Keywords: covid19; immunostimulant; immunomodulator; vitamin D; vitamin C; zinc

1. Introduction

Since December 2019, a cluster of unknown pneumonia disease appears in Wuhan caused by a new coronavirus: the SARS-COV-2 [1-2-3]. Then March 11, 2020, the general director of world health organisation (WHO) declare the pandemic of covid19[4].

Since Louis Pasteur's findings on micro-organisms[5] and Alexander Fleming[6] with his discovery of penicillin in the eighteen centuries; the infectiology principle does not change a lot. Indeed, the main strategy in infectiology is to identify pathogens and to fight them with drugs. Another strategy used is to train immune system with vaccination to avoid the expansion of

infection[7]. Therefore many trial starts to find an efficient therapeutic against covid19 [8-9] using some molecules: Remdesivir, Lopinavir/Ritonavir Lopinavir/Ritonavir plus interferon β -1a, Hydroxychloroquine. All trials[10], while promising, have not yet proved their effectiveness.

We propose a new therapeutic approach, a new paradigm in the field of infectiology face to sars-cov-2. The host immune system and virulence of the pathogen are the two competing elements in infectiology. Face to sars-cov-2, we noticed that all solutions respecting this principle have remained unsuccessful for the moment. Why not take the opposite way and focus our actions on the host's immune system to win the fight? Why not stimulate and modulate the immune system's response to make it more effective against sars-cov-2. Mostly, we know that the main complication of the disease is related to the development of a thrombogenic pro-inflammatory ground [11-12] and the cytokine storm[13]. These complications are all related to dysfunction of the immune system. For this reason, it seemed logic to focus research on the stimulation and modulation of the immune system to avoid this disaster. Good nutrition, vitamins and oligo-elements play an important role in immune system enhancement[14].

2. Materials and Methods

We searched on PubMed and Google Scholar databases for French and English-language studies, without a limit of date of publications, for randomized clinical trials (RCT), meta-analyses, reviews, systematic reviews, observational studies, case report. A first look with the terms: immunity, immune system, immuno-stimulant, immune-modulator, a second look with the terms: immune system AND (vitamin C OR vitamin D OR zinc OR selenium OR nutrition); then a third look with the terms: covid19 AND (vitamin C OR vitamin D OR zinc OR selenium OR nutrition). Emphasis was given to more recent RCT, systematic reviews and meta-analyses.

3. Results

3.1. Influence of latitude and climate

Many studies were interested in the repartition of respiratory virus outbreak in the world[15-16]. The epidemics of this virus seem to respect a certain latitude [17-18] and seasonality around the world. Indeed, we remark that influenza and coronavirus outbreak occurs, in north hemisphere at winter[16]. In tropical areas it seems that outbreak occurs when it is humid-rainy condition during rainy season [19]. The peak is less important than temperate one[18]. This demonstrates that the environment plays an important role in the outbreak and spread of this kind of disease. Therefore, we need to be aware of an upsurge of covid19 spread in tropical areas as rainy season approach towards June –July. According to the precedent SARS-CoV outbreak[16], which occur in winter, it is possible think that this SARS-CoV-2 will have the same seasonality.

Studies show that seasons play a certain role in the virulence of the virus and host immunity[16]. Indeed, the temperature and humidity of air breathing can accelerate the replication of the virus in airway. Furthermore, the climate plays a role on host innate immunity in decrease phagocytose and maturation of macrophage granulocyte monocyte according to daylight period and vitamin D(VD) rate[16-20]. Thus, we see that southern people have a lower mortality level from covid19 because to their level of VD[21].

3.2. Immunostimulant and immunomodulation therapy

3.2.1. Role of vitamin D

The classical role of VD is known in phosphor-calcic homoeostasis and bone turnover[22]. VD is brought to the body, 20% by diet intake and 80% skin synthesis; then is transformed to its biological active form in 25(OH)D3 by enzymes cytochrome P450 2R1 and P450 27 into liver[23-24]. Then the fully active metabolite 1,25(OH)D3 is hydroxylate in the kidney by the enzyme CYP27B1[25]. However, CYP27B1 is expressed by other cells as immune system cells, and the activity of CYP27B1 is controlled by inflammatory signals, such as lipopolysaccharide cytokines, unlike kidneys.

A consensus of experts proposes a rate between 20 to 125nM/L to avoid skeletal complications, without toxic effect[23-25]. Moreover, the mortality related to 25(OH)D3 follows a "u shaped curve", and level more than 150nM/L of 25(OH)D3 are associated with increase of mortality for patients pre-hospitalised[26].

The level of 1,25(OH)2D3 increase the microbial activity of macrophage and monocyte keratinocytes[25]. Moreover, 1,25(OH)2D3 increase chemotaxis, autophagy, and phagolysosomal fusion of innate immune cells[25]. VD also has a role on adaptive immune system by suppressing its activity and down regulate the production of pro-inflammatory cytokines such interferon-gamma, IL-6, IL-2 and TNF-alpha[25-27]. So a trial testing high dose of VD in tuberculosis treatment shows that it accelerates resolution of inflammatory responses[28].

The whole challenge here is to find the type of VD and the right level of supplementation to achieve the desired effects without toxicity. A high dose of VD 250,000 or 500,000 UI trial in critical care unit ventilated patients with a low rate of VD, reduce hospital length of stay from 36+/-19 days in control group, 25+/-14 days in the 250,000 UI group(25(OH)D=45+/- 20 ng/ml), 18+/-11 days in the 500,000 UI group (25(OH)D= 55+/- 14ng/ml) [29]. An observational study shows that the rate of 38 ng/ml of VD is needed to reduce the risk of community acute pneumonia. The good rate seems to be between 40-60 ng/ml to have an immune-modulation action [30].

Fortunately, VD appears its toxicity for serum levels in 25-OH VD up to 150 ng/ml[31-32]. However, attention should be paid to possible signs of VD toxicity, such as dehydration, neurological disorders including behavioural disorders and hypercalcaemia in biology.

To achieve the correct rate upper than 50-60ng/ml we can use a high dose bolus or a daily intake. A daily intake between 400-1000 UI for infants, 600-4000 UI for children, 1500-10,000 UI for adults, pregnant and lactation [33]. A bolus of 100000 UI is also possible in children[34]. In adulthood a bolus is possible by 200,000 to 500,000 UI [30]. Some study shows that the supplementation of magnesium is need to potentialized the effect of VD and maintain the rate VD in a normal range, because of its role in numerous enzyme reaction[35-36]. A supplementation of magnesium with organic salt as magnesium citrate, gluconate or aspartate at the posology of 5 mg/kg/day is necessary to improve VD function [37].

3.2.2. Role of vitamin C

Known as an anti-scurvy drug, nowadays, vitamin C(VC) is known to play many functions in organism, like its role in immune system[38-39]. Indeed, many trials tested VC in common cold , show some benefit in healing against infection[38-40-41]. The action of innate, adaptative immune and antibody response is directly correlated with the blood level of VC[42]. The lymphocyte proliferation and activation are enhanced with VC supplementation. VC is accumulated in neutrophils, many trials assessed that neutrophil's chemotaxis, phagocytosis, oxidative burst activity is enhance according with the level of VC [43-44]. VC has a epigenetic property on immune cells, as dendritic cells, monocyte/macrophages, T-cells, NK cells, in modulate maturation, life duration of cell, modulate inflammation mediator[45]. VC application diminishes the secretion of pro-inflammatory cytokines such as IL-6 and tumor necrosis factor alpha. An oral supplementation increase serum immunoglobulin levels in elderly[46]. Due to this effect on immune system, VC is more and more use for this purpose. In critical care, high dose of VC infusion enhance recovery of inpatient[47]. Indeed, critical ill patients see their VC amount decrease very low, and a correct supplementation is needed to enhance immune system function [48]. In a similar situation, VC supplementation show benefit in winter illness, demonstrate again a function in immune system[49]. In covid19 physiopathology, we assist to a cytokine storm, that is a dysregulation of immune system function. The seriousness of the situation is an acute respiratory distress syndrome. Many studies show that VC high dose diminishes the cytokine storm, enhance the function of immune cells, have a pro-inflammatory action and direct antiviral properties[50]. And this function can use to fight covid19 with great change of success[51]. Richard Z. Cheng have the same hypothesis in high VC use against covid19, showing that an early and adequate dose of infusion of VC, can mitigate mortality and morbidity of covid19[52]. So, on covid19, we can see new trial using high-dose VC with 24 g/day

infusion for 7 days [53]. Here, the problem to resolve before use VC is the route and doses administration. Indeed, bioavailability of VC in oral route versus parenteral route is different[54]. Oral administration of VC about 1,25g produce a plasma peak concentration at 134,8 +/-20,6 μ mol/l contrarily with a plasma peak at 885+/- 201,2 μ mol/l with the same dose administered by intravenous route. The maximal oral route doses is 3 g every 4 hours according to gastroenteric side effect, and the maximal save dose with intravenous route is 1,5g/kg/day[54]. This different between both routes are explained by saturable active transport of VC in intestinal absorption and renal reuptake[55]. The need of VC increases with aggression such infection, smoking or cancer. But we do not know which level of supplementation achieve in viral infection case such as sars-cov-2. According to half-life and clearance of VC in intravenous route , which is 2+/-0,6h and 21+/- 5 dl/h m² [55] , maximal concentration is raised to 50 mM for dose between 70-80g/m² to continue infusion[56]. Then a national institute of health expert panel state that high-dose VC at 1,5g/kg/day is saved in person without chronic renal disease and Glucose-6-PhosphateDehydrogenase (G6PD) deficiency[57]. When use high dose of VC , we have to be aware of some issue as oxalate nephropathy, pro-oxidative activity of VC and G6PD deficiency which can lead a red cell haemolysis[58]. Fortunately, these advert effects are rare[59-60]. In more, a synergism is found, in administration of VC, with thiamine and hydrocortisone, due to some metabolism interaction[59]. An association of VC and zinc relieve common cold symptoms and duration[41].

3.2.3. Role of Zinc

Zinc is a rare element, that is essential for human metabolism, and this observation was found since 1963[61]. More than 300 enzymes and more than 2000 transcription factors require zinc to function well[61-62]. We know that zinc play too, an important role in immune system[63]. Zinc have an inflammatory, antioxidant and antiviral properties[61-64-65].Intracellular free zinc deficiency mitigate of lipopolysaccharide-mediated CD4+ T-cell activation by dendritic cells[61-66]. Zinc deficiency contribute to increase nuclear factor-kappa B, which increases TNF-alpha and IL-1B[64-65]. The development of monocyte/macrophages and their function in phagocytosis, proinflammatory cytokine production is dependent on zinc levels in the organism[67]. Zinc has affected the development of both innate and acquired immune system. Lymphocyte activation, antibody production , intracellular killing and apoptosis of immune cells is affected by zinc deficiency[66-68]. Zinc has a direct action on virus, such as influenza and coronavirus, perhaps through inhibition of RNA-dependent RNA polymerase[69]. It interacts with interferon-lambda3 binding to IFNL receptor 1 on HCV and influenza[70]. So, zinc improves the immune system and has a direct antiviral action on many viruses whose coronavirus. Zinc has demonstrated its action in common cold by reducing the duration of symptoms with a dose up to 75 mg/day[71]. A zinc supplementation trial in elderly decrease the incidence of infection by 66% and improve cell-mediated immunity[62]. Many studies propose to add zinc in protocol against covid19, according to its action on immune system[72-73-74]. A supplementation of 30 mg per day zinc element in infants(2-60 months) reduces duration of acute lower respiratory tract infections[75]. A metanalyse shows that dose under 75 mg per day of zinc acetate (22,5mg zinc element) have no effect on duration of common cold , but a dose upper 75 mg produces 42% of reduction in duration of common cold[76]. A chronic supplementation of zinc and dose upper than 60-100mg of zinc element per day can produce some side effect and toxicity by diminishing level of copper and decrease activity of immune system[77].

3.2.4. Role of selenium

Selenium is a rare element, but very important compound in the organism, because of its role in multiple reaction in metabolism[78]. Selenium is a cofactor of many enzymes such as glutathione peroxidase or thioredoxin reductase and exerts its functions linked with protein forming selenoprotein[79]. The ideal range of selenium in plasma, according to a U shaped, is 80-120 μ g/l[80]. The selenium has an antioxidant and immune properties[81]. It increases activity of macrophages, production of immunoglobulins, cytolysis of natural killer. The selenium in adequate levels can

reduce inflammation by lowered expression of pro-inflammatory mediators, including cytokines, redox-sensitive transcription factor NF-kappa B, increase interferon-gamma production[82-83-84]. Furthermore, selenium acts directly in immune system by initiating well function of immunity, regulate excessive immune responses. Supplementing volunteers with 50-100 μ g/d increased anti-poliovirus and anti-diphtheria immunity[78]. A selenium deficiency under 1 μ M/l increase virulence of viruses such as coxsackievirus and decrease immunocompetence of host[79-85-86]. The minimum requirement of selenium according to American recommended dietary allowance is 70 μ g and 50 μ g per day respectively for men and women[85], for children a mean of 20-50 μ g/day[78]. Upper dose tolerate in supplementation is 400 μ g/day[87]. Then, studies demonstrate that supplementation at 200 μ g/day, is safe and can be used as adjuvant therapy again virus such as HIV, influenza type A[82-86-88]. A recent trial show in China an association between selenium deficiency and covid19 cure rate[89]. Toxicity with this element is very rare in recommend supplementation[78]. Selenium excess can be eliminated by urine[90]. But in case of acute poisoning, we can find early symptoms: hypotension, tachycardia, dermatological lesions, hair loss, odour of garlic in the exhaled breath, anaemia , dry cough[81].

3.2.5. Role of diet nutrition

More and more, nutrition takes a great place in the field of human health. Nutrition is not only a means to feed, but means to heal too. Nowadays nutrition plays a role in many health problems and it has a link between host's immune system and macro and micronutrient deficiency[91]. "Malnutrition is the primary cause of immunodeficiency worldwide" affecting both innate and adaptative immune system[92]. Furthermore western diet affects immune system and correlate with an epidemic inflammatory diseases[93]. Western diet, with its high level of saturated fatty acids, can lead to chronic activation of the innate immune system and inhibition of the adaptative immune system[94].

When immune system is activated, it needs a great level of energy and micronutrients to be functional, for example: fever[95]. Malnutrition impacts the performance of the immune system such as enzyme reaction and immune cell activity. In the way of caloric restriction, it demonstrates that reducing age-associated elevation in cytokines to levels comparable to that of young , and increase concentrations of anti-inflammatory in animals, enhance immune functions[96].

In elderly, protein energy malnutrition decreased immune functions and a refeeding can enhance immunity, but more slowly in inflammatory processes such as infection[97].

We found that the immune system needs macro and micronutrients function well, including vitamins A,D,C,E,B6 and B12, folate, zinc, iron, copper, and selenium [14]. Especially VC and D and zinc have the strongest evidence for immune support[82].

So, a nutritional and dietetics approach must be done to avoid any deficiency in micro and macronutrients. A screening of patients must be done to identify malnutrition risk people to bring them an adequate nutrition supply. This supply must bring 1,5g/kg/day amino-acid including essential ones, energy 40 kcal/kg/day, vitamins, unsaturated fat and trace elements support[98].

4. Discussion

The emergency of the current situation requires us to propose effective, and easy solutions to eradicate the pandemic worldwide at a lower cost. We believe that, the administration of immunostimulant and immunomodulator therapies, at a very early stage, can stop the spread of this covid19 pandemic and its medical consequences. Our therapeutic proposal is resumed, in table 1, by administration of VD and VC, magnesium, zinc, selenium, nutrition care approach; in specific dosage. To achieve this goal, we propose 2 therapeutics protocols for different intervention groups: a preventive and a curative one. Of course, this treatment protocol does not contraindicate or interferes with a standard care management. It must be used together, for any exposed person to sars-cov-2, suspected or confirmed covid19 patient.

A preventive intervention group whose aim is to prevent the spread of the disease or occurrence of any asymptomatic forms. This intervention will be given to non-infected people, but potentially exposed people. It is easy to apply on a large scale, with a simple medical monitoring.

A curative intervention group whose aim is to avoid the complication of the disease: embolism, respiratory failure, intensive care supply, death; into infected or suspected people.

Table 1. therapeutic proposition.

Preventive intervention group	Curative intervention group		Monitoring
	No-intensive care needed and gravity score under 5[99]	Intensive care needed or gravity score superior or equal 5[99]	
	Curative protocol	Intensive curative protocol	
Vitamin D protocol: Children up to 16-year-old and adult	Two boluses of 200,000UI per os separated from 48 hours, control serum rate to achieve 50 ng/ml minimum if possible. Then a daily dose of 4000 UI/day until the end of pandemic	200,000UI per os every 48 hours with serum rate control with a targets 50-60ng/ml. Then a daily administration of 4000 UI/day	Bolus of 500,000 IU before serum rate control. Serum control at 48 hours, if rate under 50 ng/ml, bolus administration of 200,000UI every 48 hours until a serum 50-60ng/ml. Then a daily administration of 4000 UI/day
Vitamin D protocol: Infant in children under 16-year-old	Only a daily dose of 1000 UI/day until the end of pandemic, control serum rate to achieve 50 ng/ml minimum if possible	Two boluses of 100,000UI per os separated from 48 hours, control serum rate to achieve 50 ng/ml. Then a daily dose of 2000 UI/day until recovery	bolus of 200,000 IU before serum rate control. Serum control at 48 hours, if rate under 50 ng/ml, bolus administration of 100,000UI every 48 hours until a serum 50-60ng/ml. Then a daily administration of 2000 UI/day
Magnesium supplementation	5 mg/kg/day during all the intervention	Idem	idem
Vitamin C protocol: Children up to 16-year-old and adult	3 g per os every 6 hours. the dose may be reduced to 2 g per intake in case of gastric discomfort	continuous intravenous infusion with 0,5g/kg/day	Continuous intravenous infusion with 1,5g/kg/day
Vitamin C protocol: Infant in children under 16-year-old	0,5g/kg/day taken 4 times a day, without exceeding 3 g by taken. dose may be reduced in case of gastric discomfort	continuous intravenous infusion with 0,5g/kg/day	Continuous intravenous infusion with 1,5g/kg/day
Zinc element supplementation: In paediatric and adult population	30 mg per os	Idem	idem

Selenium supplementation: Children up to 16-year-old and adult	200µg/day	Idem	idem	hypotension, tachycardia, dermatological lesions, hair loss, odour of garlic in the exhaled breath, anaemia, dry cough
Selenium supplementation: Infant in children under 16-year-old	100µg/day	Idem	idem	
nutrition care	an adequate nutrition supply with 1,5g/kg/day amino-acid including essential ones, energy 40 kcal/kg/day, vitamins, unsaturated fat and trace elements	Idem	idem	

Decryption of nutrients and posology in the aim to enhance the immun system.

5. Conclusions

The spread of the covid19 pandemic will lead to a review of our health systems organisation, our way of thinking, but also of the way we deal with emerging new pathogens. Considering the seriousness of the situation, any research leads should not be discarded. Our point of view, although off the beaten track, is very promising and hopeful. It deserves its place in a clinical trial such as other approaches already tested.

Conflicts of Interest: The authors declare no conflict of interest.

Authors' contribution: Louis Sylvain Peng-wende Ouedraogo contributed to the conception, and design of the research, acquisition and analysis of the data; Louis Sylvain Peng-wende Ouedraogo, Sodjehoun Apeti, Dieudonné Ouedraogo equally contributed to the interpretation of the data; Louis Sylvain Peng-wende Ouedraogo and Sodjehoun Apeti drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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