

REVIEW

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Dexamethasone and Nutraceutical Therapy Can Reduce the Myalgia Due to COVID-19 – a Systemic Review of the Active Substances that Can Reduce the Expression of Interlukin-6

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ABSTRACT

Background: Myalgia reflects generalized inflammation and cytokine response and can be the onset symptom of 36% of patients with COVID-19. Interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) levels in plasma and upper respiratory secretions directly correlate with the magnitude of viral replication, fever, and respiratory and systemic symptoms, including musculoskeletal clinical manifestations. **Objective:** The aim of our work is to report literature scientific investigation clinical protocol to reduce the immunomodulation and inflammatory response nutraceutical therapy associated with dexamethasone and how can reduce the expression of Interlukina-6(IL-6) and myalgia due to COVID-19.

Methods: We searched in Pubmed and Cochrane the nutraceutical drugs to treat the immune modulation of organism to COVID-19. We put these keywords: immune inflammation, disease descriptions, epidemiology COVID-19; immunomodulations; IL-6; Rheumatic Symptoms; Joint; Musculoskeletal Disorders; dexamethasone; Polydatin; Zinc; Melatonin; N-Acetyl Cysteine; Colostrum; L-Glutamine; Vitamin D3. **Results:** We found 61 papers. All the authors analyze them. After the Analyze we suggest the use of response nutraceutical therapy associated with dexamethasone can reduce the expression of Interlukina-6(IL-6) and myalgia due to COVID-19. **Conclusion:** According the scientific literature nutraceutical therapy associated with dexamethasone can reduce the expression of Interlukina-6(IL-6) and myalgia due to COVID-19.

Keywords: COVID-19, cytokine storm, joint pain, musculoskeletal pain, fatigue, long covid, covid long haul, nutraceutical factors, dexamethasone, um-PEA, polydatin, melatonin, colostrum freeze drying, vitamin D3, N-acetyl cysteine, L-Glutamine, zinc.

1. BACKGROUND

The outbreak of covid-19 in Italy officially started on 31 January 2020, after two Chinese visitors staying at a central hotel in Rome tested positive for the new coronavirus SARS-CoV-2. They had landed at Milan Malpensa airport on a flight from Wuhan on 23 January (1). Italy at the date of 12 December 2020 recorded 63.387 deaths due to this COVID-19 outbreak. Myalgia is a common symptom in patients with viral infections such as novel coronavirus disease 2019 (COVID-19) and influenza. Myalgia reflects generalized inflammation and cytokine response and can be the onset symptom of 36% of patients with COVID-19 (2). Interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) levels in plasma and upper respiratory secretions directly correlate with the magnitude of viral replication, fever, and respiratory and systemic symptoms, including musculoskeletal clinical manifestations (3). Indomethacin has a potent antiviral activity against SARS coronavirus (4) but trails are still in progress. Since nowadays no scientific evidence establishes a correlation between NSAIDs or Cox-2 and the worsening of COVID-19, patients should be advised against any NSAIDs self-medication when COVID-19 like symptoms begins (5). The use of dexamethasone was based on the severity of respiratory symptoms or in myalgia problems (2-6).

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2. OBJECTIVES

The aim of our work was: A) to report our literature scientific investigation clinical protocol to reduce the immunomodulation and inflammatory response nutraceutical therapy associated with dexamethasone can reduce the expression of Interlukina-6(IL-6) and myalgia due to Covid-19; b) to try to control this dysregulated immune response through the protocol and therefore reduce musculoskeletal symptoms in Covid-19 infection; c) to review of nutraceutical therapy as I Vir protocol (Micronized palmitoylethanolamide 400mg + transpolydatin 40mg, Ultra-micronized Palmitoylethanolamide 200mg 1cp/die; zinc 50mg 1 cp/die; L- Glutamine 3 gr; Melatonin 4 mg 1cp/die; N-acetylcysteine 600mg 2cp/die; colostrum 500mg 1 cp/die; Vitamin D 25.000 UI 1 week) associated with dexamethasone can reduce the expression of Interlukina-6(IL-6) and myalgia due to Covid-19.

3. MATERIALS AND METHODS

A systematic computer search of EMBASE, PubMed and Cochrane for literature related to the Covid 19: immune inflammation, disease descriptions, epidemiology Covid-19; immunomodulations; IL-6; Rheumatic Symptoms; Joint; Musculoskeletal Disorders; dexamethasone; Polydatin; Zinc; Melatonin; N- Acetyl Cysteine; Colostrum; L- Glutamine; Vitamin D3.

The eligibility criteria for literature was determined before the search by the authors. Inclusion criteria specified both retrospective and prospective studies, case reports, case series and randomized controlled trials. Studies were included if they were conducted on human subjects or in laboratory.

The three authors reviewers completed the title, abstract and full-text screening assessing for study inclusion, and any discrepancies were resolved by discussion. A third party was involved if there was no mutual agreement.

The extracted evidence was collected and analyzed with Microsoft Excel 2007 (Microsoft Corporation, Redmond, Washington). Statistical analyses focused on descriptive statistics.

4. RESULTS AND DISCUSSION

A total of 423 articles were identified in the original search. After the removal of duplicates between databases, a total of 213 records were identified for title screening. After the exclusion of 158 papers based on title, 123 records remained for abstract screening, of which 61 full texts were deemed relevant based on the inclusion and exclusion criteria.

Coronaviruses are a large group of single-stranded RNA viruses so called for their "crown" shape at electron microscope. They cause various diseases involving respiratory, enteric, hepatic and neurological systems, with widely different clinical presentations between humans and animals (7-9). They are responsible for respiratory infections in humans.

At the end of December 2019, in Wuhan, in the province of Hubei, in China, numerous cases of an unknown

pneumonia began to occur, which initially was therefore called pneumonia of unknown. The outbreak initially spread uncontrollably until the causative agent was identified, which is a new coronavirus.

From a clinical point of view, Covid-19 infection varies from totally asymptomatic forms to forms characterized by severe respiratory failure. The main symptoms include fever, fatigue, myalgia, anosmia and ageusia (10, 11). Less frequent symptoms are diarrhea and hemoptysis.

Regarding the age of the affected patients, the average age is between 49 and 59 years; cases in children under 15 are rare, and more than half of the patients are male (12, 13).

Almost half of the diagnosed cases had associated conditions such as diabetes, cardiovascular disease and hypertension (12-14).

In clinically severe cases there is a worsening of the symptoms approximately 8 days after the onset of symptoms and after about 10.5 days there is a need to enter intensive care.

Leukopenia and lymphopenia are typical laboratory results. Being lymphopenia especially characteristic of Covid-19 infection. In around half of the cases there is an elevation of the GOT and GPT; lactic dehydrogenase and creatine kinase are usually elevated, as is reactive protein C. An increase in D-Dimer is present in approximately 30% of patients (12, 13). D'Silva et al (15) mentioned that patients with and without rheumatic disease had similar symptoms and laboratory findings, but those with rheumatic disease were more likely to require mechanical ventilation.

Significantly elevated blood levels of cytokines and chemokines have been observed in infected patients including: IL1- β , IL-17, IL8, IL9, IL10, FGF2, GCSF, GMCSF, IFN γ , MCP1, MIP1 α , PDGFB, TNF α and VEGFA.

It has been reported an elevation of IL 6 in patients that need hospitalization, and that increase of IL 6 is related to bad prognosis. Most severe cases requiring ICU admission showed elevated levels of pro-inflammatory cytokines including IL2, IL7, IL-17, IL10, and TNF α and therefore are thought to be the main factors promoting the severity of the disease (16). Based on this information, we thought about developing a protocol that could reduce the risks of COVID-19 infection or, in the case of contagion, modulate the inflammatory response in order to develop a milder course of infection.

POLYDATIN, PEA

Polydatin (resveratrol-3-Ob-mono-D-glucoside) is a natural glycosylated precursor of resveratrol, it represents the most abundant form of resveratrol in nature and it is found in grape juice and in the root of the *Polygonum cuspidatum* plant. Chemically it derives from stilbene, which has shown antioxidant and anti-inflammatory properties and a neuro, nefro and hepatoprotective role. The antioxidant properties of polydatin depend on the fact that it inhibits lipoperoxidation and is also capable of sequestering free radicals such as 2,2-diphenyl-1-picrilhydracil (DPPH). Various studies suggest

that polydatin may have biomedical properties similar to those described in resveratrol: anticancer, inhibition of platelet aggregation and inhibition of oxidation of low density lipoproteins (LDL) (17, 18). A study carried out on peripheral blood mononuclear cells has shown that polydatin decreases the production of IL-17 as well as oxygen free radicals (19, 20).

In another 2017 study, resveratrol significantly inhibited MERS-CoV infection and also decreased the expression of the nucleocapsid (N) protein essential for MERS-CoV replication. In addition, resveratrol down-regulated MERS-CoV-induced apoptosis *in vitro* (21).

Also in the same study, the authors tested the effect of resveratrol in another emerging positive-sense RNA virus, the chikungunya virus. Resveratrol has been shown not only to inhibit viral production of MERS-CoV, but also to reduce the production of the chikungunya virus at concentrations of 250 and 125 μ M. Therefore the study authors suggest that resveratrol may have antiviral activity for MERS-CoV and other emerging RNA viruses. In another study of 2006, the authors showed *in vitro* on cells that the SARS virus was completely inhibited by stilbene derivatives (22).

As regards PEA, on the other hand, it has been shown to have a high neuroprotective effect, reducing the infiltration of neutrophils at the level of the nervous system, the expression of pro-inflammatory cytokines and iNOS and through the activation of NF - κ B (23, 24) . It has also been seen that the association of PEA with other oral antioxidants (especially polydatin) increases its effectiveness, especially when micronized/ultramicro-nized . Likewise, PEA also exhibits high security, as recently reported by Nestmann et al (25).

One of the main symptoms of Covid-19 infection is respiratory distress and neurological symptoms such as headache, nausea and vomiting are often present. It has been seen that in the case of SARS-CoV the infection was present in the brain especially at the level of the brain stem. In Covid-19 typical symptoms are anosmia and ageusia, which might mean an involvement of the nerve fibers. Therefore, neuroprotection can represent a useful element in the prophylaxis of severe forms of infection (22).

Furthermore Food and Drug Administration (FDA) from may 2020 has given the company permission to submit an Investigational New Drug Application (IND) for the use ultramicro-nized palmitoylethanolamide, um-PEA) to treat COVID-19, the disease caused by the SARS-CoV-2 virus.

ZINC

As far as zinc supplementation is concerned, increasing the intracellular concentration of Zn (2+) with zinc ionophores such as pyrithione (PT) can very effectively alter the replication of numerous RNA viruses, including poliovirus and influenza virus (27).

Zinc deficiency increases production of proinflammatory cytokines such as IL-1 β , IL-6, and tumor necrosis factor (TNF) - α , while its supplementation is able to downregulate inflammatory cytokines by decreasing the gene expression of IL-1 β and TNF- α through the upreg-

ulation of mRNA and specific binding of DNA for A20, subsequently inhibiting the activation of NF- κ B (28).

At the level of the pulmonary epithelium cell adhesion proteins are directly responsible for the formation of the mechanical barrier. It has been seen that an increase in inflammatory cytokines, in combination with zinc deprivation, would induce caspase-3, leading to the degradation of junction proteins, loss of cell-cell contact and impaired barrier function of the pulmonary epithelium (29).

MELATONIN

Melatonin (N-acetyl-5-methoxytryptamine) (MEL) is a neurohormone secreted by the pineal gland following a circadian rhythm with peak concentrations at night.

An increasing daily number of studies highlights the fundamental role of melatonin in regulating circadian rhythms (30-32). In addition, melatonin has a very important function in numerous pathophysiological processes, including the defense against viral infections and the modulation of the immune response. Finally, melatonin plays an important role in antioxidant and neuroprotective processes (28). Carrillo-Vico in a 2013 study defines melatonin as an immune buffer, which acts as a stimulant in basal or immunosuppressive conditions and as an anti-inflammatory compound in the presence of exacerbated immune responses, such as acute inflammation (33).

Melatonin reduces neutrophil infiltration and levels of inflammatory mediators during pulmonary inflammatory processes and airway hyperreactivity. Melatonin and its derivate AFMX also suppress the production of IL-8, a chemotactic factor of neutrophils, in lung fibroblasts. human and peripheral blood neutrophils activated by LPS (34). Additionally *in vitro* melatonin neutralizes the excessive production of pro-inflammatory mediators, especially cytokines, including TNF- α , IL-1 β , IL-6, IL-8 and IL-10 (35).

N ACETYL CYSTEINE

Acetylcysteine is an N-acetylated derivative of cysteine; when administered orally it is deacetylated to cysteine, with a consequent increase in the concentration of glutathione reduced in the plasma and in the respiratory tract (36, 37). High levels of pro-inflammatory cytokines have been reported in patients with influenza A virus infection (H1N1, H7N9 and H5N1) (38). These cytokines can be caused by viral infection (primary cytokines) or immune response (secondary cytokines). This high level of inflammatory cytokines is often called "cytokine storm" or "cytokine dysregulation" (39). NAC has been shown to inhibit the production of pro-inflammatory molecules in highly pathogenic influenza A virus (H5N1) infected epithelial lung cells and inhibit the synthesis of mucins and pro-inflammatory mediators in type II alveolar epithelial cells infected with flu viruses A and B (40). The influenza virus induces reactive oxygen species that activate the nuclear factor κ B resulting in hyperproduction of cytokines. High-dose N-acetylcysteine (600 mg 2 times / day) reduces this cytokine storm and therefore alleviates the symptoms of influenza in elderly patients with chronic degenerative diseases (41).

COLOSTRUM

Vaccine colostrum is a brownish-colored liquid, which mainly contains immunoglobulins, growth factors, immunoregulators and immunologically active substances among which Lactoferrin is very important (antiviral properties aimed both against enveloped viruses and against naked viruses). Lactoferrin is particularly effective in the early stages of infection, preventing the virus from entering the cell by binding to both receptors for heparan-sulphate-glycosaminoglycans either directly to the viral particles. The nuclear localization of Lactoferrin means that it is active both in the initial phase of contact between the cell and the virus and when the virus itself has already penetrated the cell (42).

Vaccine colostrum can modulate the cellular response mediated by TLRs, in particular TLR-3, 4 and 5, in a dose-dependent way (43). Bovine coronavirus (BCoV) is an important viral pathogen associated with neonatal calf diarrhea (NCD), winter dysentery in adult cattle and respiratory tract disorders in cattle of all ages (42, 43). Colostrum intake is a natural and very effective method useful for controlling BCoV infection in calves. BCoV is composed of a single-stranded RNA, belongs to the Betacoronavirus genus and has several structural proteins among which protein S is involved in the interaction between virus and cell receptor and is also the target of neutralizing antibodies, this is a common feature with Covid-19 (44).

In a 2018 study (45) it was seen that the severity of the BCoV infection depended on the antibodies passively purchased from the colostrum, resulting milder in the calves that had taken maternal colostrum. The outcome of BCoV infection was clearly influenced by passively acquired ABS from colostrum. IgG1 sub-type is the main IgG Ab isotype actively concentrated during colostrogenesis. Based on these observations it can be assumed that vaccine colostrum contains antibodies that are also effective against Covid-19.

L- GLUTAMINE

Glutamine is a polar amino acid; the enantiomer L is one of the 20 ordinary amino acids; its lateral group bears a carboxamide group. It is the amide of glutamic acid. From a biological point of view, glutamine acts as a source of nitrogen for rapidly dividing cells including lymphocytes, where it is important for energy production and for the synthesis of nucleotides. Furthermore, glutamine is essential for the proliferation of T cells following their activation. The activation of naive T lymphocytes is associated with a rapid absorption of glutamine, which requires the ASCT2 amino acid transporter (46, 47).

Furthermore, activated T lymphocytes require glutamine for the production of IFN- γ ; therefore, the depletion of glutamine inhibits the proliferation of T cells and reduces the production of IFN- γ and IL-2 (48).

Although glucose is a critical substrate for T cells, glutamine is essential during the activation of T cells. Activated T cells in fact increase the expression of glutamine transporters and their deletion impairs the transition to an effector T cell (42). In human Coronavirus (HCoV) in-

fections there is a dysregulation of glutamate homeostasis which can lead to neuronal loss (neurodegeneration). Dysregulation of glutamate following HCoV infection is evidenced by an increase in extracellular glutamate and the release of LDH. Therefore, the homeostasis of glutamate is fundamental. The latter is regulated by glutamine synthetase: after recovery, glutamate is converted into glutamine by the astroglial enzyme GS. Glutamine is then transported in the nerve terminals and converted back to glutamate for a possible new glutamate-glutamine cycle (49).

VITAMIN D3

Vitamin D has some very important functions for human health; The European Food Safety Authority recommends an intake of 600 IU (15 mg) / day in healthy adults, with a maximum recommended intake of 4000 IU / day (100 mg) (50). The innate immune system is the first defense against infections and its main function is to fight quickly against invading pathogens. The innate immune system consists of: microbiota, physical barriers against infections (mucous membranes, mucus, skin), enzymes expressed by epithelium and phagocytic cells (lysozyme), peptides and antimicrobial proteins (defensins, cathelicidins,) inflammatory humoral components (complement and opsonine) cellular components (natural killer, macrophages, dendritic cells, mast cells, neutrophils cells) (51). Cholecalciferol 1.25 (OH) 2D3 increases the chemotaxis autophagy, and phagolysosomal fusion of innate immune Cells. It also increases the production of defensin-2 and cathelicidin antimicrobial peptide (CAMP) by macrophages and monocyte keratinocytes consequently increasing their antimicrobial activity (52, 53).

Various studies show that vitamin D upregulates the activity of Th2 cells (54-56). Furthermore, vitamin D is able to suppress among the immunomodulatory effects of vitamin D its ability to increase Treg cells and suppress Th17; the latter produce IL-17 and have been implicated in the pathogenesis of various autoimmune diseases (57-59). Several studies indicate an important role of vitamin D as an immunomodulator and in increasing the response capacity of the innate immune system against pathogens (60-62).

5. CONCLUSION

Healthcare professionals represent a high-risk category of COVID-19 infection. Many studies have shown that inflammation and lung damage in SARS, MERS and recently in COVID-19 is due to an increase in serum pro inflammatory cytokines and chemokines (inflammatory storm) and that disease severity and adverse outcome are related to the level of increase, suggesting a possible role for hyper-inflammatory responses in COVID-19 pathogenesis. Dexamethasone and some nutraceutical factors here described can be useful for the modulation of the inflammatory storm in light of the fact that nutraceutical factors do not add more collateral effects than dexamethasone, which mainly causes sarcopenia and axis suppression.

- **Authors' contributions:** UR, LM, and MB have made substantial contributions to conception and design of the study. UR, MB, and LM have made substantial contributions to acquisition and analysis of data. UR has contributed substantially to data analysis and interpretation. MB and LM have written and revised the manuscript. All authors read and approved the final manuscript.
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