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Article

Is Ozone therapy an adjunct treatment for SARS-CoV-2 / COVID-19 infection?

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Up to today, there is no specific treatment against SARS-CoV-2 / COVID-19 infection; there the necessity to search for alternatives that help patients with COVID-19. The objective of this study was to review the use of ozone therapy as adjunct treatment for SARS-CoV-2 / COVID-19 infection, highlighting the mechanisms of action, forms of application and current clinical evidence. A systematic review was conducted in electronic databases, searching the terminology Ozone "or" Ozone therapy "and" SARS-CoV-2 or COVID-19 or Coronavirus. Results: nineteen studies were included; ten were editorials, comments, brief reports or reviews, and nine clinical studies. We found that ozone therapy could be favorable for treating patients infected with SARS-CoV-2 / COVID-19, through a direct antiviral effect, regulation of oxidative stress, immunomodulation and improvement of oxygen metabolism. Patients who were treated with ozone therapy responded favorably; therefore, ozone therapy appears to be a promising treatment for patients infected with SARS-CoV-2 / COVID-19. Its mechanism of action justifies its use as an adjuvant therapy; however, scientific evidence is based on case series and clinical trials are necessary to corroborate its effectiveness and safety.

Keywords: Ozone therapy. Infection. COVID-19.

INTRODUCTION

Up to today, there is no specific treatment for SARS-CoV-2 / COVID-19 infection; several drugs including hydroxychloroquine or chloroquine, azithromycin, ivermectin, a combination of antivirals (such as Lopinavir, Ritonavir, Favipiravir, Remdesivir), immunomodulators (such as Tocilizumab and corticosteroids) have been used without achieving the expected response; therefore, support treatments have been utilized to help patients with COVID-19 (Pascarella *et al*., 2020; Hongzhou, 2020; Zhai *et al*., 2020; Sanders *et al*., 2020).

In the absence of a standard treatment, it is necessary to search for alternative strategies that induce a favorable clinical evolution, help tolerate the symptoms, and reduce the probability of critical complications or death.

It has been proposed that ozone therapy could function as an adjunctive treatment of infectious diseases (Rowen, 2019); furthermore, ozone therapy may be useful in the treatment of viral infections (Elvis, Ekta, 2011; Smith *et al*., 2017). The fundamental mechanism of action of ozone consists of reacting with polyunsaturated fatty acids of cell membrane, which generates reactive oxygen species such as hydrogen peroxide and lipid ozonation products (lipid peroxyl radicals, malondialdehyde, isoprostanes, alkenals and 4-hydroxynonenal) that increase cellular oxidative stress (Smith *et al*., 2017). This biochemical process triggers all the mechanisms that induce the therapeutic effects of ozone therapy.

Therefore, the objective of this study was to review the mechanisms of action of ozone therapy and relate them to the physiopathology of COVID-19, to identify its benefits in the treatment of patients infected by the SARS-CoV-2 virus.

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A second objective was to review forms of application and effectiveness of ozone therapy in the treatment of patients infected with SARS-CoV-2 / COVID-19.

MATERIAL AND METHODS

A systematic search in electronic databases PUBMED, SCIELO, SCOPUS, DIALNET, and GOOGLE SCHOLAR was performed using a search period up to September 10, 2020, for scientific articles with the terminology Ozone "or" Ozone therapy "and" COVID-19 or Coronavirus. The methodology used in this work was based on the PRISMA process for the presentation of systematic reviews. We included editorials, brief reports, review studies, clinical trials, case series, case-control studies and case reports, as long as the treatment strategies with ozone therapy aimed at patients infected with SARS-CoV-2 / COVID-19 and the mechanisms of action were mentioned. Pre-print studies that already had a DOI number assigned were also included. Data of interest were extracted and analyzed integrating the mechanisms of action, theoretical aspects of ozone therapy and their relationship to the pathophysiology of SARS- CoV-2 / COVID-19 infection. Likewise, the application forms and effectiveness of ozone therapy for treating patients infected with SARS- CoV-2 / COVID-19 were analyzed.

RESULTS AND DISCUSSION

We identified 226 citations; of those, 72 were duplicates and therefore excluded. The titles and abstracts of the 154 remaining studies were reviewed; 91 studies were additionally excluded as they did not match our search terminology. Of the remaining 63 studies, 44 were excluded for the following reasons: related to environmental ozone (n = 40), generic reviews that only mention ozone as a possible COVID treatment (n = 3) and studies that did not provide exact data for the dosage of the ozone therapy used (n =1). Finally, nineteen studies met our eligibility criteria (Figure 1).

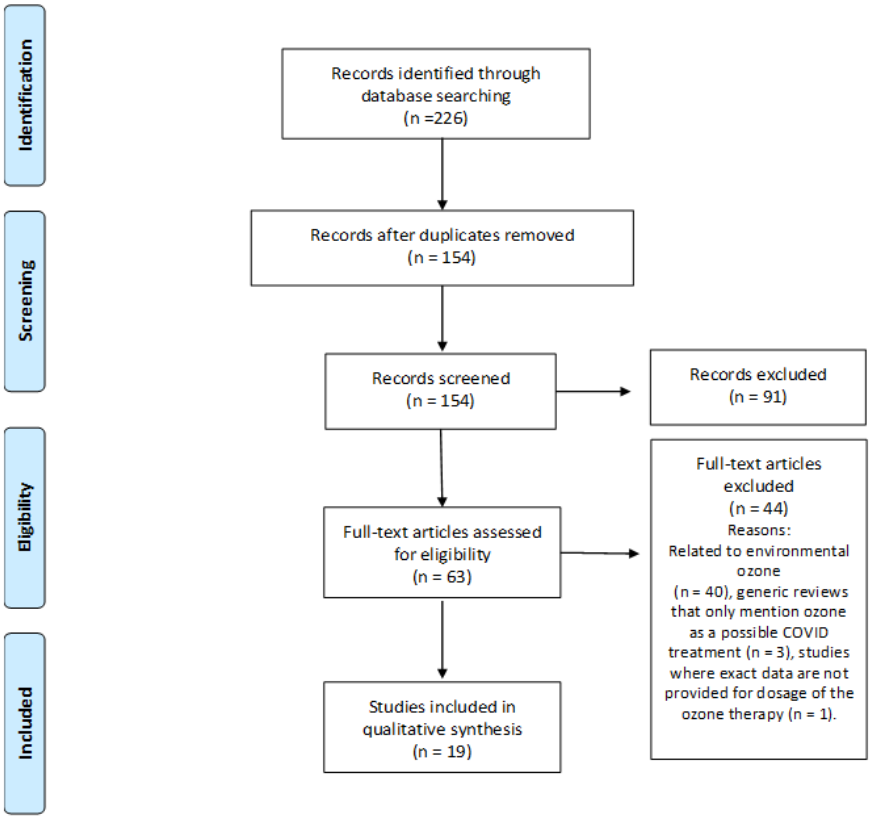

FIGURE 1 - Flowchart of the systematized review.

Ten studies were comments, editorials, brief reports or reviews where the mechanisms of action of ozone therapy and its relationship with SARS-CoV-2 / COVID-19 were discussed (Farias, Farias, Souza, 2020; Fernández–Cuadros *et al*.,2020a; Hernández *et al*., 2020a; Marini *et al*.,2020; Martínez–Sánchez, Schwartz, Donna, 2020; Menéndez-Cepero *et al*., 2020; Obeid, 2020; Ricevuti, Franzini, Valdenassi, 2020; Rowen, Robins, 2020; Valdenassi *et al*., 2020).

Additionally, we found nine clinical studies including type case report, case series and cohort study, where ozone therapy was used for treating patients infected with SARS-CoV-2 / COVID-19 (Wu *et al*., 2020; Zheng, Dong, Ku, 2020; Fernández–Cuadros *et al*., 2020b; Hernández *et al*., 2020b; Peña-Lora, Albaladejo-Florín, Fernández-Cuadros, 2020; Hernández *et al*., 2020c; Franzini *et al*., 2020; Schwartz *et al*., 2020; Schwartz, Narro, 2020). (Table I).

TABLE I - Summary of clinical studies that were included in this systematic review

Author and year.	Design	Patients treated	Treatment characteristics	Results	Level of Evidence
Wu *et al*., 2020.	Case report study.	One patient (56 years) with severe pneumonia due to COVID-19, with hypoxemia and need of high-flow nasal cannula oxygen therapy.	Antiviral therapy, antibiotics, immunoglobulin, corticosteroid and high-flow nasal cannula oxygen therapy. Ozone Therapy: Major Autohemotherapy with 100 ml of venous blood ozonized at 40 µg/ml for 5 consecutive days.	Clinical improvement with decreased need of high-flow nasal cannula and decreased inflammatory markers.	IV
Zheng, Dong, Ku, 2020.	Case report study	Two patients (53 and 66 years) with severe COVID-19, pneumonia with hypoxemia and need of supplemental oxygen.	Antiviral therapy, antibiotics, immunoglobulin, supplemental oxygen. Ozone Therapy: Major Autohemotherapy with 100 ml ozonized venous blood at 20 µg/ml for 7 consecutive days.	In both cases there was clinical improvement with a decrease in the need for supplemental oxygen and a decrease in inflammatory markers. After treatment, in both patients remitted symptoms and discharged testing negative for SARS-CoV-2.	IV
Fernández-Cuadros *et al*., 2020b.	Case report study.	Four patients (median 66.2 years) with severe bilateral pneumonia due to COVID-19, with hypoxemia and need of supplemental oxygen with nasal glasses or face mask in three of them.	Hydroxychloroquine, antiviral therapy, antibiotics, corticosteroids, monoclonal antibodies and high flow high-flow oxygen therapy. Ozone Therapy: Rectal insufflation of 100 ml of ozone at concentration of 35 µg/ml 5 consecutive days.	Clinical improvement with decreased need for supplemental oxygen, improved oxygen saturation and decreased inflammatory markers.	IV

TABLE I - Summary of clinical studies that were included in this systematic review

Author and year.	Design	Patients treated	Treatment characteristics	Results	Level of Evidence
Hernández *et al*., 2020b.	Case report study.	Three patients (49, 61 and 64 years) with COVID-19 pneumonia, with hypoxemia and respiratory distress, with need of supplemental oxygen with face mask.	Unspecified drug treatment. Supplemental oxygen with face mask Ozone Therapy: Major Autohemotherapy with 200 ml ozonized venous blood at 40 µg/ml for 4 to 6 daily sessions.	Improvement of hypoxemia and decreases in inflammatory markers. No patient required invasive mechanical ventilation. All patients were discharged home on days 3–4 after ozone therapy.	IV
Peña-Lora, Albaladejo-Florín, Fernández-Cuadros, 2020.	Case report study.	One patient (84 years) with COPD and pneumonia due to COVID-19, with hypoxemia and increase in the requirement of supplemental oxygen.	Antibiotics, corticosteroids and oxygen therapy. Ozone Therapy: Rectal insufflation of 100 ml of ozone at concentration of 35 µg/ml 5 consecutive days.	Decreases in inflammatory and thromboembolic markers, normalization of oxygen demand and radiological improvement. Medical discharge	IV
Hernández *et al*., 2020c.	Prospective cohort study.	Eighteen patients with COVID-19 pneumonia with oxygen saturation <94%. Nine patients with standard treatment for pneumonia due to COVID – 19 (age 71 years± 18). Nine patients with additional ozone therapy (age 64 years± 11).	All patients received usual clinical care for COVID-19 pneumonia: hydroxychloroquine, antivirals, corticosteroids, and antibiotics. Supplemental oxygen therapy. Ozone Therapy: Major Autohemotherapy with 200 ml ozonized venous blood at 40 µg/ml twice daily for a median of 4 days.	The ozone therapy group showed a shorter time to achieve clinical improvement (-11.3 days 95% CI -22.25 to -0.42), as well as significantly shorter time to a 2-fold reduction in concentrations of C-protein reactive, ferritin, D -dimer and lactate dehydrogenase.	III
Franzini *et al*., 2020.	Case series study.	Fifty patients (mean age 75 years ± 11.4) with COVID-19 pneumonia, with acute respiratory disease syndrome undergoing non-invasive mechanical ventilation. 48 patients completed the study, 2 died.	Hydroxychloroquine, anticoagulants, corticosteroids, and antibiotics. Supplemental oxygen therapy. Ozone Therapy: 3 - 5 (median = 4) cycles of Major Autohemotherapy with 100-200 ml (median 125 ml) ozonized venous blood at 45 µg/ml with daily application.	A significant reduction of inflammatory and thromboembolic markers was observed. Furthermore, amelioration in respiratory and gas exchange markers were reported.	IV

TABLE I - Summary of clinical studies that were included in this systematic review

Author and year.	Design	Patients treated	Treatment characteristics	Results	Level of Evidence
Schwartz, Narro, 2020.	Case report study.	Two cases with skin lesions due to COVID-19: First case: (4-year-old girl) with itchy skin rashes. Second case: (70-year-old man) with erythematous prugiriform type rash.	First case: Acetaminophen Ozone Therapy: Rectal insufflation: 50 ml at 25 µg/ml 2 sessions. 50 ml at 30 µg/ml 2 sessions. 75 ml at 30 µg/ml 3 sessions. 100 ml at 30 µg/ml 3 sessions. Ozonated oil, dermal application twice a day. Antioxidants. Second case: Anticoagulant. Ozone Therapy: Ozonized Saline Solution at 5 µg/ml applied daily for 5 days, followed by 5 days at 3 µg/ml. Ozonized oil, dermal application twice a day. Antioxidants.	In both cases, the lesions disappeared at the end of the 10 treatment sessions.	IV
Schwartz *et al.*, 2020.	Case series study.	Twenty-five patients (mean age 55 years) with mild to severe COVID-19 pneumonia, 14 of them needed supplemental oxygen. All patients completed the study.	Hydroxychloroquine, Tocilizumab, anticoagulants, corticosteroids, antibiotics. Ozone Therapy: 200 ml of Ozonized Saline Solution at 5 µg/ml applied daily for 5 days, followed by 5 days at 3 µg/ml.	Improvement in 76% of treated patients, with reduction of symptoms such as dyspnea, weakness and fever, as well as decreased inflammatory markers. None of the patients treated with ozone therapy died.	IV

Mechanisms of action of ozone therapy and its relationship with SARS-CoV-2 / COVID-19 infection

Ozone therapy could be useful for treating patients infected with SARS-CoV-2 / COVID-19 via multiple mechanisms of action:

Direct antiviral effect

It has been described that systemic ozone therapy can have a direct antiviral effect. The administration of ozone creates peroxides that interact with the rich in lipids and cysteine-rich surface glycoproteins viral membrane; therefore, ozone causes damage by peroxidation altering

the fusion capacity of the virus and its entry into the host cells. Ozone can also damage the viral capsid and interrupt the virus-cell membrane junction, limiting the virus replication cycle (Farias, Farias, Souza, 2020; Fernández–Cuadros *et al*., 2020a; Hernández *et al*., 2020a; Martínez–Sánchez, Schwartz, Donna, 2020; Menéndez-Cepero *et al*., 2020; Obeid, 2020; Rowen, Robins, 2020; Valdenassi *et al*., 2020). However, when the virus is already inside the host cells, viricidal activity in vivo is uncertain, as the potent antioxidant system of the cell could protect viral integrity (Martínez–Sánchez, Schwartz, Donna, 2020). Clinical studies have reported ozone therapy is effective for treating patients with viral infections such as Hepatitis C (Zaky *et al*., 2011) or Ebola (Rowen *et al*., 2016). These studies have opened a therapeutic window for ozone therapy in the treatment of viral infections, which could include the infection with SARS-CoV-2 / COVID-19.

Immunomodulation

Ozone therapy can indirectly activate immunomodulation mechanisms. Oxidative stress caused by ozone administration favors the activation of transcription factors such as hypoxia inducible factor type 1 alpha (HIF-1α) and nuclear factor Kappa Beta (NF-κβ); it also favors the release of interferons and anti-inflammatory cytokines such as IL-4, IL-10, IFN Gamma, TNF-β; additionally, it decreases pro-inflammatory cytokines release including IL-6 and TNF-alpha (Farias, Farias, Souza, 2020; Hernández *et al*., 2020a; Marini *et al*.,2020; Martínez–Sánchez, Schwartz, Donna, 2020; Menéndez-Cepero *et al*.,2020; Obeid, 2020; Valdenassi *et al*., 2020). Ozone therapy has also been used for treating other diseases such osteoarthritis (Hashemi *et al*., 2017) and rheumatoid arthritis (Takon-Oru *et al*., 2019), and reports indicate an immunomodulation response generated by ozone. This immunomodulation mechanism could favorably influence the dysregulated inflammatory process (cytokine storm) that occurs in patients infected with SARS-CoV-2 / COVID-19. It has been observed that the use ozone therapy during the initial stages of COVID-19 favors the clinical evolution via mitigating (at least partially) the onset of cytokine storm syndrome observed in these patients (Marini *et al*, 2020). Similarly, it has been proposed that ozone could be useful in the most advanced stages of COVID-19 by modulating the inflammatory response and cytokine storm (Fernández–Cuadros *et al*., 2020a; Obeid, 2020).

Regulation of oxidative stress

Ozone administration also favors the activation of the transcriptional mediating nuclear factor-erythroid 2-related factor 2 (Nrf2), which is responsible for activating the transcription of antioxidant enzymes that act as free radical scavengers including superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione S-transferase (GST), catalase (CAT), heme oxygenase-1 (HO-1), and NADPH quinone-oxidoreductase (NQO-1) (Farias, Farias, Souza, 2020; Menéndez-Cepero *et al*., 2020; Ricevuti, Franzini, Valdenassi, 2020; Smith *et al*., 2017; Valdenassi *et al*., 2020). The regulation of oxidative stress has been observed in other diseases such as rheumatoid arthritis (Takon - Oru *et al*., 2019), where ozone favorably influences the clinical course of the disease. The restoration of the cellular redox balance state is a cytoprotective effect on vital organs and limits viral replication in patients infected with SARS-CoV-2 / COVID-19 (Martínez–Sánchez, Schwartz, Donna, 2020; Fernández–Cuadros *et al*., 2020a).

Improvement in oxygen metabolism

Another benefit of ozone therapy for treating patients infected with SARS-CoV-2 / COVID-19 is by improving oxygen metabolism. It has been reported that ozone therapy increases the concentration of 2-3 diphosphoglycerate in erythrocytes, shifting the hemoglobin curve to the right, thereby improving tissue oxygen disposition; ozone also increases the activity of nitric oxide synthase which increases nitric oxide release, thereby increasing peripheral vasodilation (Smith *et al*., 2017; Martínez-Sánchez, Schwartz, Donna, 2020; Menéndez-Cepero *et al*., 2020; Obeid, 2020). Ozone therapy has already been used for treating lung diseases with hypoxemia (COPD, emphysema) resulting in an increase of oxygen levels as well as clinical and functional

improvement (Calunga *et al*., 2011). These effects could be favorable in patients infected with SARS-CoV-2 / COVID-19, via preventing hypoxemia (Fernández–Cuadros *et al*., 2020a).

Ozone therapy for patients infected with SARS-CoV-2 / COVID-19

Systemic administration of ozone through major autohemotherapy has been proposed for treating patients infected with SARS-CoV-2 / COVID-19, suggesting an application of 150-200 ml of venous blood initially ozonized using a concentration of 50 μg/ml and then increased to 70 μg/ml, one to four times per day according to the needs of each individual (Hernández *et al*; 2020a). In five of the clinical studies reviewed, a total of 74 patients with COVID-19 were treated with major autohemotherapy, applying 100 to 200 ml of ozonated blood at 20 – 45 μg/ml once a day during 4 - 7 days, reporting improvement in 97% of them (Wu *et al*., 2020; Zheng, Dong, Ku, 2020; Hernández *et al*., 2020b; Hernández *et al*., 2020c; Franzini *et al*., 2020). To date, major ozone autohemotherapy has been the main modality used for treating patients with COVID-19.

The expert and official opinion of the International Scientific Committee on Ozone Therapy regarding the potential use of ozone in SARS-CoV-2 / COVID-19 indicated that in addition to major autohemotherapy, ozonated saline solution and minor autohemotherapy can also help. Ozonated saline solution has been reported to be especially effective in the treatment of viral diseases, with the advantage of requiring less frequent administrations compared with major autohemotherapy. For the treatment of SARS-CoV-2 / COVID-19 infection, a daily dose is recommended during 10 days, with ozonated saline solution of 5 μg/ml for the first 5 sessions and then 3 μg/ml for the following sessions (International Scientific Committee on Ozone Therapy, 2020). In our review, one clinical study reported the use of ozonated saline solution for treating one patient with COVID-19 who had dermatological manifestations, and observed a good response to the treatment (Schwartz, Narro, 2020). Additionally, a pre-print manuscript reported 25 patients hospitalized with mild to severe COVID-19 symptoms, who received the standard care plus 200 ml of ozonated saline solution at a concentration of 5 μg/ml for the first 5 sessions and then of 3 μg/ml for the following sessions during 10 days, observing clinical improvement, reduction of dyspnea, as well as an improvement in inflammatory markers without complications (Schwartz *et al*., 2020).

As for The Spanish Association of Medical Professionals in Ozone Therapy (AEPROMO) issued a statement indicating that approximately 600 treatments with ozonated saline solution were administered to hospitalized individuals infected with SARS-CoV-2 and showing COVID-19 complications, as adjuvant therapy to conventional treatment; they reported that inflammation markers significantly decreased after 24 h of starting the treatment, oxygen saturation values were normalized at 72 h after starting the ozone therapy, and that the majority of patients were discharged after 10 days despite the fact that some of them had been hospitalized for more than one month (Spanish Association of Medical Professionals in Ozone Therapy, 2020). Also, the FSBI "NMITs AGP named after V.I. Kulakov" of the Ministry of Health in Russia reported an efficacy of ozonated saline solution in the treatment of patients with COVID-19: 134 patients were treated with 6 daily applications of 400 ml of ozonated saline solution using a concentration of 4 - 5 μg/ml, reporting reduction of symptoms such as dyspnea and fever, improvement in oxygen saturation and decreased inflammatory markers; therefore, fewer complications and shorter hospitalization periods (FSBI "NMITs AGP named after V.I. Kulakov" of the Ministry of Health of Russia, 2020).

On the other hand, The World Federation of Ozone Therapy indicates that a rectal insufflation application could be a good alternative for treating patients infected with SARS-CoV-2 / COVID-19 in whom an intravenous application is not feasible; for the rectal insufflation is also considered a systemic application. It is recommended to start with one application of 100 ml using a concentration of 30 μg/ml on day 1, subsequently 150 ml of 30 μg/ml on day 2, followed by 200 ml at 30 μg/ml until completing 14 days, with applications every 12 h (World Federation of Ozone Therapy, 2020). In our review, three clinical studies reported that 6 patients (5 adults and 1 child) with COVID-19 received ozone therapy through rectal

insufflation (100 ml of ozone at 35 µg/ml during 5 days for adults, and 50-100 ml at 25 – 30 µg/ml during 10 days for the child), with a good response, achieving clinical improvement without complications (Fernández–Cuadros *et al*., 2020b; Peña-Lora, Albaladejo-Florín, Fernández-Cuadros, 2020; Schwartz, Narro, 2020). Among the adults who were treated with this modality there was an 84-year old individual, which suggests that this ozone therapy modality could be an option for treating COVID-19 patients of all ages.

We did not find publications of clinical trials where ozone therapy was used for treating patients infected with SARS-CoV-2 / COVID-19. The most recent evidence on the use of ozone therapy in patients infected with SARS-CoV-2 / COVID-19 according to the American Society of Surgeons Scale for therapeutic studies is level IV (case series studies) (Sullivan *et al*., 2011). In international platforms such as Clinicaltrials.gov, we found six registered protocols of clinical trials where ozone therapy is used in patients infected with SARS-CoV-2 / COVID-19 (U.S. National Library of Medicine: ClinicalTrials.gov Ozone / COVID, 2020). Additionally, at the International Scientific Committee of Ozone Therapy (ISCO3) official website, there is a follow-up to the current studies on ozone therapy in patients with COVID-19, mentioning about 16 studies being performed in more than eight countries. The conclusion of these clinical trials could provide a better level of evidence for the optimal outcomes observed up to now.

CONCLUSIONS

Ozone therapy is a promising treatment for patients infected with SARS-CoV-2 / COVID-19. The mechanisms of action of ozone therapy justify its integration as adjuvant therapy for patients infected with SARS-CoV-2 / COVID-19; furthermore, several clinical studies have reported favorable results. Ozone therapy has the advantage of improving outcomes when applied at early stages of the disease, as well as when applied to critically ill patients. Nevertheless, as the current scientific evidence is based mostly on case series studies, it is necessary to analyze the results of ongoing clinical trials in order to corroborate the effectiveness and safety of ozone therapy.

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