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Dihydrogen inhalation in the Management of Patients with Moderate Oxygen-Requiring COVID19: Towards an Innovative Therapy

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Abstract

The Coronavirus Disease 2019 (Covid-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has resulted in a substantial global health crisis, with millions of deaths reported since its initial discovery in China in November 2019. The global variability in immunization access underscores the critical necessity for ongoing research into therapeutic strategies.

This study explores the application of molecular dihydrogen (H_2) inhalation as a potential adjuvant treatment for Covid-19. H_2 therapy has shown promise in inhibiting inflammation-related intracellular signaling pathways, particularly when administered early in conjunction with nasal oxygen therapy.

Presented here are two cases from an ongoing phase one study evaluating the safety and Dose Limiting Toxicity (DLT) of H_2 therapy delivered via a nasal cannula in addition to conventional oxygen therapy for Covid-19 patients requiring nasal oxygen (1 to 6 L/min). Tolerance was excellent in both cases, with no adverse events attributed to H_2 reported.

Patient 1, a 56-year-old man, and Patient 2, a 59-year-old woman, exhibited positive responses to the H_2 therapy, demonstrating improvements of O_2 saturation and a decrease in C-Reactive Protein (CRP) levels. The gas mixture's safety and efficacy were supported by clinical and biological observations, aligning with existing literature on H_2's anti-inflammatory effects.

This preliminary study suggests that inhaled H_2, administered alongside oxygen therapy, may expedite the clinical improvement of pulmonary SARS-CoV-2 disease, potentially preventing Intensive Care Unit (ICU) transfers. The positive outcomes observed in these cases warrant further investigation in larger, controlled clinical trials.

Keywords: COVID 19; Anti-inflammatory Agents; Non-Steroidal; Inhalation

Key Clinical Message: Dihydrogen (H_2) inhalation has shown promising results as a treatment for two hospitalized patients with moderate COVID 19.

Introduction

Coronavirus Disease 2019 (Covid-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has led to millions of deaths since its discovery in China in November 2019 [1]. The primary manifestation is severe and potentially fatal lung damage, often associated

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with a significant release of cytokines (particularly interleukins IL-6, IL-8, and IL-10) due to macrophagic activation, primarily at the pulmonary level. Immunization access varies widely globally, emphasizing the crucial need for ongoing research into therapeutic strategies [2].

Hyperbaric molecular hydrogen (H_2) inhalation was initially explored in the 1970s for potential cancer treatment, with the first atmospheric pressure experimental study conducted in 2007 on a rat model of cerebral infarction [3]. Subsequent research, such as that by Ito et al. [4], revealed that H_2 inhibits inflammation-related intracellular signaling pathways independently of its anti-free radical effects.

Xie et al. [5] demonstrated that two 60-minute sessions of inhaling a gaseous mixture containing 2% H_2 effectively limited multiple organ damage and reduced mortality in a mouse model of generalized inflammation [5]. Their research further revealed that H2 inhalation restored the PaO_2 / FiO_2 ratio in both a mouse model of sepsis induced by cecal ligation [6] and a model of lung damage induced by lipopolysaccharides [7]. Furthermore, although there is no reason to expect an anti-viral effect, H_2 has been identified as a factor attenuating the considerable inflammatory stress exerted on the lung parenchyma during Covid-19 [8].

Early use in conjunction with nasal oxygen therapy has shown promise in preventing respiratory deterioration. Regarding administration, various methods have been explored, with the most prevalent being the ingestion of hydrogen-enriched water and the inhalation of a gaseous mixture. Due to hydrogen's high flammability (for concentrations exceeding 4.1% in the air), recent gas mixtures have typically maintained H_2 levels between 2% and 4% [9,10].

Our ongoing phase one study assesses the safety and Dose Limiting Toxicity (DLT) of H_2 therapy delivered via a nasal cannula in addition to conventional oxygen therapy for Covid-19 patients requiring nasal oxygen (1 to 6 L/min). We present two cases from this study demonstrating the tangible benefits of inhaled H_2.

Case History or Examination

On September 03, 2021, a 56-year-old man was admitted in infectious diseases department for a moderate Covid-19 infection. He did not show previous diseases, was not a smoker and had a Body Mass Index of 29. He had no significant medical history. Symptoms had begun 10 days before admission. They consisted in fever (39°C), chills, anosmia, agueusia, asthenia and weight loss (5 kg). The first specific Polymerase Chain Reaction (PCR), done on 03/12/2021, was positive with English variant. C-Reactive Protein (CRP) test was high (185 mg/L), arterial gasometry showed before H_2 therapy a significant hypoxemia with adjunction of 4L/min O_2 by nasal canula (pO_2: 8,41 kPa with normal values (NV): 9,50-13,30; pCO_2: 4,98 kPa with NV: 4,70-6,10, pH: 7,44 with NV : 7,37-7,45 and bicarbonates : 24,5 mmol/L with normal values : 21,0-26,0). CT lung imaging is shown in Figure 1.

Concerning thoracic auscultation, crackles were found on both sides of the lung. The respiratory frequency was about 30 cycles per minute. Concerning chest X ray, performed on the day of admission, it showed multiple opacities, with infiltration confirmed by CT scan on the same day, which also highlighted extension of infiltrates to 50%, which suggests a severe pulmonary disease, as represented in Figure 2.

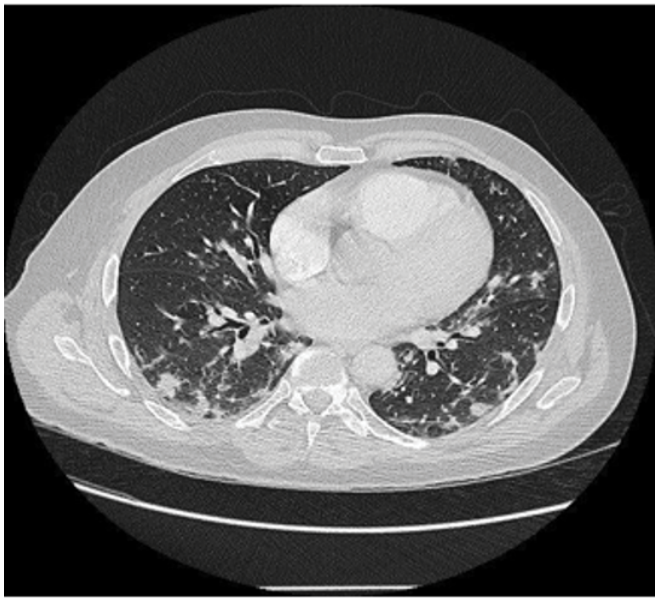

Figure 1: CT lung imaging.

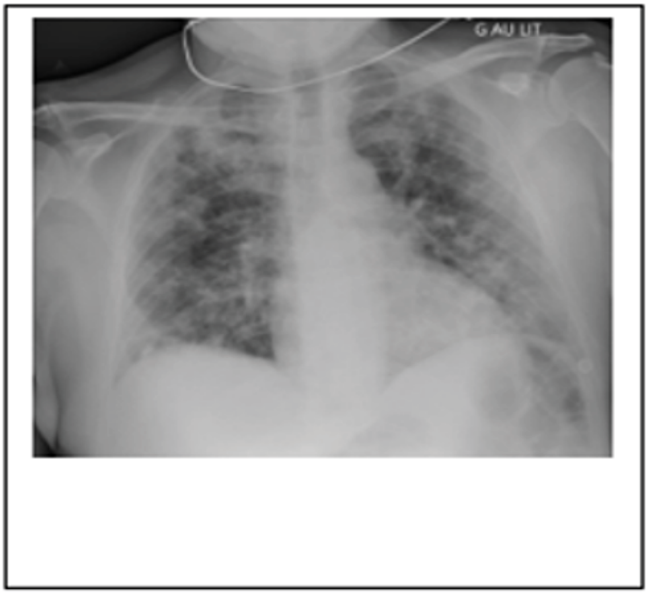

Figure 2: Chest x-ray.

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On April 6th 2021, a second patient was admitted to emergencies. She was 59 years old and had no specific medical history other than hypertension, treated with Lercanidipine. She was hemodynamically and respiratory stable, despite 89% saturation on room air, with a positive Covic-19 PCR. Symptoms had begun 8 days before admission She had respiratory alkalosis with mild hypoxemia ($p0_2$: 69.8mmHg; $pC0_2$:36.2mmHg; pH:7.46). She also had a biological inflammatory syndrome (CRP 69 mg/L), without hyperleukocytosis. D-Dimer were elevated at 1.02 mg/L. Troponin was 8 ng/L and BNP was 245 ng/L.

Concerning medical imaging, she had a typical Covid-19 infection, with extensive infiltration of lung parenchyma (25 - 50%), superinfection of both bases, without additional pulmonary embolism (Figure 3).

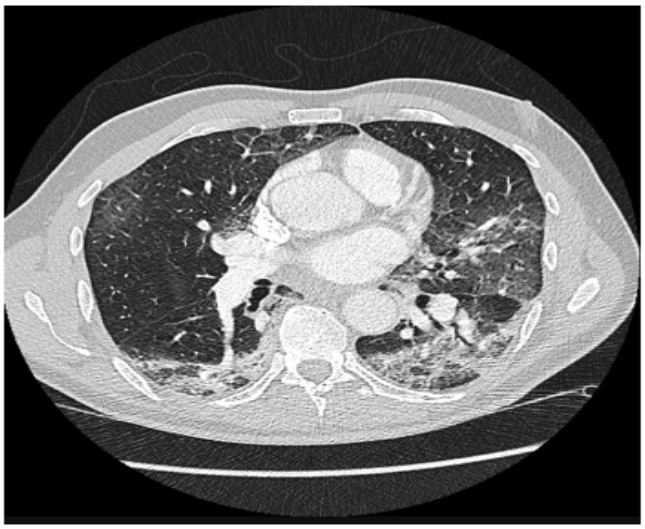

Figure 3: CT lung imaging.

Methods

An original medical delivery device has been designed by our team and has undergone a risk analysis by an independent organization. This device includes a flow regulator (a CE-marked medical device for clinical trials) allowing to guarantee a fixed flow of 1 L/min of a specific medical grade gas mixture (3,6% H_2; 96.4% N_2), manufactured and supplied by AIR PRODUCTS, packaged in B50 type cylinders. The gas mixture is combined with O_2 from the oxygen outlet of the wall (adapted to the needs of the patient in accordance to standard of care).

Patient 1 and 2 were both included in H_2 protocol for a three days treatment. They both received the usual standard of care during their hospitalization. They also required treatment with corticosteroids 0.6mg/kg for 5 days, then at half-dose for the following 5 days, combined with preventive anticoagulation. O_2 flow for these two patients was between 3 and 4 L/min, to achieve a target of 95% of O_2 saturation.

Results and Conclusion

Tolerance was excellent for both patients, with no adverse effect. Concerning patient 1, the clinical evolution during exposition was correct with improvement of hypoxemia and a decrease of CRP (33mg/L at the end of the 3 days of H_2-therapy). Three months later the patient was examined for a control visit. He was well and did not show any respiratory symptom. Concerning patient 2, clinical evolution during exposition was correct with improvement of hypoxemia and a decrease of CRP (on 14th April, CRP returned to a normal value of 0 mg/L.) Hemoglobin was at 128 g/L, with no hyperleukocytosis, thrombocytosis was 591 Giga/L, neutrophils was 7.9 Giga/L. Given the good clinical and biological evolution, the patient was discharged on April 15, seven days after onset of H2-therapy.

Discussion

The clinical and biological observations of these clinical cases are consistent with the literature, considering that H_2 has been described as able to reduce lung injury and thus to reduce the number of critically ill patients [11]. Another review of the literature has indicated that H_2 may directly access lung tissue through respiratory activities, providing anti-inflammatory effects at various stages of the inflammatory response. This helps alleviate airway damage caused by the excessive activation of inflammatory cells and the substantial release of inflammatory factors [12]. Furthermore, in the context of Covid-19 related pulmonary injury, the activation of resident alveolar macrophages has resulted in the release of potent proinflammatory mediators and chemokines, fostering the accumulation of neutrophils and monocytes. Inhaled H_2 exhibits a non-specific anti-inflammatory impact on macrophages, neutrophils, and lymphocytes, while also inhibiting the production of reactive oxygen species (ROS) [13]. When we initiated this research, the only established therapies demonstrating effectiveness were anti-inflammatory compounds like corticosteroids. Nevertheless, their application has not been without side effects. The use of H_2 to address COVID-19 was initially proposed only in the Chinese recommendations [14,15]. Subsequently, a Chinese research team reported results in 2020 from an open-label clinical trial demonstrating efficacy. The trial involved administering a mixture comprising 67% H_2 and 33% O_2, showing statistically significant improvements in both clinical and biological parameters [16]. Our results seem to point in the same direction as this study, but our methodology does not involve use of very inflammable gas mixtures. Indeed, although our methodology does not allow us to test hypotheses of efficacy, clinicians were genuinely impressed by the positive evolution of all patients who had received hydrogen therapy. For example, at the same time as patient 1, a younger patient (54 years old, BMI 30) with no previous history and with positive PCR was admitted in infectious diseases department.

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He did not agree to be included in the study. He showed the same radio-clinical picture of SARS-CoV-2. He was admitted one day later in Intensive Care Unit (ICU) for high flow nasal O_2 (40L/min) delivered by OPTIFLOW™.

The absence of adverse events attributed to H2 is also consistent with the literature, since the tolerability of H_2 has always been demonstrated in all clinical trials published in the literature.

These observations suggest a real efficacy of H_2-therapy during 3 days combined treatment with oxygen to accelerate clinical improvement of pulmonary Covid-19 and notably to prevent ICU transfer.

We are currently preparing a phase II/III study to confirm this positive effect of inhaled H2 versus placebo on pulmonary inflammation during SARS-CoV-2.

Author's contribution

Conceptualisation: J.Giai, M.Roustit, F.Boucher, P.Cinquin, JP Brion

Study procedures and analysis: C.Salomez-Ihl, J.Giai, M.Roustit, F.Boucher, P.Cinquin, JP Brion

Investigation: JP Brion

Writing – original draft preparation: C.Salomez-Ihl, F.Boucher, P.Cinquin, JP Brion

Writing – review and editing: all

Consent: Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy

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