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Molecular Hydrogen Therapy for SLE-PAH: Case Report on Immune Marker Modulation

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Abstract

Background/Aim: Systemic lupus erythematosus-associated pulmonary arterial hypertension (SLE-PAH) is a severe complication marked by elevated pulmonary artery pressure, leading to exertional dyspnea and right-sided heart failure. Standard treatments frequently fall short in effectively controlling symptoms, highlighting the need for innovative therapeutic approaches. This aim of this study was to investigate the efficacy of molecular hydrogen therapy in a patient with SLE-PAH with decompensated right-side heart failure.

Case Report: We present the case of a 51-year-old female diagnosed with SLE-PAH in 2012. Despite treatment with vasodilator agents, her condition worsened following an episode of sepsis, leading to severe dyspnea and oxygen desaturation since 2018. In March 2024, molecular hydrogen therapy was introduced as an adjuvant treatment. The patient received daily hydrogen capsules, which resulted in an increased percentage of Tr1 cells, and a decreased percentage of Treg cell subsets, B cell subsets, marginal cell, and plasma cell. Her clinical symptoms stabilized, and no adverse effects or complications were observed.

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Conclusion: This case study highlights the potential efficacy of molecular hydrogen therapy in a patient with SLE-PAD and decompensated right-sided heart failure precipitated by sepsis. Further research is needed to confirm its therapeutic benefits, particularly its ability to modulate immune markers and improve clinical outcomes.

Keywords: Case report, Systemic lupus erythematosus, Hydrogen therapy, Treg cell, B cell, plasma cell.

Introduction

Pulmonary arterial hypertension (PAH) is a common complication in patients with systemic lupus erythematosus (SLE), often leading to cardiorespiratory disorders or thromboembolic diseases. SLE-associated PAH is hemodynamically defined by an elevated mean pulmonary artery pressure (≥25 mmHg at rest) and increased pulmonary vascular resistance, with a normal pulmonary capillary wedge pressure (≤15 mmHg) (1). Clinical symptoms include exertional dyspnea, generalized fatigue, weakness, and progression to dyspnea at rest (2). Risk factors for PAH in SLE patients include female gender, smoking, Raynaud's phenomenon, serositis, digital vasculitis, pericardial effusion, pulmonary interstitial lesions, systemic hypertension, alopecia, and positive anti-U1 ribonucleoprotein antibodies (3, 4). Higher mean pulmonary arterial pressure (mPAP), increased pulmonary vascular resistance (PVR), reduced six minutes walking distance (6MWD), and elevated brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) levels are important predictors of mortality in these patients. Treatment typically involves a combination of immuno-suppressive therapies and PAH-targeted therapies, including oxygen, anticoagulants, calcium channel blockers, and vasodilators (selective and nonselective endothelin receptor antagonists, phosphodiesterase-5-inhibitors, and prostanoids) (1, 5).

Molecular hydrogen therapy, known for its significant reduction of inflammatory factors and oxidative stress, has been studied extensively in animal models since 2007, demonstrating therapeutic effects in various diseases (6). Although the precise molecular mechanism remains unclear, this is thought to modulate oxidative stress, inflammatory response, and apoptosis *via* nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and nuclear factor erythroid 2-related factor 2/Heme oxygenase-1 (Nrf2/HO-1) signaling pathway, thereby mitigating organ and barrier damage (7-9). Previous studies have shown that hydrogen inhalation reduces epithelial apoptosis in ventilator-induced lung injury by indirectly modulating NF-κB signaling through the reduction of oxygen free radical (10, 11). Additionally, Nrf2 plays a key role in regulating the expression of HO-1 and Phase II genes, which act synergistically to scavenge reactive oxygen/nitrogen species (ROS/RNS) and detoxifies electrophiles and xenobiotics (12).

Hydrogen administration has been explored in numerous clinical studies for its potential therapeutic effect on cardiovascular disease, cancer, respiratory disease, central nervous system diseases, and infections (13). In cancer patients, a high proportion of CD8+ T cells express the programmed cell death protein-1 (PD-1), which hampers the immune system's ability to recognize and attack cancer cells. Elevated PD-1 expression is linked to poor cancer prognosis. However, hydrogen therapy has been shown to reduce the proportion of PD-1+ CD8+ T cells in the blood of cancer patients, potentially improving clinical outcomes (14, 15).

To ensure efficiency of hydrogen delivery and demonstrate its antioxidative properties, hydrogen is immobilized and encapsulated with coral calcium, derived from coral exoskeletons (16, 17). The safety, lipid-lowering effects, as well as the antioxidative and anti-inflammatory properties of these hydrogen capsule have been well-documented in numerous human and animal studies (16-18). In a study using a methionine-and-choline-deficient (MCD) diet-induced non-alcoholic fatty liver

disease (NAFLD) mouse model, hydrogen capsules were shown to reduce lipid accumulation and improve liver dysfunction, further emphasizing their antioxidative and anti-inflammatory effects (18). Another study reported increased levels of resting regulatory T cells in a patient with progressive fibrosing interstitial lung disease (PF-ILD) complicated by pneumonia after treatment with hydrogen capsules. This was accompanied by improvements in lung infiltrations and a significant decrease in Fas+ helper T cells and cytotoxic T cell subtypes (19). Hydrogen capsules demonstrate therapeutic potential with antioxidative, anti-inflammatory, and lipid-lowering properties, particularly in the contexts of liver health, lung disease, and autoimmune disorders.

This article presents a case study of a 51-year-old female diagnosed with SLE-PAH, who was admitted with sepsis shock and multiple organ dysfunction syndrome. Despite receiving standard treatments, her condition remained refractory, leading to the administration of hydrogen therapy as an adjuvant treatment. This study was approved by the Institutional Review Board (IRB) of Tri-Service General Hospital, National Defense Medical Center, Taiwan, and complied in accordance with relevant guidelines (IRB: B202105106, approval date: 18 July 2023). Written informed consent was obtained from all patients (No. B202105106-41). The study adhered to the ethical principles outlined in the 1964 Helsinki Declaration and its subsequent amendments, or comparable ethical standards.

Case Report

This case involves a 51-year-old Taiwanese female diagnosed with SLE in 2004 and SLE-PAH in 2012. Since September 2018, she had been under regular follow-up in our cardiovascular department, receiving combination therapy with macitentan, selexipag, and riociguat for PAH management (Figure 1). Over the years, she had been hospitalized multiple times due to acute decompensated right-sided heart failure, the World Health Organization functional classification III (WHO FC III) precipitated by sepsis. The patient declined parenteral treprostinil infusion and lung transplantation. Right heart catheterization (RHC) performed on November 20, 2020, confirmed pulmonary hypertension, WHO classification group I [mean pulmonary artery (PA) pressure: 45 mmHg, pulmonary vascular resistance (PVR): 14.91 Wood units, total pulmonary resistance (TPR): 17.66 Wood units].

In March 2024, she presented with a two-day history of fever and shortness of breath. Upon arrival at the emergency department, her vital signs showed hypotension (58/42 mmHg) and oxygen desaturation (82%), along with acute kidney injury (blood urea nitrogen: 34 mg/dl; creatinine: 1.8 mg/dl), elevated C-reactive protein (23.34 mg/dl), procalcitonin (4.93 ng/ml), and brain natriuretic peptide (9,576 pg/ml). Physical examination revealed bilateral rhonchi, and chest X-ray (CXR) indicated cardiomegaly and pulmonary hypertension, with enlargement of the cardiac silhouette and prominence of the bilateral pulmonary hilum. Chest computed tomography (CT) showed marked dilation of the pulmonary trunk and bronchial wall thickening, suggestive of pulmonary hypertension and chronic bilateral bronchitis/bronchiolitis. Due to hypoxic respiratory failure, a high-flow nasal cannula was administered, along with norepinephrine for hypotension. She was admitted to the intensive care unit with diagnoses of acute decompensated heart failure, sepsis shock, and multiple organ dysfunction syndrome.

Upon admission, empirical antibiotic therapy with meropenem was initiated for sepsis management, and a high flow nasal cannula was used to maintain adequate oxygen saturation. One hydrogen capsule per day was administered, and Ventavis was prescribed for PAH management (Figure 1). The norepinephrine infusion was gradually tapered as her blood pressure stabilized. Serial blood tests showed a decreasing C-reactive protein level, and no fever was observed following admission. As her condition improved, the patient was transferred to a general ward on April 1, 2024. Meropenem therapy was continued until April 8, 2024, and her breathing remained stable with nasal cannula support. The patient's symptoms significantly improved with treatment, and she was discharged in a relatively stable condition on April 10, 2024.

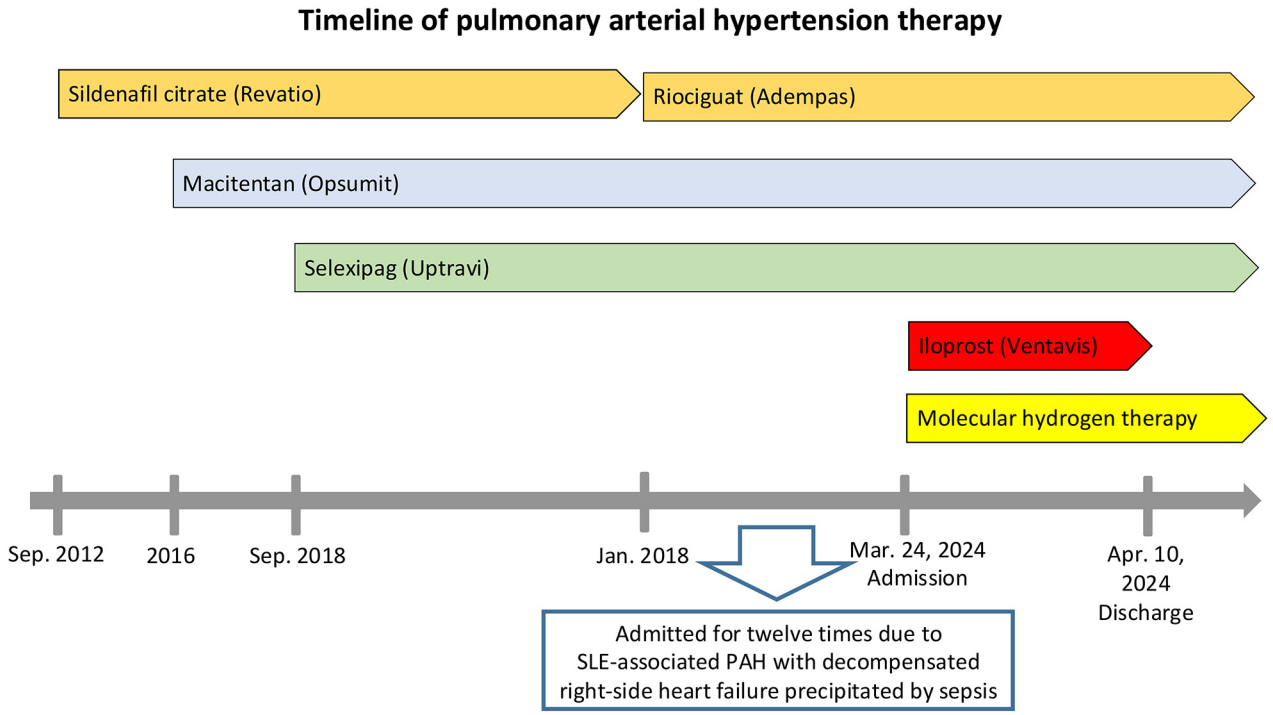

Figure 1. *The timeline of pulmonary arterial hypertension therapy. The hollow arrow indicates decompensated right-sided heart failure precipitated by sepsis, occurring twelve times between January 2018 and March 24, 2024. The orange, blue, green, and red squares represent the periods during which the patient received vasodilator therapy. The yellow square highlights the duration of molecular hydrogen therapy.*

In July 2024, follow-up CXR and CT scans revealed persistent marked dilation of the pulmonary trunk (Figure 2). Despite this finding, the patient was able to perform routine activities with adequate oxygen saturation, without the need for supplemental oxygen. Using stereoscopic imaging technology, we visualized the dilation of the pulmonary trunk in blue. A dynamic stereoscopic video of this visualization is available at the following link: https://youtube.com/shorts/grYY1Xbvet4?feature=share.

She began molecular hydrogen therapy on March 29, 2024, taking one hydrogen capsule daily, purchased from HoHo Biotech Co., Ltd. (Taipei, Taiwan, ROC). Each capsule consisted of 170 mg of hydrogen-rich coral calcium, which provided approximately 1.7×10^{21} molecules of hydrogen, equivalent to the hydrogen content found in 24 cups of water at a concentration of 1,200 ppb. We continued to monitor her clinical symptoms and signs following molecular hydrogen therapy. Notably, analysis of her blood samples using flow cytometry revealed a decrease in the percentage of resting Treg, naïve Treg, Naïve B cell PD-1+, SM B cell PD-1+, SM B cell Fax, Marginal cell Fas+, DN B cell Fax, DN B cell PD-1, and plasma cells (Figure 3). This change was observed alongside an improvement in her shortness of breath. Furthermore, the percentage of Tr1 cells decreased during the desaturation phase; however, these data showed recovery after the patient underwent molecular hydrogen therapy (Figure 4). No adverse events or complications were reported during the period when the patient was receiving hydrogen capsules. Flow cytometry was utilized for whole-blood analysis to evaluate changes in immune cell populations before and after hydrogen therapy. For subsequent analyses, blood samples were prepared using standard

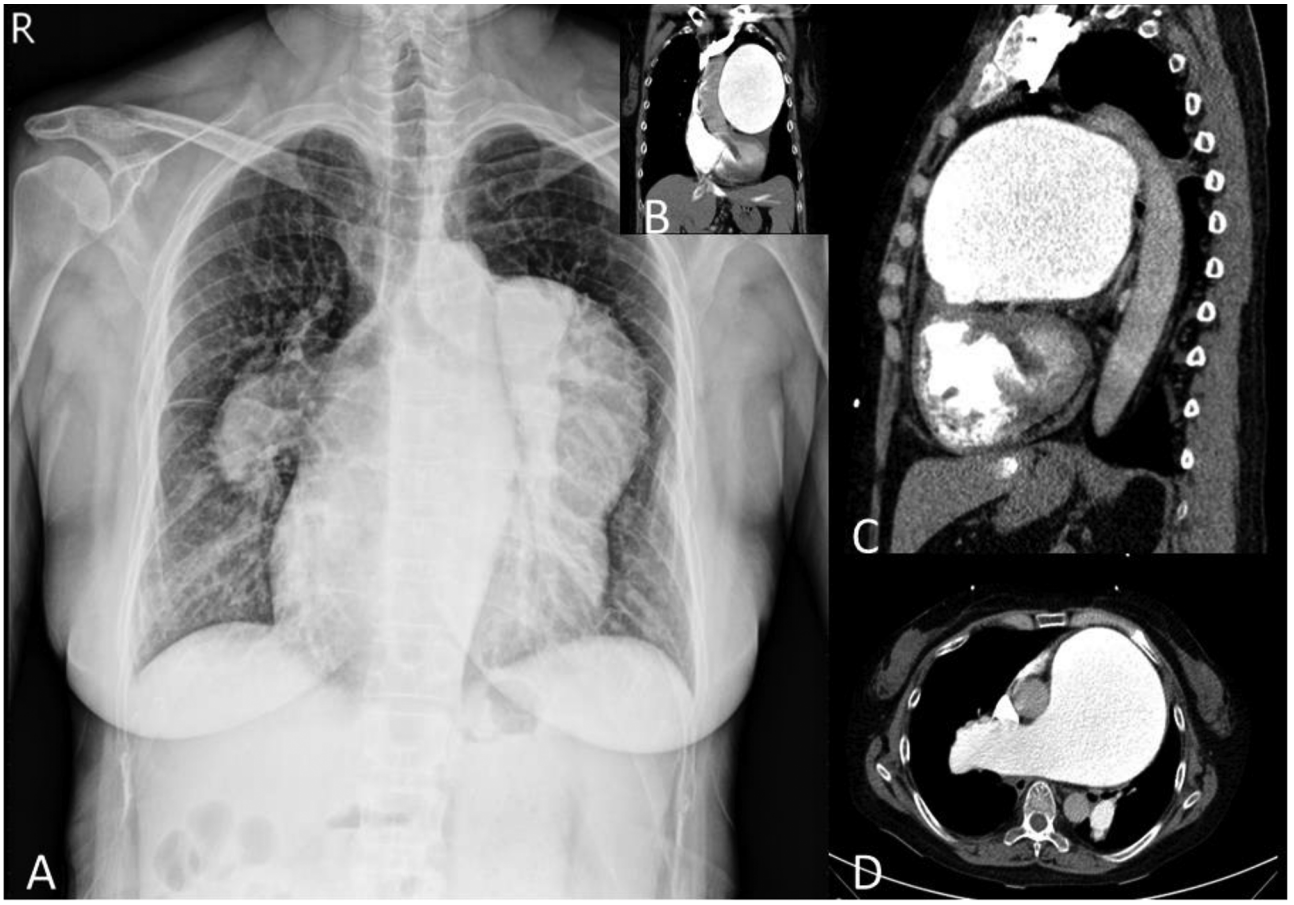

Figure 2. *Clinical course of the patient. (A) Chest X-ray (CXR) image obtained on July 26, 2024, demonstrates an enlarged cardiac silhouette, prominence of the bilateral pulmonary hilum, and increased interstitial markings in both lungs, along with aneurysmal dilation of the pulmonary trunk. (B to D) Chest computed tomography (CT) scans with contrast, acquired on July 29, 2024, reveal significant dilation of the pulmonary trunk, measuring 11.4 cm × 10.8 cm in panel B, 11.4 cm × 10.0 cm in panel C, and 11.8 cm × 9.6 cm in panel D.*

fluorescent dye preparation techniques and fluorescent antibody reagent kits with dried reagents (Beckman Coulter, Brea, CA, USA). The methods, steps, immunophenotypic analyses, and cell gating procedures were performed according to previously established protocols (19-21). Our immunophenotypic analysis before and after hydrogen therapy revealed an increase in Tr1 cells and a decrease in Treg and B cell subsets following treatment. This study complies with the CARE guidelines for case reports, as outlined in the 2013 CARE Checklist.

Discussion

This case study of SLE-PAH with decompensated right-sided heart failure brings out the urgent need for novel therapeutic approaches beyond the standard combination therapy of riociguat, macitentan, and selexipag. Despite several years of combination treatment, the patient continued to experience persistent dyspnea, ultimately requiring emergency interventions due to sepsis. Tr1 cells, known for producing immunosuppressive cytokines interleukin-10 (IL-10) and transforming growth factor-beta

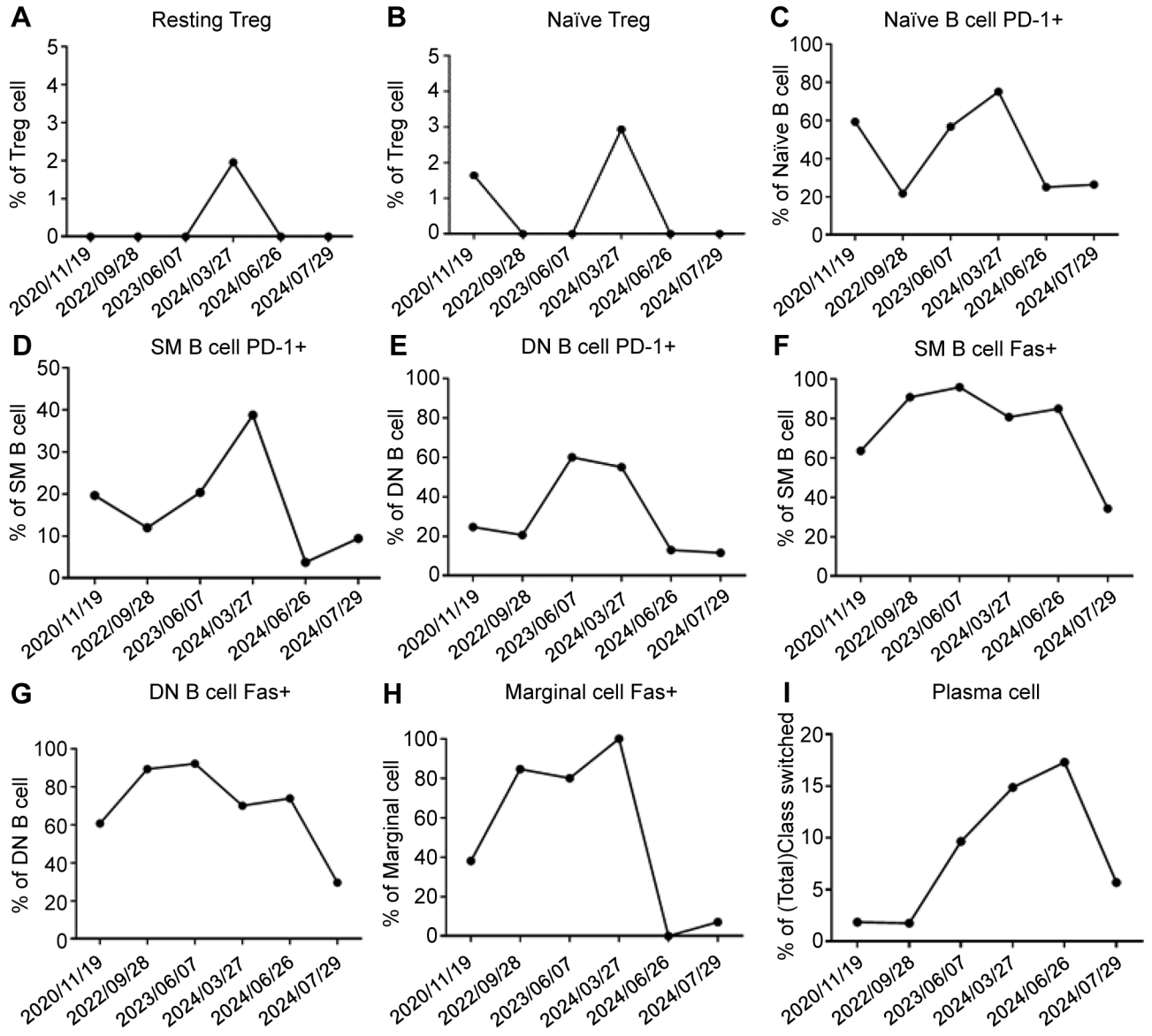

Figure 3. *Immunophenotypic changes before and after receiving molecular hydrogen therapy on March 27, 2024. Whole-blood analysis was conducted six times: prior to molecular hydrogen therapy (up to November 19, 2020) and post-therapy (from March 27, 2024 to July 29, 2024. (A to B) The percentage change in T regulatory (Treg) cell subsets, including resting Treg and Naïve Treg cells, shows a decreasing trend following molecular hydrogen therapy (C to E). The percentage change in B cells PD-1+ subsets, including Naïve B cells PD-1+, switch memory (SM) B cells PD-1+, double-negative (DN) B cell PD-1+, also exhibits a decreasing trend after therapy. (F to G) The percentage change in B cell Fas+ subsets, including SM B cells Fas+ and DN B cell Fas+, demonstrates a decreasing trend post-therapy. (H) The percentage change in marginal cell Fas+ shows a decreasing trend after molecular hydrogen therapy. (I) The percentage change in plasma cells reveals a decreasing trend post-therapy.*

(TGF-β), play a key role in down-regulating inappropriate immune responses to both pathogenic and non-pathogenic antigens (22). A previous study has demonstrated the ability of Tr1 cells to reduce inflammation in a preclinical model of inflammatory bowel disease (IBD) (23). In this case, following molecular hydrogen therapy, the patient

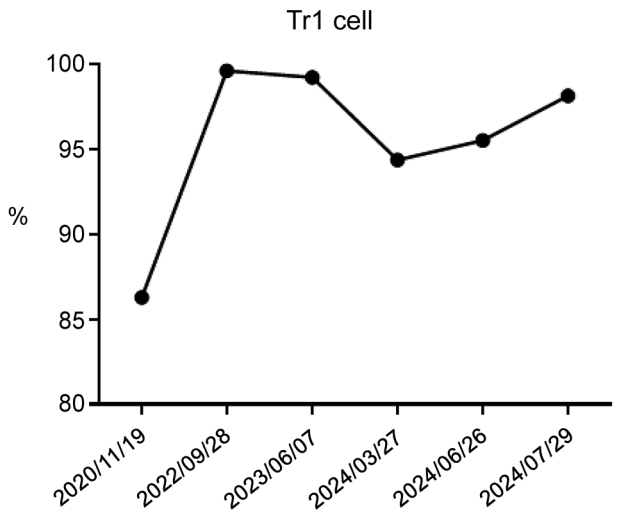

Figure 4. *Immunophenotypic changes in Type 1 regulatory (Tr1) cells before and after receiving molecular hydrogen therapy on March 27, 2024. Whole-blood analysis was conducted six times: prior to molecular hydrogen therapy (up to November 19, 2020) and post-therapy (from March 27, 2024 till July 29, 2024). The analysis indicates an increasing trend in Tr1 cells following molecular hydrogen therapy.*

showed an increase in Tr1 cells, suggesting a potential immunomodulatory effect that may have helped prevent further progression of her autoimmune disease. Conversely, Treg cells are critical for maintaining immune homeostasis and self-tolerance, with their expansion often associated with the suppression of autoimmune disorders and allergic reactions (24). Prior to March 2024, Treg cells were barely detectable in the patient's blood. However, a significant increase in Treg cells was observed upon her admission in March 2024, likely indicating an active flare of her underlying disease. This suggests that Treg cells were mobilized to control the inflammatory response. After initiating molecular hydrogen therapy, Treg cells once again became nearly undetectable, implying that the previous inflammatory episode has been resolved.

The activation of B cells and plasma cells plays a crucial role in vascular remodeling in hypertension patients, which may contribute to the worsening of pulmonary hypertension (25). Following the administration of molecular hydrogen therapy, a decreasing trend in B cell subset percentages was observed, suggesting that this therapy has the potential to modulate B cell function. Dysregulated B cell responses are known to contribute to the pathogenesis of several autoimmune diseases, including pulmonary hypertension (26). By targeting B cell subsets, molecular hydrogen therapy may reduce abnormal immune activation and prevent further vascular damage in patients with SLE-PAH. Additionally, the disease activity of SLE has been linked to the frequency of circulating plasma cells (27). Our findings suggest that molecular hydrogen therapy also improves SLE disease activity, as evidenced by a decrease in the percentage of plasma cells after initiating the therapy.

Overall, the findings from this case study suggest that molecular hydrogen therapy may offer therapeutic benefits in managing SLE-PAH with decompensated right-sided heart failure complicated by sepsis. With its anti-inflammatory and immunomodulatory properties, molecular hydrogen therapy has shown promise in slowing disease progression and improving clinical symptoms in patients who have responded poorly to conventional treatments. Additionally, its favorable safety profile, as demonstrated by the absence of adverse reactions in this case, underscores its potential as a well-tolerated adjunctive therapy for SLE-PAH. However, larger-scale studies with long-term follow-up are needed to confirm its efficacy and to establish practical guidelines for its use in managing SLE-PAH.

Conclusion

This case study demonstrates the potential efficacy of molecular hydrogen therapy in a patient with SLE-PAH and decompensated right-sided heart failure precipitated by sepsis. The therapeutic promise of molecular hydrogen is notable, given its diverse mechanisms of action and its modulation of immune markers. However, further studies with larger sample sizes and long-term follow-up are necessary to confirm its clinical efficacy.

Conflicts of Interest

The Authors declare no conflicts of interest related to this study.

Authors' Contributions

THT: Conceptualization, methodology, writing – original draft, writing review and editing. JWL: Conceptualization, methodology, writing original draft, writing review and editing. CHW: Conceptualization, methodology, project administration, writing original draft, writing review and editing. YJH: Conceptualization, methodology, project administration, writing review and editing. SWL: Conceptualization, methodology, writing review and editing. TYH: Conceptualization, methodology writing review and editing. KYW: Conceptualization, methodology, writing review and editing. FCL: Conceptualization, investigation, supervision, writing review and editing.

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