

Successful treatment with hydrogen rich water in a case of chronic graft-versus-host-disease

Li-ren Qian*, Jian-liang Shen

Department of Hematology, Navy General Hospital, Beijing, China

*Correspondence to: Li-ren Qian, M.D., qlr2007@126.com.

orcid: 0000-0002-7750-9177

Abstract

The incidence of chronic graft-versus-host-disease is rising year by year, which has become the leading cause of non-transplantation related death and has become the most difficult complication of allogeneic hematopoietic stem cell transplantation to deal with. Inflammation and fibrosis play dominant roles in the pathogenesis of chronic graft-versus-host-disease. Studies have shown that molecular hydrogen has anti-inflammatory, antioxidant, anti-fibrosis effects. Therefore, we hypothesized that molecular hydrogen may have therapeutic effects on chronic graft-versus-host-disease. Here, we report a patient with severe chronic graft-versus-host-disease successfully treated by drinking hydrogen rich water which may be a safe and effective method for chronic graft-versus-host-disease.

Key words: graft-versus-host disease; hydrogen; cytokines; transplantation

Funding: This study was supported by Innovative Cultivation Foundation of Chinese Navy General Hospital, No. CXPY201603.

doi: 10.4103/2045-9912.191366

How to cite this article: Qian LR, Shen JL (2016) Successful treatment with hydrogen rich water in a case of chronic graft-versus-host-disease. *Med Gas Res* 6(3):177-179.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been widely used in many hematological diseases. Chronic graft-versus-host disease (cGVHD) is one of the most common complications of allo-HSCT which has become the leading cause of non-transplantation related death (Martin et al., 2010). With the increase application of allo-HSCT in elderly patients, the wide application of peripheral blood stem cells as a graft and improvement of the early survival rate after transplantation, the incidence of cGVHD is rising year by year (Anasetti et al., 2012). cGVHD is a kind of disease similar to systemic lupus erythematosus (SLE) and scleroderma (Lee et al., 2003).

It is widely accepted that imbalance of inflammatory factors (such as tumor necrosis factor alpha (TNF- α), interleukin (IL)-2, IL-6, IL-10, IL-12, interferon (INF)-gamma, transforming growth factor (TGF)-beta, *etc.*) and fibrosis occupy the dominant position in the mechanism of cGVHD (Flowers and Martin, 2015).

In 2007, Ohsawa et al. (2007) discovered that hydrogen

gas has antioxidant properties. Since then, hydrogen gas has come to the forefront of therapeutic medical gas research. Recent basic and clinical research (Fukuda et al., 2007; Cai et al., 2008; Nagata et al., 2009; Sun et al., 2009) proved that hydrogen could down-regulate cytokines, including chemokine (C-C motif) ligand 2 (CCL2), IL-1 β , IL-6, IL-12, TNF- α , *etc.* In 2011, Terasaki et al. (2011) also demonstrated that hydrogen has anti-fibrosis effect. Since 2009, hydrogen was applied on the field of organ transplantation including intestinal transplantation, lung transplantation, renal transplantation and heart transplantation. It was demonstrated that hydrogen could protect allograft function in those models (Buchholz et al., 2008; Nakao et al., 2009; Cardinal et al., 2010; Kawamura et al., 2010, 2011; Chuai et al., 2012). We also reported the therapeutic effects of hydrogen gas on acute graft-versus-host disease (Qian and Shen, 2013; Qian et al., 2013). We reasoned that hydrogen may have therapeutic effects on cGVHD.

CASE REPORT

A 54-year-old Chinese man in our outpatient clinic was



Table 1: Clinical characters of the patient with chronic graft-versus-host disease treated by hydrogen rich water

Score	Before therapy	3 months after therapy	6 months after therapy
NIH global severity score	3	2	1
NIH organ severity scores			
Performance	2	1	0
Skin	3	2	1
Mouth	2	2	0
Eyes	3	2	1
Gastrointestinal tract	2	1	0
Liver	2	0	0
Lung	2	1	0
Joints and fascia	1	0	0

Note: NIH: National Institutes of Health.

diagnosed with myelodysplastic syndromes French-American-British (FAB) subtype refractory anemia with excess blasts-2 (RAEB-2) based on bone marrow morphology and developed cGVHD 3 years after allo-HSCT. He was diagnosed to have cGVHD. Clinical characters are shown in **Table 1** according to National Institutes of Health (NIH) standards (Jagasia et al., 2015). He was given treatment of prednisone and tacrolimus, but the symptoms were not controlled. When he came to our outpatient clinic, he was still treated with oral 10 mg prednisone daily and 0.5 mg tacrolimus. We added hydrogen-rich water (500 mL three times per day, 0.6 mM) which was prepared as we previously described (Qian et al., 2013). Prednisone and tacrolimus were tapered in three months. After 3 and 6 months, the patient's clinic characters were evaluated again as shown in **Table 1**. The patient is still alive until this report with good life quality.

CONCLUSIONS

The incidence of cGVHD is rising year by year, and there is no ideal treatment, cGVHD has become the most intractable complications after allo-HSCT, which greatly reduces the patient's life quality and survival rate. In the past three decades, glucocorticoids (*e.g.*, prednisone, prednisolone, dexamethasone), calcineurin inhibitors (*e.g.*, tacrolimus, cyclosporin) and other immunosuppressive agents still play critical roles in cGVHD. cGVHD is often with long course, and side effects of these drugs are always too severe to be tolerated (Flowers and Martin, 2015). Hydrogen, however, has few side effects, making it able to be used safely for a long term. Further studies with large sample size are needed to verify whether hydrogen results in a significant improve-

ment in patient outcomes.

Author contributions

LRQ and JLS designed the research. LRQ analyzed the data and prepared the typescript. Both authors read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

REFERENCES

- Anasetti C, Logan BR, Lee SJ, Waller EK, Weisdorf DJ, Wingard JR, Cutler CS, Westervelt P, Woolfrey A, Couban S, Ehninger G, Johnston L, Maziarz RT, Pulsipher MA, Porter DL, Mineishi S, McCarty JM, Khan SP, Anderlini P, Bensinger WI, et al. (2012) Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med* 367:1487-1496.
- Buchholz BM, Kaczorowski DJ, Sugimoto R, Yang R, Wang Y, Billiar TR, McCurry KR, Bauer AJ, Nakao A (2008) Hydrogen inhalation ameliorates oxidative stress in transplantation induced intestinal graft injury. *Am J Transplant* 8:2015-2024.
- Cai J, Kang Z, Liu WW, Luo X, Qiang S, Zhang JH, Ohta S, Sun X, Xu W, Tao H, Li R (2008) Hydrogen therapy reduces apoptosis in neonatal hypoxia-ischemia rat model. *Neurosci Lett* 441:167-172.
- Cardinal JS, Zhan J, Wang Y, Sugimoto R, Tsung A, McCurry KR, Billiar TR, Nakao A (2010) Oral hydrogen water prevents chronic allograft nephropathy in rats. *Kidney Int* 77:101-109.
- Chuai Y, Qian L, Sun X, Cai J (2012) Molecular hydrogen and radiation protection. *Free Radic Res* 46:1061-1067.
- Flowers ME, Martin PJ (2015) How we treat chronic graft-versus-host disease. *Blood* 125:606-615.
- Fukuda K, Asoh S, Ishikawa M, Yamamoto Y, Ohsawa I, Ohta S (2007) Inhalation of hydrogen gas suppresses hepatic injury caused by ischemia/reperfusion through reducing oxidative stress. *Biochem Biophys Res Commun* 361:670-674.
- Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, Palmer J, Weisdorf D, Treister NS, Cheng GS, Kerr H, Stratton P, Duarte RF, McDonald GB, Inamoto Y, Vigorito A, Arai S, Datile MB, Jacobsohn D, Heller T, et al. (2015) National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant* 21:389-401 e381.
- Kawamura T, Huang CS, Peng X, Masutani K, Shigemura N, Billiar TR, Okumura M, Toyoda Y, Nakao A (2011) The effect of donor treatment with hydrogen on lung allograft function in rats. *Surgery* 150:240-249.
- Kawamura T, Huang CS, Tochigi N, Lee S, Shigemura N, Billiar TR, Okumura M, Nakao A, Toyoda Y (2010) Inhaled hydrogen gas therapy for prevention of lung transplant-induced ischemia/reperfusion injury in rats. *Transplantation* 90:1344-1351.
- Lee SJ, Vogelsang G, Flowers ME (2003) Chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 9:215-233.



- Martin PJ, Counts GW, Jr., Appelbaum FR, Lee SJ, Sanders JE, Deeg HJ, Flowers ME, Syrjala KL, Hansen JA, Storb RF, Storer BE (2010) Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. *J Clin Oncol* 28:1011-1016.
- Nagata K, Nakashima-Kamimura N, Mikami T, Ohsawa I, Ohta S (2009) Consumption of molecular hydrogen prevents the stress-induced impairments in hippocampus-dependent learning tasks during chronic physical restraint in mice. *Neuropsychopharmacology* 34:501-508.
- Nakao A, Kaczorowski DJ, Wang Y, Cardinal JS, Buchholz BM, Sugimoto R, Tobita K, Lee S, Toyoda Y, Billiar TR, McCurry KR (2009) Amelioration of rat cardiac cold ischemia/reperfusion injury with inhaled hydrogen or carbon monoxide, or both. *J Heart Lung Transplant* 29:544-553.
- Ohsawa I, Ishikawa M, Takahashi K, Watanabe M, Nishimaki K, Yamagata K, Katsura K, Katayama Y, Asoh S, Ohta S (2007) Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. *Nat Med* 13:688-694.
- Qian L, Mei K, Shen J, Cai J (2013) Administration of hydrogen-rich saline protects mice from lethal acute graft-versus-host disease (aGVHD). *Transplantation* 95:658-662.
- Qian L, Shen J (2013) Hydrogen therapy may be an effective and specific novel treatment for acute graft-versus-host disease (GVHD). *J Cell Mol Med* 17:1059-1063.
- Sun Q, Kang Z, Cai J, Liu W, Liu Y, Zhang JH, Denoble PJ, Tao H, Sun X (2009) Hydrogen-rich saline protects myocardium against ischemia/reperfusion injury in rats. *Exp Biol Med* (Maywood) 234:1212-1219.
- Terasaki Y, Ohsawa I, Terasaki M, Takahashi M, Kunugi S, Dedong K, Urushiyama H, Amenomori S, Kaneko-Togashi M, Kuwahara N, Ishikawa A, Kamimura N, Ohta S, Fukuda Y (2011) Hydrogen therapy attenuates irradiation-induced lung damage by reducing oxidative stress. *Am J Physiol Lung Cell Mol Physiol* 301:L415-426.