Early-stage lupus nephritis treated with N-acetylcysteine: A report of two cases

MING LI[1,2], WENJUAN GAO[3], JINGJING MA[2], YUN ZHU[2] and XINGFU LI[1]

[1]Department of Rheumatism and Immunity, Qilu Hospital of Shandong University, Jinan, Shandong 250012; Departments of [2]Rheumatism and Immunity, and [3]Ultrasound, Weifang People's Hospital, Weifang, Shandong 261041, P.R. China

Received January 14, 2015; Accepted April 21, 2015

DOI: 10.3892/etm.2015.2510

Abstract. The oxidative-antioxidative status is closely associated with the progression of systemic lupus erythematosus (SLE), and oxidative stress is customarily found in patients with SLE. N-acetylcysteine (NAC), a typical antioxidant, is reliable and often applied for clinical treatment. Lupus nephritis (LN) is a kidney disorder associated with SLE, but the treatment of LN with antioxidants is rarely documented. The present report describes two cases of early-stage LN that were orally treated with 1,200 mg NAC in addition to the standard therapy with hydroxychloroquine and calcitriol. Following the NAC administration, the glutathione level largely increased while the level of the lipid peroxidation biomarker 8-iso-prostaglandin F2α declined in both cases. In addition, the routine blood counts, 24-h urine protein, erythrocyte sedimentation rate and the SLE disease activity index were markedly improved. In conclusion, the present report of two cases has shown that NAC, as an antioxidant, may exert a beneficial effect to modulate the oxidative status in LN; however, the underlying mechanisms require further investigation.

Introduction

Systemic lupus erythematosus (SLE), a chronic and multi-system autoimmune disorder that is characterized by dysregulated immune responses and production of pathogenic autoantibodies by immune cells such as B-cells, T-cells and dendritic cells (1). The clinical presentations of SLE include rash, oral ulcers, fatigue and arthralgias, and the course of the disease is unpredictable, with periods of flares alternating with remission (1). The pathogenesis of SLE remains unclear, and autoantibodies, proinflammatory and anti-inflammatory cytokines, lymphocyte subset abnormalities as well as genetic predispositions may contribute to the development of SLE (2). The disease occurs more often in women, with an incidence about nine times higher compared to men, and is also more common in non-Caucasian descent (1). SLE can affect the majority of organs and tissues such as skin, joints, lungs, blood vessels and kidneys. Lupus nephritis (LN) is a sever consequence of SLE, and ~ 40-70% of patients with SLE would develop LN (3).

At present, LN is primarily treated with corticosteroids and immunosuppressive drugs, but is often associated with high morbidity and suboptimal outcomes (4). As an inflammation of the kidney caused by systemic lupus erythematosus (SLE), LN has been documented to be closely associated with the imbalance between oxidative and antioxidative activities during the pathogenesis of LN (5,6). The few studies that have investigated the use of antioxidants in the treatment of LN have resulted in a satisfactory outcome (7,8). N-acetylcysteine (NAC) is a typical antioxidant that is often used during clinical treatments (9). It is believed that NAC primarily acts as a glutathione precursor to minimize the hepatic risk caused by paracetamol poisoning (10). The present report describes two cases of early-stage LN that were treated with NAC.

Case report

Two female patients were diagnosed with SLE in accordance with the criteria of the American College of Rheumatology (2009) (11): i) Polyarthritis, ii) leucopenia, iii) renal involvement and iv) positive for antinuclear antibodies (ANA+). As no serious damage in the target organs or obvious damage to the skin was evident, and considering the possible adverse effects of corticosteroids and immunosuppressive drugs, the two cases were treated with hydroxychloroquine (400 mg/day; Shanghai Zhongxi Pharmaceutical Co., Ltd., Shanghai, China), calcitriol (0.25 μg/day; Qingdao Haier Pharmaceutical Co., Ltd., Qingdao, China) and NAC (1.2 g/day; Zambon S.p.A., Bresso, Italy). The NAC effervescent tablet was dissolved in warm water and taken twice a day, at a dose of 600 mg each time. The 3-month (12-week) intervention was decided according to a previous study (8). The routine blood and urine, 24-h urine protein,

Correspondence to: Dr Ming Li, Department of Rheumatism and Immunity, Weifang People's Hospital, 151 Guangwen Road, Weifang, Shandong 261041, P.R. China
E-mail: lalwlm@aliyun.com

Key words: lupus nephritis, N-acetylcysteine, oxidative stress, case report

Table I. Examination of the relative indexes prior to and following treatment with N-acetylcysteine.

A, Case 1

Indexes	Pre-treatment	8 weeks after treatment	12 weeks after treatment
Weight (kg)	77	70	65
White blood cell ($x10^9$/l)	2.5	3.4	3.9
24-h urine protein (g)	2.1	1.8	1.0
ESR (mm/h)	56	40	32
GSH (mg/g)	0.46	0.95	1.13
8-iso-PGF2α (μg/l)	66.3	50.5	56.7
GFR (μl/min)	105	106	93
Creatinine (μmol/l)	95	84	90
Urinalysis[a]	pro3+	pro2+	pro1+
SLEDAI	9	8	4

B, Case 2

Indexes	Pre-treatment	8 weeks after treatment	12 weeks after treatment
Weight (kg)	56	55	53
White blood cell ($x10^9$/l)	2.9	3.5	3.8
24-h urine protein (g)	1.5	1.2	0.9
ESR (mm/h)	49	45	33
GSH (mg/g)	0.56	1.02	1.21
8-iso-PGF2α (μg/l)	70.2	61.4	55.8
GFR (μl/min)	103	102	97
Creatinine (μmol/l)	63	70	65
Urinalysis[a]	pro2+	pro1+	pro1+
SLEDAI	9	8	4

[a]Hematuria, urinary casts and pyuria were not observed in urinalysis of either patient. ESR, erythrocyte sedimentation rate; GSH, glutathione; 8-iso-PGF2α, 8-iso-prostaglandin F2α; GFR, glomerular filtration rate; SLEDAI, systemic lupus erythematosus disease activity index; Pro, proteinuria; pro1+, proteinuria <0.3 g/l; pro2+, 0.3 g/l ≤ proteinuria≤1 g/l; pro3+, 1 g/l<proteinuria<5 g/l.

liver and kidney function, erythrocyte sedimentation rate (ESR), glomerular filtration rate (GFR) and creatinine test results were examined. In addition, the levels of glutathione (GSH) and 8-iso-prostaglandin F2α (8-iso-PGF2α) in the whole blood were determined. The SLE disease activity index (SLEDAI) (12) and adverse effects were recorded and the therapeutic outcomes were evaluated at 8 and 12 weeks after treatment, respectively. Written informed consent was obtained from the patients.

Case 1. The patient was 17 years old and had suffered from tenderness and swelling of the knee joints and right wrist for 2 months prior to admittance in 2012. No obvious skin erythema, hair loss or lymph node swelling was observed, and the heart and lungs were normal in function. The biochemical examination revealed the following: White blood cells (WBC), $2.5x10^9$/l; hemoglobin (Hb), 110 g/l; blood platelets (PLT), $260x10^{12}$/l; ESR, 56 mm/h; ANA, +1:320; 24-h urine protein, 2.1 g; GSH, 0.46 mg/g; and 8-iso-PGF2α, 66.3 μg/l. Urinalysis showed urinary casts (-), pyuria (-) and pro3+ (proteinuria value between 1-5 g/l). The SLEDAI score was 9 (arthritis, 4; proteinuria, 4; leukopenia, 1) (Table I). At 8 weeks after treatment, the clinical presentation was in remission, and the relative indexes, such as WBC, 24-h urine protein and ESR, were improved. The SLEDAI score was 8 (arthritis, 4; proteinuria, 4). At 12 weeks after treatment, the biochemical examination revealed the following: WBC, $3.9x10^9$/l; ESR, 32 mm/h; 24-h urine protein, 1.0 g; GSH, 1.13 mg/g; and 8-iso-PGF2α, 56.7 μg/l. Urinalysis showed urinary casts (-), pyuria (-) and pro1+. The SLEDAI score was 4 (proteinuria, 4), which was significantly different from that prior to treatment (Table I). The tenderness and swelling of the knee joints and right wrist were greatly alleviated, and the level of WBC returned to normal. The levels of GSH and 8-iso-PGF2α were considerably improved, and were significantly different from those prior to treatment (Table I). The 24-h urine protein and ESR were also notably improved (Table I).

Case 2. The patient was 26 years old and had suffered from tenderness and swelling of the wrists and joints of the hands for 6 months prior to admittance in 2013. No obvious skin erythema, hair loss or lymph node swelling was observed, and

the heart and lungs were normal in function. The laboratory examination revealed the following results: WBC, $2.9x10^9$/l; Hb, 115 g/l; PLT, $231x10^{12}$/l; ESR, 49 mm/h; ANA+, 1:160; 24-h urine protein, 1.5 g; GSH, 0.56 mg/g; and 8-iso-PGF2α, 70.2 μg/l. Urinalysis showed urinary casts (-), pyuria (-) and pro2+ (0.3 g/l ≤ proteinuria ≤ 1 g/l). The SLEDAI score was 9 (arthritis, 4; proteinuria, 4; leukopenia, 1) (Table I). Eight weeks after treatment, the clinical presentation was in remission, and the relative indexes, such as WBC, 24-h urine protein and ESR, were improved. The SLEDAI score was 8 (arthritis, 4; proteinuria, 4). At 12 weeks after treatment, the biochemical examination results were as follows: WBC, $3.8x10^9$/l; ESR, 33 mm/h; 24-h urine protein, 0.9 g; GSH, 1.21 mg/g; and 8-iso-PGF2α, 55.8 μg/l. These results were significantly different from those prior to treatment (Table I). Urinalysis showed urinary casts (-), pyuria (-) and pro1+ (proteinuria <0.3 g/l). The SLEDAI score was 4 (proteinuria, 4), as the tenderness and swelling of the wrists and joints of the hands were greatly alleviated, and the level of WBC returned to normal. The levels of GSH and 8-iso-PGF2α were largely improved, and were significantly different from those prior to treatment (Table I). The 24-h urine protein and ESR were also notably improved (Table I).

Discussion

The depletion of GSH in lymphocytes in patients with SLE was first reported in 2002 (13); thereafter, the increase in 8-iso-PGF2α (a biomarker of lipid peroxidation) and the reduction in GSH levels have been frequently observed in patients with SLE (5,6), suggesting that oxidative stress plays an essential role in the progression of SLE. Consistent with previous studies (5,6), the 8-iso-PGF2α level was high while the GSH level was low in both cases of early-stage LN in this report, indicating the existence of oxidative stress in the early stage of LN.

The treatment of LN with antioxidants has been rarely reported. A previous animal experiment showed that treatment with the antioxidant NAC in mouse models of SLE could reduce the rates of mortality (7). A study by Lai *et al* (14) indicated that NAC could improve SLE by blocking mammalian target of rapamycin (mTOR) activity in T cells. This is consistent with the results of the present study, which showed that NAC treatment could enhance the GSH levels in SLE and improve the disease outcome. It should be noted, however, that the dose of NAC used in the study by Lai *et al* (14) was very high (2.4 and 4.8 g daily), to a level that has rarely been reported previously, although the study declared that 2.4 g/day was safe and tolerate. A study by Garcia *et al* (15) has used similar doses to what was used by Lai *et al* (14). High doses of NAC have been demonstrated to frequently cause adverse effects (16), and the dose of 4.8 g/day used in the study by Lai *et al* (14) caused certain uncomfortable reactions. In a report by Tewthanom *et al* (8), NAC at the relatively high dose of 1.8 g/day was used to treat a patient with an LN-history of several years and achieved a satisfactory therapeutic outcome. In the present study, considering that the two cases were early-stage LN and that a high dose of NAC may have caused a higher risk of adverse effects (16), the moderate dose of NAC at 1.2 g/day was selected, to be administered in combination with the basic treatment using hydroxychloroquine and calcitriol (17,18). This dose of NAC achieved a good therapeutic effect in the present study and has been most widely used in the treatment of nephropathy (19,20), suggesting that it is effective for patients with early-stage LN.

The mechanism of NAC in the treatment of SLE is associated with its effect on oxidative stress. Studies have indicated that NAC can decrease the oxygen consumption in mitochondria (21) and block mTOR, a regulator of oxygen consumption and oxidative stress in mitochondria (22), which is consistent with the present finding that NAC increased the GSH and decreased the 8-iso-PGF2α levels in LN. Accordingly, after 12 weeks of treatment, the relative indexes, such as WBC, 24-h urine protein and ESR, were largely improved, and the SLEDAI was notably decreased, reflecting a satisfactory therapeutic outcome. In conclusion, this study suggests that the combination of NAC (1.2 g/day) with hydroxychloroquine and calcitriol may be suitable for the treatment of early-stage LN.

References

1. Yuen HK and Cunningham MA: Optimal management of fatigue in patients with systemic lupus erythematosus: a systematic review. Ther Clin Risk Manag 10: 775-786, 2014.
2. Yap DY and Lai KN: Pathogenesis of renal disease in systemic lupus erythematosus-The role of autoantibodies and lymphocytes subset abnormalities. Int J Mol Sci 16: 7917-7931, 2015.
3. Mohan C and Putterman C: Genetics and pathogenesis of systemic lupus erythematosus and lupus nephritis. Nat Rev Nephrol: March 31, 2015 (Epub ahead of print) doi: 10.1038/nrneph.2015.33.
4. Rovin BH and Parikh SV: Lupus nephritis: The evolving role of novel therapeutics. Am J Kidney Dis 63: 677-690, 2014.
5. Gopaul NK and Anggård EE: Measurement of 8-epi-PGF2alpha as a marker of lipid peroxidation in vivo by immunoaffinity extraction and gas chromatography-mass spectrometry. Methods Mol Biol 225: 329-342, 2003.
6. Jiang X and Chen F: The effect of lipid peroxides and superoxide dismutase on systemic lupus erythematosus: A preliminary study. Clin Immunol Immunopathol 63: 39-44, 1992.
7. Suwannaroj S, Lagoo A, Keisler D and McMurray RW: Antioxidants suppress mortality in the female NZB x NZW F1 mouse model of systemic lupus erythematosus (SLE). Lupus 10: 258-265, 2001.
8. Tewthanom K, Janwitayanujit S, Totemchockcyakarn K and Panomvana Na Ayudhya D: The effect of high dose of N-acetylcysteine in lupus nephritis: A case report and literature review. J Clin Pharm Ther 35: 483-485, 2010.
9. Holdiness MR: Clinical pharmacokinetics of N-acetylcysteine. Clin Pharmacokinet 20: 123-134, 1991.
10. Prescott L: Oral or intravenous N-acetylcysteine for acetaminophen poisoning? Ann Emerg Med 45: 409-413, 2005.
11. Petri M: Systemic lupus international collaborating clinic (SLICC) revision of the ACR classification criteria for SLE. Arthritis Rheum 60 (Suppl 10): 895, 2009.
12. Gladman DD, Ibañez D and Urowitz MB: Systemic lupus erythematosus disease activity index 2000. J Rheumatol 29: 288-291, 2002.
13. Gergely P Jr, Grossman C, Niland B, Puskas F, Neupane H, Allam F, Banki K, Phillips PE and Perl A: Mitochondrial hyperpolarization and ATP depletion in patients with systemic lupus erythematosus. Arthritis Rheum 46: 175-190, 2002.
14. Lai ZW, Hanczko R, Bonilla E, *et al*: N-acetylcysteine reduces disease activity by blocking mammalian target of rapamycin in T cells from systemic lupus erythematosus patients: A randomized, double-blind, placebo-controlled trial. Arthritis Rheum 64: 2937-2946, 2012.
15. Garcia RJ, Francis L, Dawood M, Lai ZW, Faraone SV and Perl A: Attention deficit and hyperactivity disorder scores are elevated and respond to N-acetylcysteine treatment in patients with systemic lupus erythematosus. Arthritis Rheum 65: 1313-1318, 2013.
16. Sandilands EA and Bateman DN: Adverse reactions associated with acetylcysteine. Clin Toxicol (Phila) 47: 81-88, 2009.

17. vinh quỗc Luong K and Nguyễn LT: The beneficial role of vitamin D in systemic lupus erythematosus (SLE). Clin Rheumatol 31: 1423-1435, 2012.
18. Willis R, Seif AM, McGwin G Jr *et al*: Effect of hydroxychloroquine treatment on pro-inflammatory cytokines and disease activity in SLE patients: Data from LUMINA (LXXV), a multiethnic US cohort. Lupus 21: 830-835, 2012.
19. Brown JR and Thompson CA: Contrast-induced acute kidney injury: The at-risk patient and protective measures. Curr Cardiol Rep 12: 440-445, 2010.
20. Maeder M, Klein M, Fehr T and Rickli H: Contrast nephropathy: Review focusing on prevention. J Am Coll Cardiol 44: 1763-1771, 2004.
21. Doherty E, Oaks Z and Perl A: Increased mitochondrial electron transport chain activity at complex I is regulated by N-acetylcysteine in lymphocytes of patients with systemic lupus erythematosus. Antioxid Redox Signal 21: 56-65, 2014.
22. Schieke SM, Phillips D, McCoy JP Jr, Aponte AM, Shen RF, Balaban RS and Finkel T: The mammalian target of rapamycin (mTOR) pathway regulates mitochondrial oxygen consumption and oxidative capacity. J Biol Chem 281: 27643-27652, 2006.