

Integrative therapy of traditional Chinese medicine and conventional medicine in the treatment of lupus nephritis from a single-center experience

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Abstract

Lupus nephritis (LN) is the most common complication of systemic lupus erythematosus and the leading cause of mortality. The complex pathogenesis and various clinical manifestations of this disease increase the difficulty of the treatments. The current treatments with Western medicine including glucocorticoids, mycophenolate mofetil and other immunosuppressants, and biological agents have greatly improved the patients' survival. However, frequent recurrence occurred and LN remained an important cause of end stage renal disease. The increasing adverse effects with the prolongation of treatment also restrained the efficacy of Western medicine. Increasing evidence has demonstrated the therapeutic efficacy of traditional Chinese medicine (TCM) which provides a theoretical basis for the integrative therapy of TCM and Western medicine for LN. We previously established a unique comprehensive treatment strategy for LN with the combination of TCM and Western medicine based on the TCM theory and achieved good clinical efficacy. This review will summarize the single-center experience that integrative therapy of TCM, represented by Lupus Recipe and artesunate, and Western medicine for LN treatment, and elucidate the potential mechanism, with the purpose to provide reliable evidence for developing more effective personalized treatment strategies in the future.

KEYWORDS

artesunate, integrative therapy, lupus nephritis, lupus recipe, traditional Chinese medicine

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can cause damage to multiple organs, and approximately 50% of patients with SLE can suffer from lupus nephritis (LN); LN is the most common complication of SLE and the leading cause of mortality [1]. The cardinal pathogenesis of this disease

included break of self-tolerance, continuously activated type I interferon (IFN-I) signaling pathway, production of autoantibodies, immune complex deposition and immune-mediated injury to the kidney, thereby promoting cell proliferation, apoptosis, and inducing inflammatory and fibrotic processes that caused damage to normal nephrons [2–6]. The clinical manifestations of LN are variable, including multiple manifestations

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related with nephritic and nephrotic syndromes and ESRD, as well as extra-renal damage [7]. The complicated pathogenesis and diverse clinical manifestations of this disease increase the difficulty of the treatments. The main goal of the treatment is to control disease activity and inhibit kidney progression. Currently, the first-line options for treatment represented by glucocorticoids, mycophenolate mofetil (MMF)/mycophenolate acid (MPA), and cyclophosphamide (CTX) have greatly improved the patients' survival [8]. Despite the advancement of treatment methods, over 10% of LN patients will develop end-stage renal disease in a 10-year follow-up period [9]. Additionally, with the long-term treatment of Western medicine, especially high-dose glucocorticoids, many patients have decreased compliance due to numerous side effects, such as osteonecrosis, bone fractures, cataracts, hyperglycemia/diabetes, and bone marrow suppression [10]. The novel biological agents including Rituximab [11–13] and Obinutuzumab [14] bring hope to the treatment of intractable lupus [15], but the expensive cost limits its application. Therefore, other treatment options should be explored to improve the therapeutic efficacy.

Traditional Chinese medicine (TCM) is a kind of natural substance that is applied to treat various diseases based on the guidance of TCM theory. The application of TCM has a history of over a thousand years, condensing the wisdom and practical experience of Chinese ancestors. According to the TCM science, the basic features of pathogenesis of LN are deficiency of the origin and excess of the essence; deficiency of the origin is characterized by the imbalance of yin and yang in Zang-fu organs, mainly manifested as loss of Shen-yin; excess of the essence is characterized by heat toxin, damp heat, dampness and turbidity, and blood stasis, with accumulation of heat toxin and stagnation of blood stasis being the main manifestations. Therefore, the therapeutic principles for LN are promoting blood circulation and clearing heat and detoxification [16]. Compared with conventional medicine, TCM has relatively fewer side effects. Moreover, TCM can provide an alternative treatment option in cases where patients appear resistant to the immunosuppressive therapy or serve as complementary treatments to exert synergistic action for therapy and decrease side effects of the immunosuppressants [17]. Actually, integrative therapy with conventional medicine and TCM for LN has been applied in clinical practice and obtained an improved therapeutic efficacy for decades in China [18–23]. Various components of TCMs have been proven to have anti-inflammatory and immunoregulatory effects in LN, such as quercitrin [24], Baicalein [25], and coptisine [26]. This provides a theoretical basis for the integrative therapy of TCM and Western medicine for LN.

In our hospital, LN patients had been treated with methods integrating TCM and Western medicine for

over 50 years. We proposed that in the course of LN, the accumulation of heat and toxin, as well as stagnation of blood stasis, were the characteristic pathogenesis that ran through the entire stages of disease and were the main factors leading to the occurrence and development of the disease. In the early or active stages of SLE, the main manifestations are excessive heat toxicity and blood stasis, which is a syndrome of excess in superficiality, and the treatment mainly focused on dispelling pathogenic factors and emphasizing the application of drugs that clear heat, detoxify, and promote blood circulation and blood stasis; in the inactive or stable stages of the disease, the main manifestations are kidney deficiency, deficiency of yin and yang qi and blood, which is a syndrome of deficiency in origin, and the syndrome of heat toxins and blood stasis still exist in this stage. The treatment should mainly focus on nourishing the body, tonifying the liver and kidney, supplemented by dispelling pathogenic factors. The key to dispelling pathogenic factors was to clear heat, detoxify, and promote blood circulation and blood stasis. We believe that in the treatment of LN, blocking or eliminating treatment should be targeted at the unique etiology and pathogenesis of heat toxin accumulation and stasis of blood. If only symptomatic or purely dialectical treatment is used, it is difficult to achieve satisfactory therapeutic effects. Based on this, we take clearing heat and detoxifying, promoting blood circulation and removing stasis as the basic treatment principles, and choose the “Lupus Recipe”(LR) as the basic Chinese medicine prescription for treating SLE and LN [27]. In the active stage, SLE or LN patients often exhibit intense heat toxicity and require extensive use of glucocorticoids combined with CTX pulse therapy. At this time, on the basis of the LR, TCM for clearing heat and detoxifying should be intensified, combined with Qingwen Baidu Yin. When the patients' symptoms improve after treatment and the dose of glucocorticoids is reduced, their dialectics are mostly characterized by yin deficiency and excessive fire and the treatment should be supplemented with nourishing yin and reducing fire methods, combined with Zhibai Dihuang Tang. When the patients' conditions are basically inactive, they often exhibit symptoms of qi and yin deficiency and the treatment should be beneficial to qi and yin, combined with Shenqi Dihuang Tang. When the patients suffer a decrease in peripheral white blood cells, TCM such as Danggui Buxue Tang should be added to the basic formula to supplement qi and nourish blood.

Additionally, we recently dominated a randomized controlled trial of artesunate combined with immunosuppressants in the treatment of LN, and the clinical trial has been completed. In this review, we will take the commonly used TCM, that is, LR and artesunate, as representatives to clarify and summarize the therapeutic efficacy of integrative therapy for LN in our center

and the potential mechanisms of the related TCM components.

INTEGRATIVE THERAPY OF LUPUS RECIPE AND WESTERN MEDICINE

LR is a specialized TCM compound invented by Professor Ye by a combination of traditional Chinese and Western medicine for the treatment of LN under the guideline of Jiedu Huoxue Treatment Method (detoxifying and activating blood). The LR is composed of seven herb medicines including Bai Hua She She Cao (*Hedyotis diffusa* Willd.), Zi Cao (*Lithospermum erythrorhizon* Sieb.et Zucc), Ban Zhi Lian (*Scutellaria barbata* D. Don.), Sheng Di Huang (*Rehmannia glutinosa* Libosch.), Yi Mu Cao (*Leonurus japonicus* Houtt.), Dan Shen (*Salvia miltiorrhiza* Bunge.), and Quan Xie (*Scorpion*), in a weight ratio of 30: 10: 10: 15: 10: 15: 2 [28]. In the TCM theory, the components *Hedyotis diffusa* Willd. and *Scutellaria barbata* D. Don. serve as the Monarch for clearing heat and detoxifying and are the major component of LR; *Salvia miltiorrhiza* Bunge. and *leonurus japonicus* Houtt. serve as Minister for promoting blood circulation and remove blood stasis; *Lithospermum erythrorhizon* Sieb.et Zucc, *Rehmannia glutinosa* Libosch., and *Scorpion* serve as a combined Assistant for cooling blood, detoxifying, nourishing yin, unblocking circulation tracts, and promoting blood circulation.

Our clinical studies have confirmed that LN patients receiving combination therapy of LR and immunosuppressants exhibited improved therapeutic efficacy, while reducing side effects and disease flares compared with patients using immunosuppressants alone [23]. Results from animal studies showed that the therapeutic effect of LR combined with half dose prednisone (2.5 mg/kg/d) on treating chronic graft versus host disease (cGVHD) lupus mice was similar to the full dose prednisone (5 mg/kg/d); the protective effect of LR treatment might through regulating the LC3-associated autophagy (LAP) signaling pathway to reduce the expression of renal inflammatory cytokines IL-1 β and IL-6, decrease IgG deposit, and ameliorate kidney injury [28]. In addition, LR could significantly inhibit the CD40 expression in spleen cells and the production of autoantibodies in cGVHD lupus mice, as well as inhibit the spontaneous proliferation response of spleen cells and proliferation response stimulated by concanavalin A (Con A), suggesting that LR has an immunosuppressive effect and partially explain the synergistic effect of LR and immunosuppressants [29]. Experimental studies have also proved the protective effect of LR on kidney injury of MRL/lpr mice, by regulating NF- κ B signaling pathway, Sirt1, and Nrf2 [30]. In vitro study found that LR contained serum could significantly suppress IFN- γ and TNF α induced

expression of CD40 and RANTES in renal tubular epithelial cells via activating the peroxisome proliferator activated receptor (PPAR) γ signaling pathway [31, 32]. The advantages of LR combined with Western medicine in the treatment of LN are summarized in Figure 1.

As the key component of LR, *Hedyotis diffusa* Willd. was confirmed to alleviate glomerular lesions, decrease proteinuria and inflammatory cell infiltration by suppressing IL-6/STAT3 signaling pathway in MRL/lpr mice [33, 34]. Its ethyl acetate fraction can also inhibit T cell proliferation by regulating STAT3 signaling pathway to exert a therapeutic effect on lupus mice [35]. Another *Hedyotis diffusa* Willd. containing TCM preparation, namely Jieduquyuziyin prescription, could inhibit the activation and secretion of proinflammatory cytokines IL-6 and TNF- α in peritoneal macrophages of MRL/lpr mice, by regulating the IRAK-NF- κ B signaling pathway [36]. Quercetin and Baicalein are proved to be the main ingredients of *Hedyotis diffusa* Willd. and *Scutellaria barbata* D. Don [37]. Quercetin treatment could prevent LN in cGVHD mice by modulating the activation of CD4 T cells and inflammatory cytokines production of macrophages [24]. Quercetin could also play a nephroprotective role in pristane-induced LN mice via inhibition of kidney inflammatory cell infiltration, apoptosis, oxidative stress, and promotion of glomerular podocytes recovering [38]. Baicalein treatment alleviates the renal pathological damage and kidney function impairment and reduces proteinuria in pristane-induced LN. The mechanism of action was to suppress the expansion of myeloid-derived suppressor cells and the activation of NLRP3 inflammasome, while promoting the activation of the Nrf2/HO-1 signaling pathway [25]. These mechanism studies confirmed the multi-target therapeutic efficacies of LR in modern medical theory.

INTEGRATIVE THERAPY OF ARTESUNATE AND WESTERN MEDICINE

Artemisinin, also named *Qinghaosu*, is extracted from traditional Chinese herbal medicinal plant *Artemisia annua*, which was firstly used by Chinese herbal medicine practitioners for more than 2000 years [39]. It is believed to have the function of clearing hectic heat, and was therefore mainly used to treat malaria and tumors in the past, with few adverse effects and good safety [40–44]. Modern studies proved that it possessed the function of anti-inflammatory and immune-suppressive effects, indicating a potential benefit for the treatment of autoimmune diseases [45]. Evidence had shown that artemisinin was effective in treating lupus mice, and the mechanism involved the suppression of NF- κ B signaling pathway [46–48]. However, the clinical application of artemisinin was restrained due to its poor water-solubility and

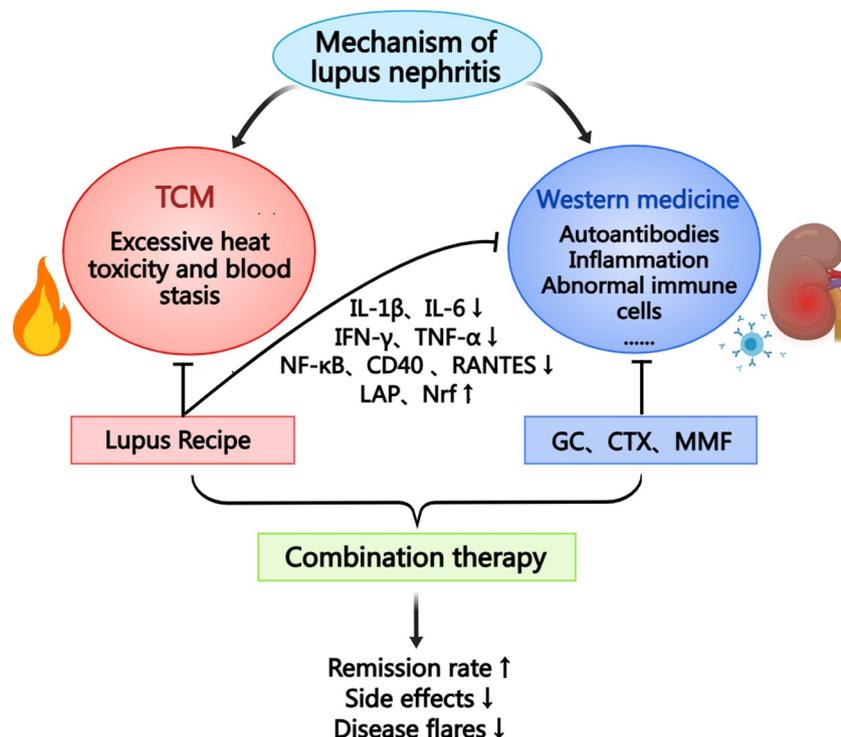


FIGURE 1 The advantages and mechanism of LR combined with Western medicine in the treatment of Lupus nephritis (LN). CTX, cyclophosphamide; GC, glucocorticoid; LAP, LC3-associated autophagy; LR, Lupus Recipe; MMF, mycophenolate mofetil; TCM, traditional Chinese medicine.

lipid-solubility, poor stability, and low oral bioavailability; so multiple derivatives were developed to modify its physical and chemical properties and improve the clinical applicability [49]. Artesunate is one of the most important derivatives of artemisinin. Experimental studies had demonstrated that artesunate could improve renal pathology, reduce serum levels of dsDNA and ANA, and prolong the survival of MRL/lpr mice via suppressing B-cell activation and reducing the expression of proinflammatory cytokine MCP-1 [50]. Artesunate could also alleviate autoimmune injuries of MRL/lpr mice by regulating the JAK-STAT signaling pathway and the differentiation of follicular regulatory T cells [51]. β -aminoarteether maleate (SM934), another water-soluble derivative of artemisinin, was also reported to ameliorate symptoms of MRL/lpr mice by inhibiting Toll-like receptor (TLR)-associated B-cell activation and differentiation of plasma cells [52]. In addition, SM934 could exert the anti-inflammatory and antioxidative effects on male NZM \times BXSB F1 mice via activating Nrf2 signaling pathway [53]. The efficacy of artemisinin and its derivatives in the treatment of LN are shown in Table 1.

Started in 2019, we conducted a multicenter, prospective, randomized, double-blind, placebo-controlled, 24-week pilot trial to investigate the efficacy and safety of artesunate when added to standard immunosuppressive therapy in patients with active LN (NCT03214731) [54]. In this pilot study, results showed

that the overall response rates of LN patients were insignificant between artesunate plus standard therapy (glucocorticoids [GCs] plus mycophenolate mofetil) and standard therapy alone. However, in the male subgroup, patients treating with the artesunate plus standard therapy had better response rate than those receiving standard therapy alone. Our study demonstrated the benefit for combination therapy of artesunate with standard therapy at least in the male LN patients. Nonetheless, a full-size trial is needed to verify the findings. The mechanism for this benefit is unclear currently. The function of GCs depends on their combination with corresponding receptors, which include the GC receptor α (GR α) and GC receptor β (GR β). The ratio of GR α to GR β in peripheral blood mononuclear cells (PBMCs) affects the function of GC. An increasing ratio suggests therapeutic sensitization of GC, while a decreasing ratio suggests therapeutic resistance of GC [55]. These two receptors share a common binding site of P300/CBP in the genetic structure, which is a transcriptional coactivator protein in renal tissue that dominates the regulation of the ratio between the two receptors [56]. Mechanism study found that integrative therapy with artemisinin and GC in LN mice significantly increased the transcriptional coactivator P300/CBP protein in renal tissue, and increased the expression of GR α mRNA while decreased the expression of GR β mRNA in PBMC. This study indicated that artemisinin had therapeutic sensitization effects on GC [48], which

TABLE 1 The therapeutic effect of artemisinin and its derivatives on LN.

Types of artemisinin	Treatment regimen	Efficacy	Mechanism	Reference
Artemisinin	Artemisinin 150 mg/kg/d, 8 weeks	Decreased urine protein/24 h, alleviated pathological renal lesions	Decreased the serum levels of TNF α and IL-6, down-regulated the expression of NF- κ Bp65, NF- κ B, and TGF- β mRNA in renal tissues	[46]
Artemisinin	Artemisinin 150 mg/kg/d + prednisone 3.225 mg/kg/d, 8 weeks	Decreased urine protein/24 h, alleviated pathological renal lesions	Increased therapeutic sensitization effects on glucocorticoid via increasing expression of GR α mRNA and transcriptional coactivator P300/CBP protein in renal tissue, and decreasing the GR β mRNA expression in PBMCs	[48]
Artemisinin	Artemisinin 5.55 mg/kg/d + HCQ 16.6 mg/kg/d, 8 weeks	Decreased UALB, SCr, BUN, anti-dsDNA, ANA, IgG, and renal lesions; increased body weight	Regulating the expression levels of inflammatory cytokines, KLF15 and NF- κ B	[47]
Artesunate	Artesunate 125 mg/kg/d, 16 weeks	Increased survival rate, body weight, and blood leukocyte counts, and reduced urine protein/24 h, ANA, anti-dsDNA, and SCr	Decreasing MCP-1 in serum, urine and kidney; decreasing BAFF in spleen	[50]
Artesunate	Artesunate 2.5, 5 mg/kg, 8 weeks	Increased survival rate, ameliorated LN symptoms, decreased anti-dsDNA deposited in the kidney and the levels of pathogenic cytokines (IL-6, IFN- γ , IL-21)	Inhibiting the differentiation of Tfh cells, altering the activation status of Jak2–Stat3 signaling	[51]
SM934	SM934 1.25, 2.5, 5 mg/kg/d, 18 weeks	Increased survival rate, ameliorated lymphadenopathy symptoms and renal lesions, decreased urine protein, BUN, ANA and pathogenic cytokines IL-6, IL-10 and IL-21, increased ALB	Suppressing B cell activation and plasma cell formation	[52]
SM934	SM934 10 mg/kg/d, 7 weeks	Increased survival rate, decreased urine protein, UACR, BUN, serum ANA, anti-dsDNA IgG	Activating the Nrf2 signaling and the downstream targets	[53]

Abbreviations: ALB, albumin; ANA, antinuclear antibodies; BAFF, B cell activating factor; BUN, blood urea nitrogen; ds-DNA, double stranded DNA; HCQ, hydroxychloroquine; IgG, immunoglobulin G; LN, Lupus nephritis; MCP-1, monocyte chemoattractant protein-1; SCr, serum creatinine; UACR, urine albumin to creatinine ratio; UALB, urine albumin.

may partially explain the benefit of combination therapy for LN patients in our clinical studies.

CONCLUSION

Due to the complicated pathogenesis and various clinical manifestations, the treatment of LN remains a challenging subject until now. Glucocorticoids, MMF

and CTX and many other Western medicines have been applied in clinical practice and obtain good curative effects. However, with the prolongation of medication multiple side effects appear, which make it difficult for patients to continue treatments. TCMS have been used to treat diseases by our ancestors for thousands of years and are considered to have multi-target therapeutic efficacies. Therefore, TCMS provide a feasible therapeutic strategy for LN treatment.

Clinicians in our center established a unique comprehensive treatment strategy for LN with the combination of TCM and Western medicine based on the TCM theory of disease differentiation and syndrome differentiation. This treatment strategy, represented by LR combined with immunosuppressants, has achieved good clinical efficacy for LN treatment. We recently also dominated a multi-center, randomized, double-blind, controlled trial of integrative therapy with artesunate and standard therapy and obtained a preliminary result. The in vivo and in vitro experiments partially explained the mechanism of the integrated TCM and Western medicine in the treatment of LN but cannot fully reflect the clinical practice in the real world. However, the efficacy of LR or artesunate combined with Western medicine in the treatment of LN both have been proved in clinical practice in our hospital. Additionally, these mechanism experiments may provide new ideas for the application of modern science to reveal the targets of integrated traditional Chinese and Western medicine in treating LN, and facilitate the development of new drugs. More multi-center, large-sample size, randomized controlled trials and mechanism studies are warrant to elucidate the efficacy, safety, and mechanism of action of integrative therapy with TCM and Western medicine, with the aim to develop more effective personalized treatment strategies. It should be noted that the toxicity of TCM and its derivatives in clinical applications cannot be ignored, and rational medication is still needed.

AUTHOR CONTRIBUTIONS

Wei Chen proposed the concept of the study. Ruihua Liu wrote the draft of the article and revised it under the supervision of Professor Wei Chen. Xiao Yang, Jianwen Yu, Qiong Wen, and Xueqing Yu were responsible for the charge of the integrative therapy of TCM and Western medicine for patients with LN.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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