Anti-tumor necrosis factor therapy in patients with difficult-to-treat lupus nephritis: a prospective series of nine patients

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Abstract

Objective

To clarify the efficacy and safety of anti-TNF-α therapy for intractable lupus nephritis.

Methods

In nine patients with systemic erythematosus who presented with lupus nephritis resistant to steroids and immunosuppressants, 200 mg/body of infliximab was drip-infused three times. No changes were made to other treatments for three months after the start of anti-TNF-α therapy, and urinary findings, renal function, serum complement, anti-DNA antibody, SLE activity, and adverse events were examined for six months after the start of anti-TNF-α therapy.

Results

One of the nine patients developed pyelonephritis after the first infliximab injection and received no further injections. The remaining eight patients received 3 infliximab injections. Of the eight patients, urinary protein decreased after anti-TNF-α therapy in six patients, and the SLEDAI improved in five patients. Urinary findings and/or SLE activity improved in six patients. Of the patients whose urinary protein levels decreased after anti-TNF-α therapy, proteinuria recurred six months after anti-TNF-α therapy in one patient. After anti-TNF-α therapy, proteinuria and the SLEDAI improved significantly. With respect to adverse events, therapy was discontinued in one patient who developed pyelonephritis, and one patient developed decreased blood pressure due to infusion reactions. In one patient in whom the steroid dosage was increased due to poor response to anti-TNF-α therapy, brainstem infarction occurred four months later. In one patient, anti-DNA antibody levels increased after therapy, but none of the patients had decreased serum complement levels or increased SLE activity.

Conclusion

In intractable lupus nephritis, anti-TNF-α therapy improved urinary protein levels and SLE activity. Although adverse events must be monitored cautiously, it may be possible to use anti-TNF-α therapy as a third-line treatment.

Key words

Lupus nephritis, infliximab, tumor necrosis factor.

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This work was supported in part by grants from the National Hospital Organization of Japan.

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Received on June 23, 2008; accepted in revised form on January 7, 2009.

Competing interests: none declared.

Introduction

Lupus nephritis is the most important organ lesion of systemic lupus erythematosus (SLE), and it often leads to renal failure. Steroids and immunosuppressants have been used to treat lupus nephritis, but in many patients, it exacerbates, and these agents cannot be administered due to adverse events.

Like the other SLE lesions, lupus nephritis is believed to be caused by immune complex and complement activation, but lupus nephritis patients have high serum TNF-α levels (1-3), and TNF-α is thought to be involved with lesion onset (4). TNF is an important proinflammatory cytokine including the activation of a cascade of inflammatory events which lead to tissue destruction. TNF is found in renal tissue in all types of lupus nephritis and is associated with disease activity. Those data indicate that blockade of TNF might have benefical effects on inflammation in SLE. Furthermore, in murine SLE models, anti-TNF-α therapy improves lesions in MRL/lpr mice (6).

However, in NZB/W mice, TNF-α improved lesions (5, 7), and when infliximab was administered for rheumatoid arthritis and Crohn's disease, lupus-like symptoms occurred (8, 9). Based on these findings, the efficacy and safely of anti-TNF-α therapy for SLE and lupus nephritis have not been clarified, though recent studies have found that infliximab therapy was effective for lupus nephritis (10-12) and improved renal lesions and SLE activity. Since infliximab therapy is very expensive, it is used to treat lupus nephritis in patients who do not respond to steroids and immunosuppressants. Past reported have included only single- and small-case studies, and there has not been a prospective study involving patients with intractable lupus nephritis. Therefore, the present study prospectively investigated the efficacy and safety of anti-TNF-α therapy in patients with intractable lupus nephritis.

Patients and methods

Patient selection

Patients satisfying all three of the following inclusion criteria were selected: 1) the 1982 revised criteria for the classification of SLE as published by the American College of Rheumatology; 2) lupus nephritis presenting with proteinuria and renal dysfunction; and 3) proteinuria and nephropathy did not improve despite receiving steroids and at least one immunosuppressant.

Prior to the study, a kidney biopsy was performed in all patients except for those in whom a renal biopsy was contraindicated. All patients were given infliximab after their written informed consent was obtained. The ethical review board of each institution approved the study. In all patients, chest x-rays and tuberculosis skin tests confirmed the absence of active tuberculosis.

Anti-TNF-α treatment schedule

In the present study, 200 mg/body of infliximab was drip-infused three times (weeks 0, 2, and 6). For three months after the start of infliximab therapy, other treatments were not changed. However, one patient developed pyelonephritis two weeks after the first infliximab infusion; this patient received no further infusions and was withdrawn from the study.

Study endpoint

In the present study, the subjects were followed for six months after receiving three infliximab injections. Urinary protein, C3, C4, and anti-DNA antibody levels (RIA assay), as well as renal function and the SLE disease activity index (SLEDAI: indicator for overall SLE activity) (13) were evaluated before therapy and 2 weeks, 6 weeks, 3 months, and 6 months after infliximab therapy.

Patients

The subjects were 9 patients (8 women, 1 man), ranging in age from 21 to 51 years (Table I). Six patients had SLE for more than 10 years, and lupus nephritis was confirmed in all patients. One patient had CNS lupus and autoimmune hemolytic anemia, and another patient had autoimmune thrombocytopenia. Prior to the present study, all patients received at least 40 mg of prednisolone, and four patients also received steroid pulse therapy using 1000 mg of methylprednisolone. Furthermore, two patients

received oral cyclophosphamide, and three patients received 500 mg/body of IVCY three times. Moreover, three patients received cyclosporine A, one patient received azathioprine, and one patient received mizoribine. None of the patients were given mycophenolate mofetil, which is not approved for use in Japan.

During infliximab administration, 6-30 mg of prednisolone were administered, and three patients also received cyclosporine A.

Prior to the study, a kidney biopsy was performed in all patients except for the one with thrombocytopenia. According to the INS/RPS classification system (14), there was one IV case, three V cases, and four III or IV+V cases. Serum TNF-α levels were measured in six patients prior to the study.

Results

Adverse events and premature treatment termination

Of the nine patients, one patient (Case 9) developed pyelonephritis two weeks after the first infliximab injection and responded well to antibiotic therapy; this patient received no further infliximab injections (Table I). The other eight patients were given three infliximab injections as scheduled. With respect to infusion reactions, Case 4 had an infusion reaction during the third infliximab injection, which was treated with adrenaline. Case 8 did not respond to three infliximab injections, and because the patient's renal function deteriorated, the prednisolone dosage was increased; however, the patient died of brainstem infarction three months after the end of infliximab treatment.

Clinical effects on lupus nephritis

Of the eight patients who received three infliximab injections, urinary protein decreased by at least 33% in six patients (Cases 1, 2, 3, 4, 5, and 6) and by at least 50% in four patients (Fig. 1). In the other two patients, proteinuria did not improve. Urinary protein levels began to decrease at different times. In Cases 1, 2, 3, and 6, urinary protein levels decreased after the first infliximab injection, which confirmed its fast onset of action. In Cases 4, 5, and 7, urinary protein levels decreased six weeks after the start of therapy. In Case 1, urinary protein levels began to decrease two weeks after the start of therapy, but no effects were observed 24 weeks after the start of therapy. When comprehensively investigating the changes in proteinuria for the entire patient population, significant decreases in proteinuria were seen two weeks after the start of therapy (p=0.0273, Wilcoxon signed rank test) (Fig. 4). Serum creatinine levels gradually increased in Case 8, but no changes were seen in the other seven patients (Fig. 1).

Clinical effects on serological SLE activity

In Cases 2, 3, 4, 7, and 8, C3 levels decreased slightly two weeks after infliximab therapy (Fig. 2), but they returned to the pretherapeutic level six weeks after infliximab therapy and then remained at that level. Anti-DNA level was relatively low before infliximab treatment, and was probably result of previous immuonosuppresive therapy. (In all cases, anti-DNA level was high at the onset of SLE) In Case 2, anti-DNA antibody levels increased 12 weeks after the start of infliximab therapy, but in the other patients, anti-DNA antibody levels did not increase. In Case 3, anti-DNA antibody levels decreased after infliximab therapy.

Clinical effects on the SLEDAI

The SLEDAI was assessed in eight patients, and it decreased by at least 40% in five patients (Cases 1, 2, 3, 5, and 7) (Fig. 3). In the remaining three patients, the SLEDAI did not change during therapy, but it increased after the end of therapy. In Case 1, in which marked effects were seen immediately after the start of infliximab therapy, the effects on the SLEDAI diminished after 12 weeks. When comprehensively assessing the SLEDAI in all cases, the SLEDAI decreased significantly 6 and 12 weeks after infliximab therapy when compared to before therapy (week 6: p=0.0116, week 12: p=0.0136) (Fig. 4).

Discussion

There is much debate about the use of anti-TNF-α therapy for SLE. In SLE mice, TNF-α has been shown to improve lesions (5, 7), and when infliximab was given for rheumatoid arthritis and Crohn's disease, anti-nuclear antibody, anti-DNA antibody, and anti-cardiolipin antibody were detected. Aringer

Table I.

Case	Age (years)	Sex	SLE duration (years)	Organ involvement	Previous therapy	Accompanying therapy	Renal biopsy	SerumTNF-α (pg/ml.)
1	27	M	12	LN	PSL40mg, IVCYX3	PSL 20 mg, CyA 100	IV(A/C)+V	1.2
2	34	F	11	LN, thrombocytopenia	PSL60mg Cs.pulse, CyA	PSL 30 mg, CyA 150	ND	5.5
3	33	F	18	LN	PSL60mg, IVCYX3	PSL 6 mg	IV(A/C)	3.2
4	42	F	17	LN	PSL60mg, CY	PSL 7.5 mg	V	18
5	27	F	3	LN, CNS lupus, hemolysis	PSL60mg, IVCYX3	PSL 17.5 mg	III(C)+V	2.1
6	31	F	8	LN	PSL40mg Cs.pulse, CyA	PSL 20 mg .CyA 100	V	ND
7	51	F	18	LN	PSL40mg Cs.pulse, CY CyA	PSL 12.5 mg	IV(C)+V	20.4
8	21	F	12	LN	PSL40mg Cs.pulse, Miz	PSL 10 mg Miz	V	ND
9	29	F	2	LN	PSL40mg azathioprine	PSL 27.5 mg	III(A)+V	ND

LN: lupus nephritis; CNS: central nerve system; PSL: predonisolone; Cs pulse: methylpredonisolone 1000mg x 3 days; CY: cyclophosphamide; IVCY: intravenous cyclophosphamide pulse therapy; CyA: cyclosporine A; Miz: mizoribine.

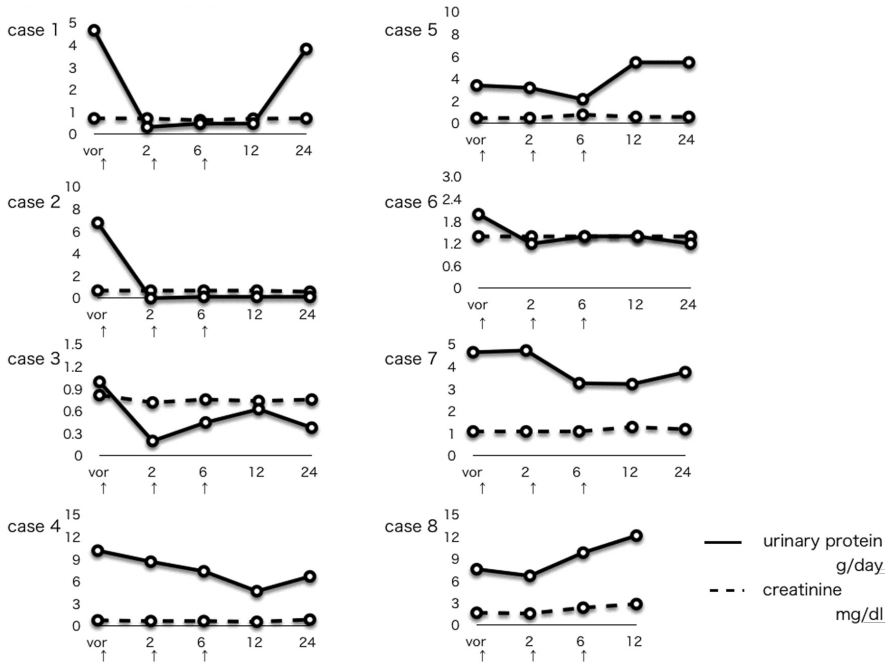

Fig. 1. Urinary protein and creatinine.

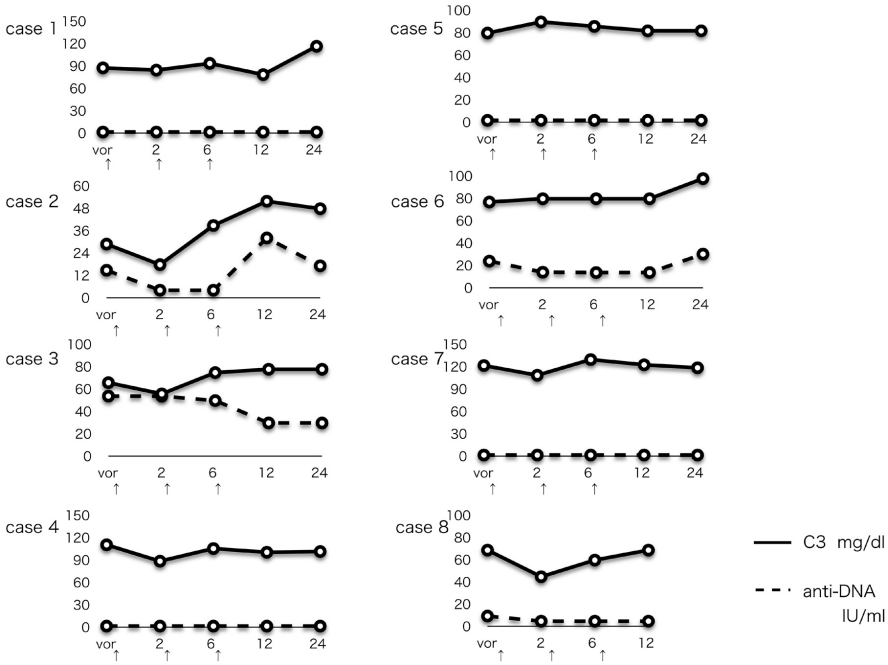

Fig. 2. C3 and anti-DNA.

and colleagues (15) gave infliximab four times to seven SLE patients, and transient anti-ds DNA antibody (5/7 patients) and anti-cardiolipin antibody (4/7 patients) were seen 4-10 weeks after the final injection. Furthermore, drug-induced lupus syndrome has been reported (8, 9). In a prospective study, a lupus-like syndrome was seen in 15 of 7700 patients who were receiving infliximab, but none of these patients had lupus nephritis (16). Based on these reports, the latent effects of anti-TNF-α therapy on SLE exacerbation have been emphasized.

Ever since a study reported the use of infliximab therapy for Crohn's disease associated with lupus nephritis (10), there have been reports of anti-TNF-α therapy improving lupus nephritis. With respect to studies involving more patients, Aringer (11) gave infliximab to six SLE patients, including four lupus nephritis patients, and all of them improved. Among the four lupus nephritis patients, either azathioprine or methotrexate was coadministered, and 300 mg of infliximab was given four times (weeks 0, 2, 6, and 10). In all four patients, proteinuria and the SLEDAI improved after the third injection. Therefore, taking into account the body weight of Japanese patients, 200 mg of infliximab was given three times (weeks 0, 2, and 6). In the present protocol, since the patients were immunosuppressed due to multiple drugs, the additive effects of infliximab were investigated without adding any new agents, including methotrexate.

Of the nine study participants, one patient developed pyelonephritis after the first infliximab injection, and the second and third injections were not given at the patient's request. This patient did not require hospitalization. The other eight patients received three infliximab injections, but one patient developed an infusion reaction after the third injection. Furthermore, another patient died of brainstem infarction three months after the end of infliximab therapy; as a result, the patient could not be followed on week 24. The incidence of infusion-related reactions in current study is similar to those reported for RA (22). However, tolerance to infliximab infusion is not perfect and RA patients treated with infliximab without methotrexate, and who are positive at baseline for ANAs are reported to be at increased risk for developing infliximab-related infusion reactions (22). Infliximab infusion should be used with caution.

The effects of infliximab therapy were assessed in the eight patients who received three injections. Proteinuria decreased by at least 33% in six patients, and in four patients, proteinuria decreased by at least 50%. For the entire patient population, urinary protein levels decreased significantly two weeks after infliximab therapy. In six patients showing nephritic syndrome in spite of immunosuppresive drugs, two patients achieved complete remission immediately after first inliximab infusion

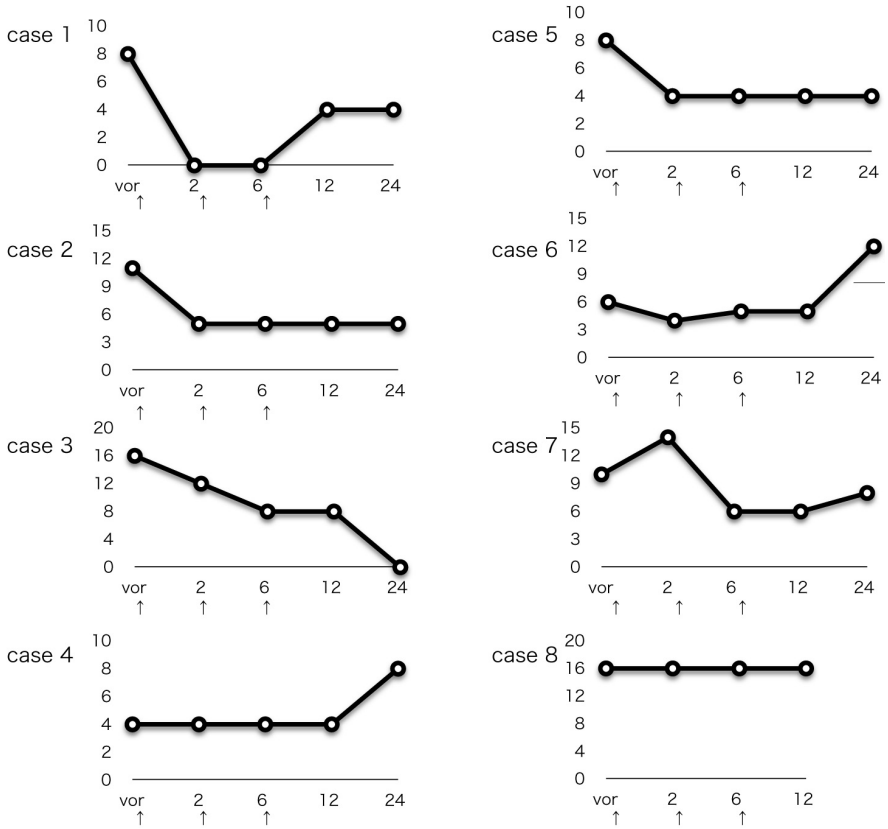

Fig. 3. SLEDAI.

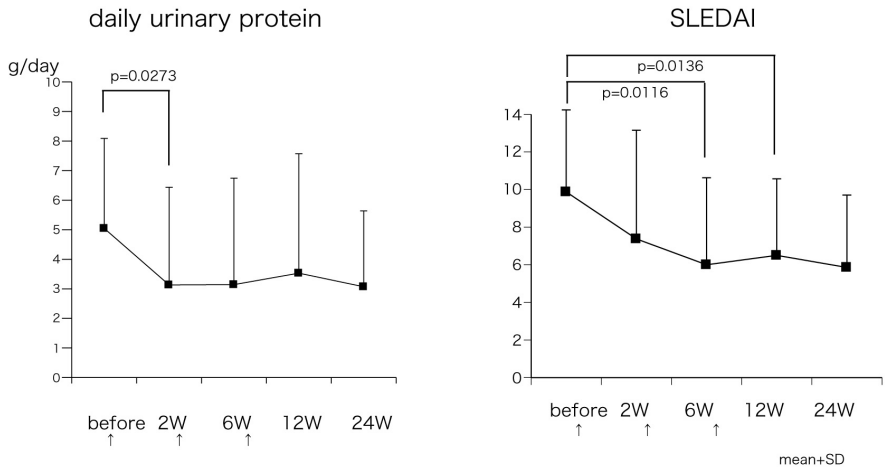

Fig. 4.

and the other two patients achieved incomplete remission. Complete remission rate of lupus nephritis treated with mycophenorate mofetil is reported to be 36% (21) and the same with this study and 12 months of mycophenorate mofetil thrapy was necessary.

In five of the eight patients, the SLEDAI improved, and for the entire patient population, significant improvements were seen at weeks 6 and 12. Hence, the present therapy improves renal function and activity in patients with lupus nephritis who are unresponsive to steroids and immunosuppressants.

However, the therapy was totally ineffective in Cases 7 and 8. In Case 7, a kidney biopsy confirmed type IV(C)+V, and this patient had the highest pretherapeutic serum TNF-α level. Since a patient who responded to infliximab had type V, this type does not necessarily indicate poor efficacy. In primary membranous nephritis, the effects of immunosuppressive therapy are delayed, and more time might have been needed to observe infliximab effects. Furthermore, since type IV(C) has only chronic lesions, but no active lesions (14), anti-TNF-α therapy may not be effective. In rheumatoid arthritis and Crohn's disease, the therapy was not effective when serum TNF-α levels were high. In such cases, increasing the infliximab dosage is effective (17, 18). In active SLE and lupus nephritis, high serum TNF-α levels have been reported (19), and in the same manner, infliximab at the conventional dose may be insufficient in lupus nephritis patients with high serum TNF-α levels.

Gonnet-Gracia *et al.* reported that in 98 RA patients treated with infliximab, significant antinuclear antibody positive rate inceased from 43.6% to 73% and anti-DNA positive rate increase from 0% to 9.5% (23). Cavazzana I *et al*. reported in RA patients with anti-Ro antibodies, anti-ds DNA and lupus like disease.were more frequent than those without anti-Ro antibodies (24). Aringer and colleagues (20) showed that anti-TNF-α therapy for SLE often transiently induced antibodies against chromatin and phospholipids. In the present study, elevated anti-DNA antibody levels were seen in only one patient. Unlike the study by Aringer and colleagues, the patients in the present study received 200 mg/body of infliximab. In this patient with elevated anti-DNA antibody levels, there was no decrease in serum complement levels, the subjective and objective symptoms of SLE improved, and the SLEDAI decreased. In the patient who died of brainstem infarction, anti-DNA antibody levels did not increase, and the anti-phospholipid antibody and lupus anticoagulant were absent just before death. Three months after the final infliximab injection, this patient's steroid dose was increased, and the patient's death did not seem to relate directly to infliximab therapy.

In patients with lupus nephritis who are unresponsive to steroids and immunosuppressants, anti-TNF therapy using infliximab is effective. It improves proteinuria and SLE activity, and it can be used as a technique to induce remission. With respect to adverse events,

one must monitor patients for infections and infusion reactions. However, infliximab is an expensive drug, and it is not economically feasible to administer as first-line treatment. Therefore, anti-TNF therapy using infliximab is useful as second or third-line treatment in patients who are unresponsive to steroids and immunosuppressants. And economical point of view, complete cost of cyclophophamide and other immunosuppresants therapy including admission and antibiotics might not be inexpensive compared with anti-TNF therapy.

Further investigations are needed to determine whether anti-TNF therapy is effective in maintaining remission following remission induction.

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