Original article

Mizoribine, tacrolimus and corticosteroids combination therapy successfully induces remission in patients with lupus nephritis

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Abstract

Background The conventional cyclophosphamide-based treatment regimens for lupus nephritis (LN) are still not considered to be optimal treatments. The aim of this study was to evaluate the efficacy and safety of mizoribine, tacrolimus and corticosteroids combination therapy for LN.

Methods We retrospectively evaluated a combination treatment of mizoribine and tacrolimus with corticosteroids for the induction therapy of eight newly diagnosed systemic lupus erythematosus (SLE) patients with biopsy-proven LN.

Results All the patients were females, and their mean (SD) age was 48.5 (20) years. All eight patients (100%) had positive anti-double-stranded DNA antibody titers, and four (50.0%) were nephrotic. The mean (SD) serum creatinine and daily proteinuria levels were 0.72 (0.4) mg/dL (range, 0.33–1.55 mg/dL) and 4.56 (2.8) g (range, 0.77–8.2 g), respectively. By month 2, significant improvements in the anti-double-strand DNA antibody titers, levels of proteinuria, serum albumin, and C3, and SLE disease activity index score were observed. By month 6, seven patients (87.5%) were in complete remission with normalized levels of both proteinuria and serum creatinine.

Conclusions This pilot study suggests that mizoribine and tacrolimus treatment with corticosteroids is well-tolerated and may prove to be an optimal alternative remission-inducing regimen for LN.

Keywords Induction therapy, Lupus nephritis, Mizoribine, Multitarget therapy, Systemic lupus erythematosus, Tacrolimus

Introduction

Systemic lupus erythematosus (SLE) is a potentially fatal autoimmune disease that involves multiple vital organs. SLE is associated with diverse clinical features that range from rash and arthritis to cytopenia, serositis, nephritis, seizures and psychosis. Lupus nephritis (LN) is a major manifestation of SLE and has the worst prognosis [1–5]. Since an early response to immunosuppressive therapy is predictive of a good long-term renal outcome [5–7], regimens that induce rapid remission are needed.

The combination of corticosteroids and cyclophosphamide pulse therapy has been the standard therapy for diffuse proliferative LN. However, a significant number of LN patients (17–57%) fail to achieve complete or partial remission despite receiving the standard therapy [8–13]. Only a small percentage of patients (8.1–8.6%) treated with mycophenolate mofetil (CellCept, MMF) or intravenous cyclophosphamide achieved complete remission, strictly defined as return to normal serum creatinine, urine protein ≤ 0.5 g/d, and inactive urinary sediment, in a large multinational study [14]. Indeed, the standard therapy for SLE has its limitations because of the heterogeneous disease mechanisms that underlie SLE. Furthermore, in comparison with patients who receive corticosteroids alone, patients receiving cyclophosphamide-based treatment regimens show higher long-term renal survival rates, but not higher overall survival rates [11]. The use of cyclophosphamide-based treatment regimens is limited by the potentially severe and toxic adverse effects, which include bone marrow suppression, hemorrhagic cystitis, opportunistic infections, malignant diseases, and premature gonadal failure [8, 15]. Since conventional treatments for LN have not provided satisfactory clinical outcomes, alternative treatments are required.

Mizoribine (Bredinin, MZB) is a purine synthesis inhibitor with similar activity to MMF, and has been used in Japan for patients undergoing renal transplantation and in patients with rheumatoid arthritis, LN and nephrotic syndrome [16–22]. Mizoribine oral pulse therapy has

been reported to be of benefit in patients with LN disease flare-up. Furthermore, mizoribine appears to be safer than cyclophosphamide and other immunosuppressive agents.

Tacrolimus (Prograf, FK506) is a T-cell-specific calcineurin inhibitor, and has been increasingly used in not only transplant medicine but also autoimmune diseases such as SLE [23–31], rheumatoid arthritis [32], inflammatory bowel disease, and myasthenia gravis.

MMF is a selective inhibitor of B-cell and T-cell proliferation, and a combined therapy comprising administration of steroids, MMF, and tacrolimus, which had been applied for patients undergoing organ transplantation, was successfully used for patients with severe LN [33].

Since clinical use of MMF and cyclophosphamide for LN has not yet been approved as a health insurance treatment in Japan, we used a combination regimen of mizoribine and tacrolimus with corticosteroids for induction treatment of LN. In the present study, we retrospectively evaluated a combination regimen of mizoribine and tacrolimus with corticosteroids for the induction therapy of newly diagnosed SLE patients with biopsy-proven LN.

Methods

We retrospectively studied eight consecutive patients with newly diagnosed SLE and LN who provided oral informed consent. The patients were treated at the Department of Internal Medicine, Himeji Red Cross Hospital (Himeji, Japan). All the patients fulfilled the revised ACR criteria for SLE and had biopsy-proven LN.

All patients received intravenous methylprednisolone pulse therapy (0.5 g/d for 3 d) at the beginning, followed by oral prednisolone. The daily dosage of prednisolone was started at 60 mg/d (80 mg/d for patients weighing above 60 kg) and then reduced by 10 mg/d every week to reach 30 mg/d, which was followed by further tapering by 5 mg/d at 2-week intervals until

20 mg/d was reached. Further tapering to 5 mg/d was allowed if the patient's condition was stable. The initial tacrolimus dose was 3 mg/d once daily. Blood trough concentrations were measured at weeks 1, 2, 3 and 4 and months 2, 4, 5 and 6, and the dosage was titrated to maintain a blood concentration below 10 ng/mL. Administration of mizoribine was initiated at a dose of 300 mg/d once daily for 3 d per week. Blood peak concentrations were measured if necessary, and the dosage (maximum, 300 mg/d) was titrated to maintain an upper blood concentration of 1.0 μg/mL [20, 34]. When the patients showed complete remission of SLE, either mizoribine or tacrolimus was stopped and another immunosuppressive agent was continued for the maintenance therapy.

The primary efficacy parameter was complete remission at 6 months, which was defined as proteinuria level < 0.2 g/d and normal level of serum creatinine or no more than 15% above the baseline value. A secondary efficacy parameter was SLEDAI [35] remission at 6 mo, which was defined as an SLE disease activity index (SLEDAI) score of 0. Additional secondary efficacy parameters examined included proteinuria level, serum creatinine level, estimated glomerular filtration rate (eGFR), serum C3 level, anti-double-stranded DNA antibody titer, serum albumin level, hemoglobin level, and SLEDAI score. Therapeutic responses were determined at 2, 4, and 6 mo. This study was approved by the ethical committee of our hospital.

Results

All the patients were females, and their mean (SD) age was 48.5 (20.3) years. At the start of the treatment, all eight (100%) patients had positive anti-double-stranded DNA antibody titers, a mean (SD) serum creatinine level of 0.72 (0.4) mg/dL (range, 0.33–1.55 mg/dL), and a mean (SD) daily proteinuria level of 4.56 (2.8) g (range, 0.77–8.2 g). In addition, four (50.0%) patients were nephrotic, four (50.0%) were hypertensive, and one (12.5%) had an

elevated serum creatinine level at start of the treatment (Table 1). The numbers of cases in the categories of the International Society of Nephrology (ISN)/Renal Pathology Society (RPS) 2003 criteria for the classification of LN were as follows: class II, one (12.5%); class III, three (37.5%); class IV-S, 0 (0%); class IV-G, one (12.5%); and class V: three (37.5%). After 6 mo of therapy, complete remission and SLEDAI remission were achieved in seven (87.5%) and three (37.5%) patients, respectively (Figure 1). Significant improvements in the urine protein levels, C3 levels and SLEDAI scores were observed in comparison with the baseline values, starting at month 2 (Table 2, Figure 2). The anti-double-stranded DNA antibody titers at 6 mo were normalized in seven (87.5%) patients. Mizoribine and tacrolimus were generally well-tolerated in most cases, except three patients whose serum creatinine levels increased (Table 3). However, all cases showed improvement with reduced doses of tacrolimus.

Discussion

Renal involvement occurs in approximately 50% of patients with SLE, and LN remains a predominant cause of morbidity and mortality. Therapeutic management of SLE is based on the type and severity of organ involvement. The ideal therapy for LN should induce an early response and remission, prevent flare-ups, have minimal adverse effects, and result in reductions in mortality and end-stage renal disease [36].

In the present study, we found that a 6-m course of a combination therapy of mizoribine and tacrolimus with corticosteroids is a safe and effective treatment for patients with LN. The suitability of cyclophosphamide-based treatment regimens, which are the standard therapy for LN, remains a matter of debate, and alternative treatments are therefore required. In 2008, Bao *et al*. [33] reported the benefits of multitarget therapy (MMF and tacrolimus with corticosteroids) in cases of severe LN (class V + IV). Multitarget therapy is possibly more

effective for LN because SLE is an extremely heterogeneous disorder. The clinical use of MMF has not yet been approved, except for conditioning therapy before transplantation, by the Ministry of Health and Welfare in Japan. Mizoribine is a purine synthesis inhibitor with similar activity to MMF, and we therefore used mizoribine instead of MMF for the treatment of LN. A correlation between the peak mizoribine blood concentration and the clinical response to the therapy has been observed in patients with LN [20], and to ensure the peak concentration in our patients, we administered mizoribine 300 mg/d once daily for 3 d per week. The mizoribine blood concentrations in the patients administered using this treatment protocol were above the target levels.

By month 12, complete remission and SLEDAI remission were achieved in eight (100%) and five (62.5%) patients, respectively. Even more surprisingly, microalbuminuria was normalized in five (62.5%) patients (data not shown). With respect to the ultimate outcome of LN, the patient survival rates at 10 years were reported to be 95% for patients in complete remission, 76% for patients in partial remission, and 41% for patients with no remission [5]. Although complete remission in that study was defined as proteinuria level <0.33 g/d and serum creatinine level ≤1.4 mg/dL, we defined complete remission more strictly as normalization of proteinuria level (< 0.2 g/d) and serum creatinine level in the present study. Considering patients directed to a treatment target, the remission in both renal and serological parameters observed in our study will definitely lead to better outcomes.

Owing to the long-term benefits, risks, and overall costs of the combination therapy, patients who showed SLEDAI remission after this combination therapy received maintenance therapy with one immunosuppressive agent. In a previous study, the occurrence of renal flare-ups was the strongest predictor of end-stage renal disease for patients who had once been in remission, and independent predictors of renal flare-ups were persistently low C3 levels despite the induction therapy and an absence of azathioprine maintenance therapy [12].

Tacrolimus treatment may be related to a lower risk of lupus flare-up [25], while beneficial effects of long-term treatment with mizoribine were also reported [19]. Therefore, both mizoribine and tacrolimus may be suitable as optional agents for the maintenance treatment for LN after this combination induction therapy. Furthermore, in comparison with the conventional treatments performed at our hospital, combination therapy may contribute to a lower cumulative prednisolone dosage and a shorter duration of hospital stay (data not shown).

There are several limitations of this study. First, the sample size was small and the data were confined to 6 m. Further randomized controlled trials are needed to compare our multitarget regimen with standard regimens for LN. Second, although we recruited consecutive patients with a mean daily proteinuria level of 4.56 g, only four (50%) patients had active proliferative LN. The sample size was too small to evaluate the therapeutic response in each type of biopsy-proven group. Third, urinary sediments were not included as a definition of the treatment response in this study because we considered that normalization of proteinuria takes longer than that of urinary sediments. Fourth, it remains unclear which immunosuppressive agents should be chosen as the maintenance therapy for different types of LN. Finally, although the dosages of mizoribine and tacrolimus administered to our patients appeared to be well-tolerated, the optimal dosage regimens of mizoribine and tacrolimus remain unclear.

In summary, our findings suggest that the combined use of two well-tolerated immunosuppressive agents with different activities for induction therapy of LN appears to be highly efficacious. Renal remission was induced by 6 m for almost all patients, who required a lower cumulative prednisolone dosage. This pilot induction regimen may be applied to various types of LN. Further studies are required for assessment of these expensive immunosuppressive agents in the treatment of LN. Physicians should thoroughly consider all

possible benefits, theoretical risks, and overall costs of each treatment regimen in each individual to provide the best care for their patients.

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Conflict of interest statement

The authors have declared that no conflicts of interest exist.

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Figure legends

Fig. 1. Remission rates with the combination therapy. Complete remission was defined as proteinuria level < 0.2 g/d and normal serum creatinine level or no more than 15% above the baseline value. SLEDAI remission was defined as a SLEDAI score of 0. The therapeutic responses were determined at 2, 4, and 6 mo.

Fig. 2. Changes in biochemical parameters after treatment. Additional secondary efficacy parameters examined included proteinuria level (a), serum creatinine level (b), serum C3 level (c), anti-double-stranded DNA antibody titer (d), and SLEDAI score (e). The therapeutic responses were determined at 2, 4, and 6 m. Each line represents an individual patient.

Tables

Table 1. Baseline characteristics of the patients treated with a combination of mizoribine and tacrolimus

Age at lupus nephritis, *years*	48.5 (20.3); range, 22–70
Females*, number (%)*	8 (100)
Systemic lupus erythematosus duration, *months*	1.1 (2.1); range, 0–5
First-time nephritis*, number (%)*	8 (100)
Extrarenal features, *number (%)*	
Musculoskeletal	4 (50)
Mucocutaneous	4 (50)
Neuropsychiatric	0 (0)
Hematologic	8 (100)
ISN/RPS classification	Class II: 1, class III: 3, class IV-G: 1, class V: 3
Anti-double-strand DNA, *number (%)*	8 (100)
Anti-double-strand DNA, *IU/L*	186 (129); range, 48–400
Hemoglobin, *g/dL*	11.1 (1.5); range, 9.4–13.7
Serum creatinine, *mg/dL*	0.72 (0.4); range, 0.33–1.55
eGFR, *ml/min per 1.73m*^{2}	89.5 (50.8); range, 27.2–178
Serum albumin, *g/dL*	2.69 (0.7); range, 1.6–3.8
Serum C3 level, *mg/dL*	41.3 (16.4); range, 23–68
Proteinuria, *g/day*	4.56 (2.8); range, 0.77–8.2
Nephrotic syndrome, *number (%)*	4 (50)
Active urinary casts, *number (%)*	7 (88)
Hypertension*, number (%)*	4 (50)
SLEDAI scores	22.0 (2.1); range, 20–26

ISN/RPS classification, International Society of Nephrology/Renal Pathology Society 2003 criteria for the classification of lupus nephritis; SLEDAI, systemic lupus erythematosus disease activity index.
Data are shown as mean (SD).

Table 2. Changes in the biochemical parameters after treatment

	Baseline	Month 2	Month 4	Month 6
Proteinuria, *g/day*	4.56 (2.8)	0.09 (0.1)**	0.34 (0.7)**	0.20 (0.3)**
Nephrotic syndrome, *number (%)*	4 (50)	0 (0)	0 (0)	0 (0)
Serum albumin, *g/dL*	2.69 (0.7)	3.89 (0.3)**	3.94 (0.5)**	4.13 (0.4)**
Serum C3 level, *mg/dL*	41.3 (16.4)	68.8 (22.1)**	83.6 (22.8)**	85.4 (22.5)**
Anti-double-strand DNA, *IU/L*	186 (129)	16.7 (16.9)**	11.6 (9.6)**	9.3 (7.4)**
Serum creatinine, *mg/dL*	0.72 (0.4)	0.84 (0.4)	0.72 (0.2)	0.70 (0.2)
eGFR, *ml/min per 1.73m^2*	89.6 (50.8)	68.7 (32.1)	76.0 (31.9)	77.5 (31.8)
Hemoglobin, *g/dL*	11.1 (1.5)	12.0 (2.1)	12.4 (1.5) *	12.6 (1.5)**
SLEDAI scores	22.0 (2.1)	3.3 (2.8)**	2.8 (4.3)**	2.0 (1.9)**

Data are shown as means (SD). *P<0.05, **P<0.01

Table 3. Dosages, blood concentrations and adverse effects

	Age/sex (years)	ISN/RPS classification	Mizoribine dosage at 6 months (mg/d)	Peak mizoribine concentration (μg/mL)	Tacrolimus dosage at 6 months (mg/d)	Trough Tacrolimus concentration (ng/mL)	PSL dosage at 6 months (mg/d)	Clinical response at 6 months	Adverse effects
Patient 1	32/F	class V	300	1.81	3	3.77	15	CR	Dyslipidemia
Patient 2	40/F	class V	300	1.16	3	5.86	15	CR	Dyslipidemia
Patient 3	27/F	class IV-G (A)	300	ND	3 → 2	7.07 → 3.95	10	None	Increase in serum creatinine Hypertension Diabetes mellitus
Patient 4	66/F	class II	300	ND	3	8.22	13	CR	None
Patient 5	22/F	class V	300	ND	3	9.03	10	CR + SLEDAI-R	Dyslipidemia
Patient 6	62/F	class V + III (A/C)	300	1.96	3 → 2	7.70 → 3.43	10	CR	Increase in serum creatinine Diabetes mellitus Dyslipidemia
Patient 7	69/F	class III (A/C)	300	1.96	3 → 2 → stopped	3.80 → 2.69	10	CR + SLEDAI-R	Increase in serum creatinine Diabetes mellitus Dyslipidemia
Patient 8	70/F	class III (A/C)	300	ND	3 → 2	6.33 → 2.90	11	CR + SLEDAI-R	Diabetes mellitus HZV

CR, complete remission; SLEDAI-R, SLEDAI remission; HZV, herpes zoster virus

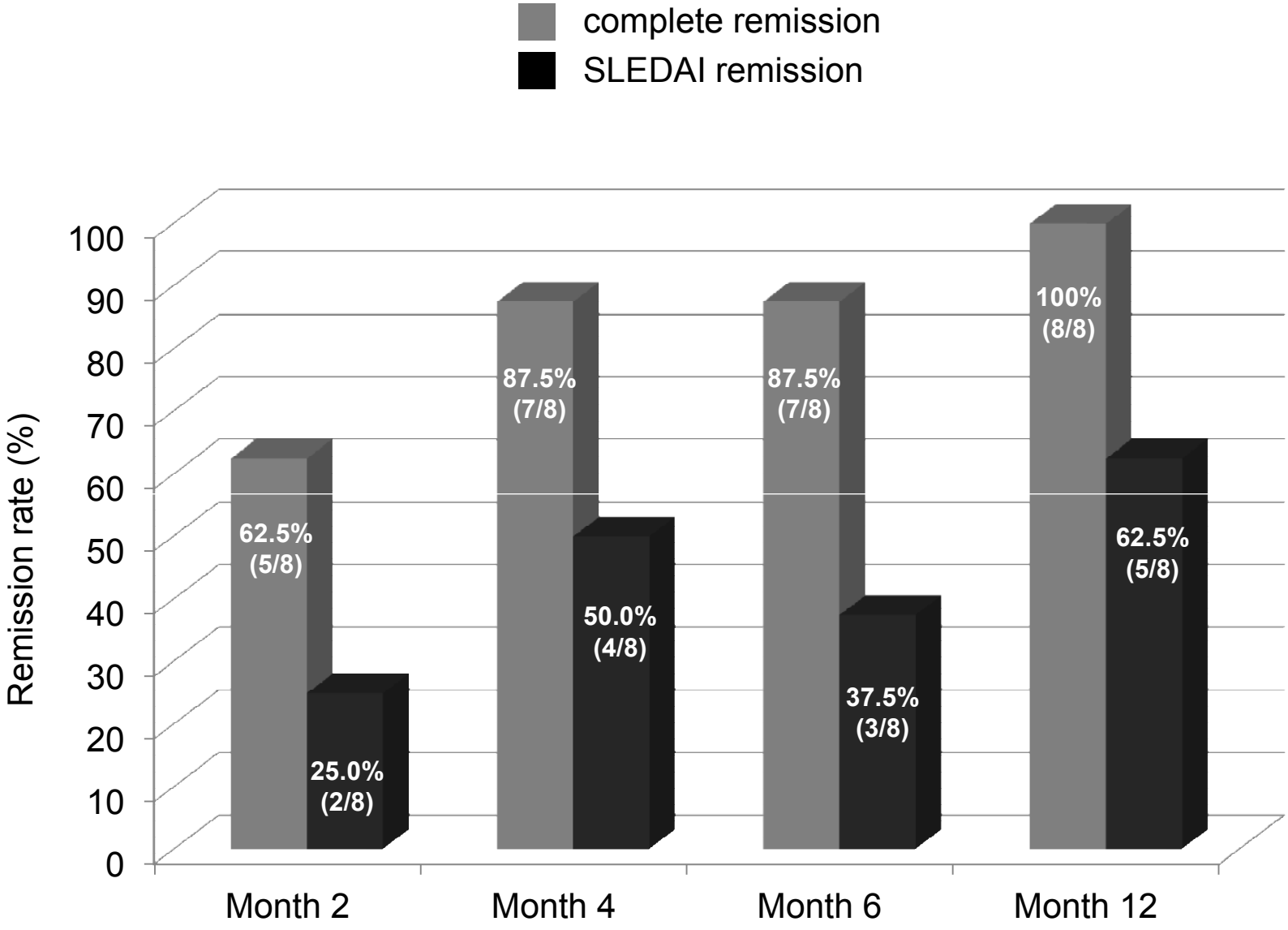

Fig 1. Remission rates with the combination therapy

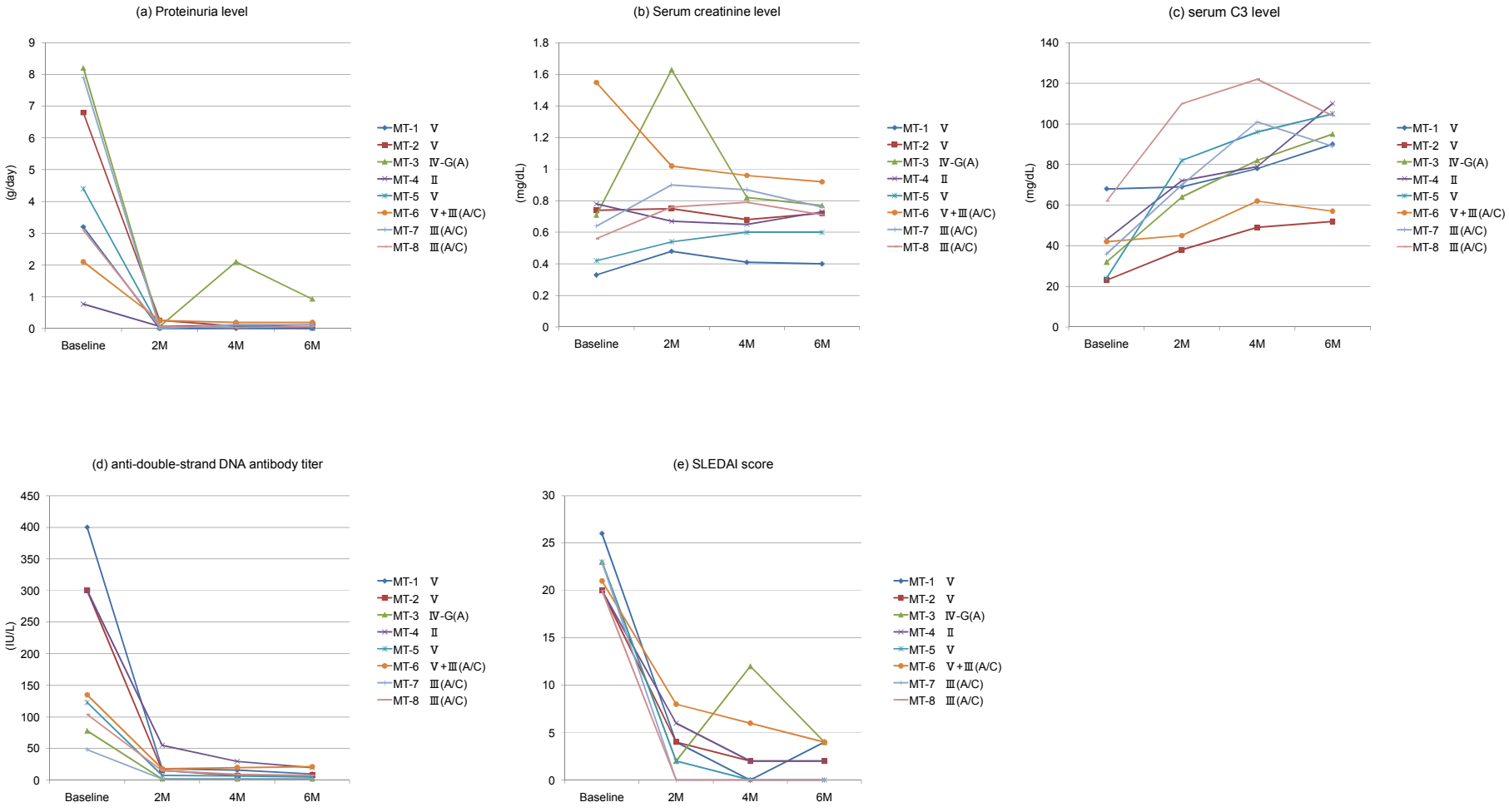

Fig 2. Changes in biochemical parameters after treatment