Attenuation of nephritis in lupus-prone mice by thalidomide

Sang-Won Lee¹, Yong-Beom Park¹, Jaeseok Yang², Kyu-Hyung Park¹, Soo-Kon Lee¹, Kyu Hun Choi³ and Beom Seok Kim³

Abstract

Objectives. Thalidomide has various effects, such as immune modulation, anti-angiogenicity, anti-inflammation and anti-proliferation. Moreover, thalidomide modulates the activity of NF-κB, which can up-regulate the expression of downstream genes involved in the pathophysiology of LN. Here we investigated the efficacy of thalidomide monotherapy or thalidomide plus prednisolone (PL) on nephritis in NZB/WF1 mice at different doses and compared both with a combination therapy of MMF plus PL.

Methods. Forty-three female NZB/WF1 mice were divided into eight groups (untreated; 1.7, 5 or 10 mg/kg of thalidomide alone; 1.7, 5 or 10 mg/kg of thalidomide plus 1.5 mg/kg of PL and 33.3 mg/kg of MMF plus PL). Proteinuria and histological damage were evaluated. Immune complex deposition and nuclear translocation of NF-κB in kidney tissues were assessed by immunofluorescence staining. Serum concentrations of anti-dsDNA and IgG subclasses were also measured.

Results. In comparison with untreated mice, mice treated with 10 mg/kg of thalidomide monotherapy showed a significant decrease in proteinuria and significantly lower glomerular and tubular damage scores, comparable to 5 or 10 mg/kg of thalidomide plus PL or MMF plus PL. Also, treatment with 10 mg/kg of thalidomide significantly decreased immune complex accumulation, reduced the serum concentration of anti-dsDNA, IgG2a and IgG2b and inhibited nuclear translocation of NF-κB in kidney tissues, comparable to standard therapy for LN.

Conclusion. These data suggest that thalidomide might play an anti-inflammatory role in the pathophysiology of LN, and it could serve as a complementary therapy to standard induction regimens for refractory LN.

Key words: thalidomide, NZB/WF1 mice, LN.

Introduction

SLE is an autoimmune disease with multiple organ involvement. Almost half of SLE patients present with asymptomatic haematuria and proteinuria [1]. The deposition of immune complexes, including anti-dsDNA and complement (mostly C3), plays a crucial role in the pathogenesis of LN [1]. The amount of proteinuria reflects the extent of involvement of peripheral glomerular capillary loops, which tends to increase with mesangial proliferation and membranous nephropathy [1]. Proliferative LN (class III and IV) is the most severe form of LN [2]. The use of i.v. or oral prednisolone (PL) plus either i.v. CYC or oral MMF is currently recommended as standard induction therapy for proliferative LN [1, 3]. However, despite improved outcomes with these induction therapies, end-stage renal disease still occurs in up to 30% of patients during a 20-year disease course [1]. Thus a new therapeutic modality is still necessary.

Thalidomide has various effects, such as immunomodulation, anti-angiogenicity, anti-inflammation and anti-proliferation [4]. In particular, thalidomide treatment can decrease the production of pro-inflammatory cytokines, including TNF-α or IL-1β, and further, it can reduce
TNF-α-induced NF-κB activation and in turn decrease the expression of TNF-α-related genes, leading to a reduction of inflammation in the immunological process [5]. With these effects, thalidomide has been used for the treatment of rheumatic diseases such as RA, ankylosing spondylitis and Behcet disease [6–8], despite its serious adverse effects of teratogenicity and peripheral neuropathy [9, 10]. NF-κB is well-known to up-regulate the expression of downstream genes involved in the development or progression of LN [11, 12]. Moreover, recently the inhibition of NF-κB activity was reported to effectively attenuate the severity of nephritis in lupus-prone mice [13, 14]. Thus, considering the immunomodulatory property and the NF-κB activity inhibitory function of thalidomide, it could be an additional treatment for LN, comparable to current regimens.

There was a report of administration of thalidomide to 10 LE patients, where thalidomide showed a potent anti-inflammatory efficacy. Thalidomide improved skin lesions and LE-related alopecia and reduced inflammatory parameters and arthritic pain. However, this report did not demonstrate its efficacy on LN [15]. In addition, there was a previous study reporting the efficacy of thalidomide used in NZB/WF1 mice, but that provided insufficient information on thalidomide’s effects because the mice were administered only a single 3-mg dose [16]. To the best of our knowledge, to date, no reports have evaluated the efficacy of thalidomide monotherapy or thalidomide plus PL as combination therapy for nephritis in lupus-prone mice in a dose-dependent manner over a long period and compared that efficacy with a standard induction therapy for LN. To address these issues, in this study, we investigated the efficacy of thalidomide monotherapy or thalidomide plus PL on nephritis in NZB/WF1 mice at different doses and compared both with the combination therapy MMF plus PL.

Methods

Animals and treatment protocol

All animals were treated in accordance with the guidelines and regulations for the use and care of animals of Yonsei University, Seoul, Korea. Forty-three female lupus-prone NZB/WF1 mice at 18 weeks of age (SLC, Hamamatsu, Japan) were purchased and housed in individual cages in a specific pathogen-free barrier facility under standard sterile conditions at Yonsei University. In our preliminary experiments using bortezomib in NZB/WF1 mice, ~25–30% of untreated mice died during the experimental period [14]; therefore we assigned eight mice to the untreated group and five mice to each treatment group (group 1 = untreated, group 2 = 1.7 mg/kg of thalidomide, group 3 = 5 mg/kg of thalidomide, group 4 = 10 mg/kg of thalidomide, group 5 = 1.7 mg/kg of thalidomide plus PL, group 6 = 5 mg/kg of thalidomide plus PL, group 7 = 10 mg/kg of thalidomide plus PL and group 8 = MMF plus PL). The dose of MMF was 33.3 mg/kg and that of PL was 1.5 mg/kg. Mice in the treatment groups started receiving thalidomide (Sigma-Aldrich, St Louis, MO, USA), MMF and PL at 24 weeks of age. Thalidomide, MMF and PL were administered orally each day for 7 weeks.

Measurement of proteinuria

Proteinuria was measured in spot urine collected from each mouse using an albumin reagent strip (URiSCAN; Yongdong Pharmaceutical Co., Seoul, Korea) twice a week during the experimental period. Proteinuria was semi-quantitatively expressed as follows: 0 = none or trace amount of proteinuria, 1+ = <100 mg/dl, 2+ = <300 mg/dl, 3+ = <2000 mg/dl and 4+ = >2000 mg/dl.

Histology

The mice were anesthetized and killed at 31 weeks of age. Kidney tissues were obtained from all mice, fixed in buffered formalin and stored in liquid nitrogen. Formalin-fixed kidney tissues were embedded in paraffin, sectioned into 4-μm-thick slices and stained with periodic acid–Schiff (PAS) according to conventional procedures. Histological abnormalities, including glomerular, tubular and vascular damage, were scored semi-quantitatively on a 4-point scale independently and blindly by two pathologists, as described in previous studies [13, 14]. Their scores were averaged. At least 50 glomeruli were examined per mouse.

Immunofluorescence staining for IgG, C3, NF-κB and the nucleus

All kidney tissues were embedded in the optimum cutting temperature compound and frozen at −20°C. Samples were sectioned into 4-μm-thick sections, fixed in 4% paraformaldehyde for 15 min and washed three times in cold PBS. Non-specific binding was blocked with 1% normal goat serum in PBS with Tween for 30 min. Samples were incubated at room temperature with goat anti-mouse IgG (1:100, Sigma-Aldrich) and rabbit anti-mouse C3 (1:100; Abcam, Cambridge, MA, USA) for 4 h and washed three times with PBS. Secondary antibodies were incubated at room temperature with Alexa Fluor 488 donkey anti-goat IgG and Alexa Fluor 568 donkey anti-rabbit IgG (both 1:100, Molecular Probe; Invitrogen, Carlsbad, CA, USA) for 1 h and washed three times with PBS. Also, samples were incubated at room temperature with goat anti-mouse NF-κB (1:100, Abcam) for 4 h and washed three times in PBS. Secondary antibodies were incubated at room temperature with Alexa Fluor 488 donkey anti-goat IgG (1:200, Molecular probe, Invitrogen) for 1 h and washed three times in PBS. Secondary antibodies were incubated at room temperature with Alexa Fluor 488 donkey anti-goat IgG (1:200, Molecular probe, Invitrogen) for 1 h and washed three times in PBS. Secondary antibodies were incubated at room temperature with Alexa Fluor 488 donkey anti-goat IgG (1:200, Molecular probe, Invitrogen) for 1 h and washed three times in PBS. Nuclei were stained with 4,6-diamidino-2-phenylindole dihydrochloride (1:1000; Invitrogen, Grand Island, NY, USA). They were mounted with mounting medium (Vector Laboratories, Southfield, MI, USA) and examined with a laser scanning confocal microscope (LSM 710 confocal microscope; Carl Zeiss AG, Germany). To analyse the extent of nuclear translocation of NF-κB, relative area (%) and co-localization coefficient Ch1-T1 of nuclei occupied by NF-κB in the merging image were calculated using the LSM ZEN 2009 image analysis program.
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(Carl Zeiss AG). Two pathologists independently assigned semi-quantitative scores for the intensity and distribution of staining, and the averages of their scores were calculated. Co-localization coefficients between nuclei and NF-κB were calculated using Zeiss co-localization coefficient function software; all background pixels were considered, and the number of co-localizing pixels (NF-κB) in channel 1 (Ch1) was calculated in comparison with the total number of pixels (nuclei).

Serum concentration of anti-dsDNA and IgG subclasses

We obtained blood samples from experimental animals after anesthetizing and killing them. The serum was separated and stored at −80°C. The mouse anti-dsDNA IgG concentration was measured by a sandwich ELISA according to the manufacturer’s instruction (Alpha Diagnostic International, San Antonio, TX, USA). The serum IgG subclasses assayed were IgG1, IgG2a, IgG2b and IgG3. The IgG subclasses were analysed by the Milliplex MAP mouse immunoglobulin isotyping kit (Millipore, Billerica, MA, USA).

Toxicity

Blood samples taken at the time of killing from mice with no treatment and those with 10 mg/kg thalidomide and 5 or 10 mg/kg thalidomide plus PL were examined for white blood cell count, haemoglobin, platelet count and the levels of aspartate aminotransferase, alanine aminotransferase, blood nitrogen and creatinine to determine bone marrow, liver and kidney toxicity of thalidomide.

Statistical analysis

All statistical analyses were conducted using SPSS for Windows, version 15 (SPSS Inc., Chicago, IL, USA). All results were expressed as the mean (s.d.). The Kaplan-Meier plot for survival rate was analysed by log-rank test. Statistical comparisons between the two groups were evaluated by a Mann-Whitney U test and among multiple groups by ANOVA followed by the Tukey method for multiple comparisons. When we compared the values among groups, we gave an asterisk to the mean value of each treated group that had statistical significance (P < 0.05).

Results

Amount of proteinuria and survival rate

To evaluate the efficacy of thalidomide monotherapy or thalidomide combined with PL and compare it with a standard induction therapy (MMF plus PL), we measured the amount of proteinuria in lupus-prone mice and analysed their survival rate. When the experiment began at 24 weeks of age, most mice had mean proteinuria values ranging from 2 to 2.2. Proteinuria gradually increased over time and reached up to 3.1 in untreated mice. From 27 weeks of age, mice treated with 10 mg/kg of thalidomide had a significant decrease in the amount of proteinuria. Mice treated with 10 mg/kg of thalidomide and 1.7 mg/kg of thalidomide plus PL, but not 5 mg/kg of thalidomide, showed significant reduction in proteinuria compared with untreated mice for 7 weeks (50% and 35% from baseline level, respectively), but this tended to be inferior to combination therapies. Mice treated with 5 or 10 mg/kg of thalidomide plus PL or MMF plus PL had significantly less proteinuria at the end of the experiment than untreated mice (67%, 99% and 62% from baseline level, respectively) (Fig. 1A). Only two untreated mice and one mouse treated with 1.7 mg/kg of thalidomide alone died during the experiment (Fig. 1B). Taken together, 10 mg/kg of thalidomide and thalidomide at all doses combined with PL could improve nephritis in lupus-prone mice with synergistic efficacy. Furthermore, at human conventional doses in clinics, 10 mg/kg of thalidomide monotherapy or thalidomide combined with PL might have an efficacy comparable to that of combination therapy [17, 18].

Histological damage

Severe glomerulonephritis, including glomerular expansion, glomerular cell proliferation, mononuclear cell infiltration and focal crescent formation, was observed in untreated lupus-prone mice. Tubular dilatation, atrophy and casts were also observed, but vascular changes such as wall thickening or capillary thrombosis were not definitely detected in untreated mice. In contrast, in mice treated with 10 mg/kg of thalidomide and thalidomide at all doses combined with PL or MMF plus PL, mild glomerular and tubular changes or even normal structures were observed (Fig. 2A).

To examine the histological renal alterations in lupus-prone mice, we investigated three categories of damage: glomerular, tubular and vascular damage. Mice treated with not only 10 mg/kg of thalidomide but also thalidomide at all doses combined with PL showed a significant decrease in glomerular and tubular damage scores compared with mice with no treatment. Although 10 mg/kg of thalidomide significantly reduced the glomerular damage score, its efficacy did not exceed that of 10 mg/kg of thalidomide or MMF plus PL. Mice treated with 10 mg/kg of thalidomide plus PL tended to have lower glomerular damage scores than mice treated with MMF plus PL, but they were not significantly different. Also, 10 mg/kg of thalidomide reduced tubular damage scores similar to combination therapies, but there were no significant differences in vascular damage scores among groups (Fig. 2B). Thus we concluded that 10 mg/kg of thalidomide could improve renal histology in lupus-prone mice comparably to combination therapies.

Immune complex deposition

To assess the deposition of immune complexes, kidney tissues obtained from NZB/WF1 mice were analysed by immunofluorescence staining with antibodies specific for mouse C3 (green) and IgG (red). In the untreated group, C3 and IgG heavily accumulated within glomeruli with immune complexes in mesangium and capillary loops. The yellow-orange colour indicates coincident fluorescence, suggesting co-localized C3 and IgG as an immune...
complex. Similar fluorescence intensity remained in kidney tissues from mice treated with 1.7 or 5 mg/kg of thalidomide, but the intensity started to diminish in mice treated with 10 mg/kg of thalidomide. Treatment with 5 or 10 mg/kg of thalidomide plus PL or MMF plus PL effectively decreased the accumulation of immune complexes compared with no treatment (Fig. 3A). In semi-quantitative analysis of the staining intensity, 10 mg/kg of thalidomide and thalidomide at all doses or MMF combined with PL reduced immune complex deposition in kidney tissues. Moreover, 10 mg/kg of thalidomide effectively mitigated glomerular deposition of IgG and C3 complex, comparable to MMF plus PL but less than 10 mg/kg of thalidomide plus PL (Fig. 3B).

The serum concentration of anti-dsDNA and IgG subclasses
To investigate the effect of thalidomide monotherapy or a combination therapy of thalidomide plus PL on the ability of B cells to produce both LN-specific anti-dsDNA and IgG subclasses, we measured their serum concentrations. Treatment with 10 mg/kg of thalidomide, 5 or 10 mg/kg of thalidomide plus PL or MMF plus PL significantly reduced the serum concentration of anti-dsDNA in lupus-prone mice by 23%, 22%, 30% and 24%, respectively, compared with no treatment (Fig. 4A). None of the therapeutic drugs affected IgG1 concentration, but treatment with 10 mg of thalidomide, 5 or 10 mg/kg of thalidomide plus PL or MMF plus PL significantly decreased the serum concentrations of IgG2a and IgG2b. In contrast, IgG3 was reduced by drugs combined with PL (Fig. 4B). Taken together, 10 mg/kg of thalidomide might inhibit the production of anti-dsDNA and IgG subclasses of B cells and plasma cells, resulting in reduced renal deposition of immune complexes and alleviation of nephritis in lupus-prone mice, comparable with 5 or 10 mg/kg of thalidomide plus PL or MMF plus PL.
To investigate whether thalidomide plus PL can interrupt transcriptional activity of NF-κB, we calculated co-localization relative area (%) and coefficient Ch1-T1 between NF-κB and nuclei by immunofluorescence. Like other results, treatment with 10 mg/kg of thalidomide and thalidomide at all doses combined with PL or MMF plus PL, mild glomerular and tubular changes or even normal structures were observed. (B) Mice treated with not only 10 mg/kg of thalidomide but also thalidomide at all doses combined with PL showed significant decreases in glomerular and tubular damage scores compared with mice with no treatment. Although 10 mg/kg of thalidomide significantly reduced glomerular damage score, its efficacy did not exceed that of 10 mg/kg of thalidomide or MMF plus PL. The asterisk indicates significant differences in the mean values of each treated group compared with the untreated group (P < 0.05).

**Nuclear translocation of NF-κB**

To evaluate the toxicity of thalidomide, we examined parameters reflecting the functions of bone marrow, liver and kidney in mice with no treatment, 10 mg/kg of thalidomide and 5 or 10 mg/kg of thalidomide plus PL. There were no differences in white blood cell counts and haemoglobin levels or in liver and kidney functions among groups, except platelet count and blood urea nitrogen (BUN). Untreated mice had lower platelet counts and higher BUN levels than treated mice. Elevated BUN levels might be a result of the deterioration of renal function in untreated mice, but the creatinine level was not different among groups.
Relative thrombocytopenia and increased BUN levels were improved after treatment with thalidomide monotherapy or thalidomide combined with PL (Table 1).

**Discussion**

In this study we demonstrated that 10 mg/kg of thalidomide can attenuate the severity of nephritis in NZB/WF1 mice, comparable to combination therapy of MMF plus PL. The major mechanisms of thalidomide action include immune modulation, anti-angiogenicity, anti-inflammation and anti-proliferation [4]. The immune modulatory functions of thalidomide in SLE, however, remain unclear. According to a previous study, thalidomide is likely to control B cell expansion in two lupus-prone mice strains by stimulating the central immune system [16]. In our study,
10 mg/kg of thalidomide not combined with PL significantly reduced glomerular accumulation of immune complex of IgG and C3 by reducing anti-dsDNA production as well as IgG2a and IgG2b, comparable to the standard induction treatment MMF plus PL. Thus thalidomide can reduce overall immunoglobulin production by controlling disease-associated autoreactive B cell expansion.

So far, IgG2a and IgG2b have been considered as the pathogenic IgG subclasses, and the direct administration of IgG2a aggravated the disease activity in lupus-prone mice [19, 20]. Also, the serum concentration of IgG3 along with IgG2a was reduced by immune suppressive treatment [21]. Based on these results from previous reports, we measured the serum concentration of IgG subclasses in mice. Additionally we found that 10 mg/kg of thalidomide did not decrease the serum concentration of IgG1 and IgG3, but it reduced those of IgG2a and IgG2b, which are considered to be pathogenic and specific for nephritis in lupus-prone mice, comparably to MMF plus PL.
Values are mean (S.D.). *Mean value of each treated group that had statistical significance (P < 0.05).

In addition, unlike IgG2a and IgG2b, IgG3 was reduced by all drugs combined with PL. This finding might suggest that PL has a superior inhibitory effect on IgG3 production to thalidomide or a synergistic effect with thalidomide or MMF. Moreover, considering that various autoantibodies in addition to anti-dsDNA can accumulate in the kidney [22], it might be feasible to obtain information on the function of autoreactive B cells to measure the serum concentrations of IgG subclasses than to simply assay the serum concentration of anti-dsDNA or its subclasses.

Treatment with 10 mg/kg of thalidomide reduced the extent of nuclear translocation of NF-κB within kidney tissues compared with no treatment. There have been several reports on the effect of NF-κB in LN; glomerular endothelial and mesangial activation of NF-κB correlated with its severity and glomerular macrophage infiltration [23], and pro-inflammatory cytokines can up-regulate mesangial FasL might contribute to glomerular inflammation in proliferative LN [11]. Although the efficacy of 10 mg/kg of thalidomide in inhibiting nuclear translocation of NF-κB was lower than the same dose of thalidomide or MMF plus PL, we concluded that 10 mg/kg of thalidomide has a regulatory potency in the transcriptional activity of NF-κB in the pathophysiology of LN, in addition to its immune modulatory functions on autoreactive B cells.

TNF-α is known to be involved in various inflammatory renal diseases, including LN, and the serum level of TNF-α was closely correlated with the serum level of IFN-α, which is one of the important cytokines in the pathophysiology of SLE [24]. TNF-α was observed in glomerular epithelial cells, endothelial cells, mesangial cells and tubular epithelium [25, 26]. Additionally the expression of TNF-α and its related signaling proteins in kidney tissues was up-regulated in LN class III and IV, and the level of its expression correlated with the renal pathology activity index [27]. Furthermore, the administration of anti-TNF-α monoclonal antibody in patients with LN showed an impressive reduction in proteinuria and maintained long-term remission of LN, despite transient increases in autoantibodies [28]. Meanwhile, NZB/WF1 mice exhibited contrary responses to TNF-α. TNF-α level was associated with relatively mild disease activity [29], and furthermore, the administration of high doses of TNF-α delayed the disease onset in lupus-prone mice early in their life [30]. In contrast, TNF-α administration to lupus-prone mice after fully developed lupus-like disease could accelerate the disease progression in NZB/WF1 mice [31]. In the present study, thalidomide was administered after most mice had proteinuria, therefore it can be speculated that thalidomide can alleviate nephritis in lupus-prone mice by cutting the vicious cycle between NF-κB and TNF-α; NF-κB is induced by TNF-α and in turn can up-regulate TNF-α in LN [23]. A combination therapy of thalidomide plus PL was more effective for nephritis in lupus-prone mice than thalidomide monotherapy. The initial effect of 10 mg/kg of thalidomide on proteinuria was comparable to that of 10 mg/kg of thalidomide plus PL, but the final outcome of 10 mg/kg of thalidomide was less effective than a combination treatment. A combination therapy of PL plus CYC or MMF is currently recommended for the treatment of proliferative LN [3]. Therefore we anticipate that the use of PL can decrease the dose of thalidomide that is needed to attain a similar outcome of nephritis through the synergistic efficacy, leading to reduction in the rate of systemic complications of thalidomide.

We used doses of thalidomide plus PL and MMF plus PL that are clinically equivalent for patients with multiple myeloma and LN: 1.7, 5 and 10 mg/kg of thalidomide equate to 100, 300 and 600 mg of thalidomide, respectively, for a 60-kg patient. Generally mouse metabolism is much higher than that of humans. Therefore higher doses of drugs would still have been relevant in mouse experiments [32]. Nevertheless, clinically conventional doses of thalidomide significantly alleviated nephritis. Moreover, 10 mg/kg of thalidomide plus PL resolved proteinuria in lupus-prone mice. Considering the faster metabolism in mice, when thalidomide might be carefully applied to humans with LN, even lower thalidomide doses could be effective.

The clinical application of thalidomide to patients with LN may still bring about many concerns over its serious complications, including teratogenic potency, peripheral neuropathy and venous thromboembolism [9, 10, 33]. In particular, the teratogenicity of thalidomide limits its use in...
young female patients of childbearing age [9]. Both CYC and MMF are also classified in class D, and they have diverse complications such as infertility and bone marrow suppression [34, 35]. Nevertheless, CYC and MMF might be administered to young female patients to improve LN and to prevent nephritis-related serious systemic manifestations when LN is rapidly progressing or refractory to relatively safe conventional regimens. Although thalidomide cannot be considered as a standard induction therapy for LN because of its serious complications, we expect that it might be considered as a complementary therapeutic modality to CYC, MMF or other currently used drugs in patients with refractory LN.

This study has several limitations. First, we did not administer thalidomide doses >10 mg/kg, therefore we cannot determine the effective dose of thalidomide monotherapy comparable to MMF plus PL. Second, we did not evaluate the alteration of cytokines involved in the pathogenesis of LN, such as TNF-α, IFN-γ and IL-12, or the immune cell population in lymph nodes or spleen [36, 37]. Third, we did not analyse the transcriptional activity of NF-κB through in vitro experiment. This study is, however, a pilot study, and a further study will be done to determine an efficient and complication-free minimal dose of thalidomide to treat LN and to overcome several limitations of this study.

In conclusion, in this study we demonstrated that 10 mg/kg of thalidomide can attenuate the severity of nephritis in NZB/WF1 mice comparably to a combination therapy of MMF plus PL. Treatment with 10 mg/kg of thalidomide significantly decreased the serum concentration of anti-dsDNA and pathogenic IgG2a and IgG2b and reduced glomerular deposition of immune complexes of IgG and C3. Further, it inhibited nuclear translocation of NF-κB in kidney tissues and alleviated both proteinuria and histological renal damage in lupus-prone mice, comparably to 5 or 10 mg/kg of thalidomide plus PL or MMF plus PL. These data suggest that thalidomide might play an anti-inflammatory role in the pathophysiology of LN, and it could be considered as a complementary therapeutic modality to standard induction regimens in patients with refractory LN.

Rheumatology key messages

- Treatment with 10 mg/kg of thalidomide or combined with PL significantly alleviated nephritis in NZB/WF1 mice.
- Treatment with 10 mg/kg of thalidomide reduced serum anti-dsDNA, IgG2a and IgG2b in NZB/WF1 mice.
- Treatment with 10 mg/kg of thalidomide inhibited the nuclear translocation of NF-κB in NZB/WF1 mice.

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