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ANTI-CD3 ANTIBODY THERAPY ATTENUATES THE PROGRESSION OF HYPERTENSION IN FEMALE MICE WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disorder with prevalent hypertension that significantly contributes to the mortality in this patient population. Pre-clinical and clinical evidence suggests that anti-CD3 antibody therapy may attenuate the development of autoimmune diseases like SLE. However, it is unclear whether this treatment impacts the development of the prevalent hypertension associated with SLE. The present study was designed to determine whether anti-CD3 antibody treatment attenuates the progression of hypertension in female SLE mice with already established renal disease (albuminuria ≥ 100 mg/dL). Female SLE (NZBWF1) and control (NZW) mice were administered either an antibody to CD3ε, a component of the T cell receptor complex expressed on all T cells, or IgG antibody (isotype control) for up to 4 weeks (intranasal; 25 μg/week). Spleen weight was lower in SLE mice treated with anti-CD3 antibody than in IgG-treated SLE mice, suggesting that immune system hyperactivity is decreased. Circulating anti-dsDNA autoantibodies were increased in SLE mice compared to controls and were blunted in the anti-CD3-treated SLE mice. The development of hypertension was attenuated in anti-CD3 treated mice with SLE independently of changes in renal injury (assessed by urinary albumin). These data suggest anti-CD3 therapy during autoimmune disease may have added clinical benefit to attenuate cardiovascular risk factors like hypertension.

Graphical abstract

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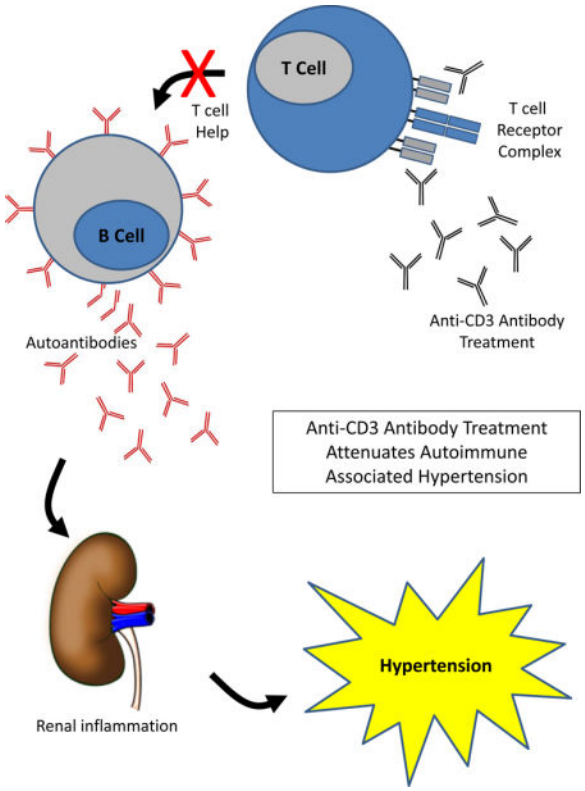
DISCLOSURES

None



Keywords

hypertension; autoimmune; T cell; antibody

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease that predominantly affects women of reproductive age. While loss of immune tolerance leading to the production of autoantibodies that promote tissue injury and inflammation is a hallmark of SLE, the major cause of mortality in these women is cardiovascular disease,[1–5] and the prevalence of hypertension, a major cardiovascular risk factor, is markedly increased in this patient population[6–11]. An important clinical goal for patients with autoimmune disease is to induce tolerance. To achieve this goal, a monoclonal antibody to CD3ε, a subunit of the T-cell co-receptor complex which is expressed on the surface of all T cells, has been used in both pre-clinical and clinical studies to induce peripheral tolerance by expanding tolerogenic regulatory T cells (T_{REG}) and by promoting the removal of apoptotic bodies[12]. Treatment with anti-CD3 antibodies reportedly attenuates disease in non-obese diabetic mice[13], models of experimental autoimmune encephalitis[14, 15], rheumatoid arthritis[16], and SLE[17]. While the efficacy of these antibodies to attenuate autoimmunity has been widely established, it is unclear whether anti-CD3 therapy can attenuate the prevalent hypertension associated with autoimmune diseases like SLE. This is an important question to address given the now widely recognized role for adaptive immunity in the pathogenesis of hypertension[18]. The

present study was designed to test the hypothesis that anti-CD3 therapy in female SLE mice with already established renal disease can attenuate the progression of hypertension.

METHODS

Animal Model

Female NZBWF1 and control (NZW/LacJ) mice were obtained from Jackson Laboratories (Bar Harbor, ME). The female NZBWF1 mouse is a well-established model of SLE with prevalent hypertension and renal injury[19–25]. Mice were randomly divided into 4 groups: control mice administered an isotype control (Control/IgG) or the monoclonal antibody to mouse CD3 (Control/Anti-CD3), and SLE mice administered isotype control (SLE/IgG) or the antibody to CD3 (SLE/Anti-CD3). Only NZBWF1 mice with already established renal disease (urinary albumin ≥ 100 mg/dL by dipstick) at 30 weeks of age were used in the SLE groups. Therefore the experiment is designed to determine whether the disease progression can be attenuated or reversed. All studies were approved by the University of Mississippi Medical Center Institutional Animal Care and Use Committee (IACUC) and were in accordance with National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals.

Antibody Administration

Mice were administered a monoclonal hamster anti-mouse CD3ε antibody (clone 145-2C11, BioXcell, #BE0001-1) or a polyclonal hamster IgG (vehicle) as the isotype control (5 μg, intranasal; West Lebanon, NH) for 5 consecutive days per week for 3–4 weeks. This route of administration, dose, and duration of anti-CD3 antibody was previously shown by others to attenuate disease severity in the (NZB × SWR)F1 (SNF1) model of SLE[17]. Spleen weight was assessed at the end of the study as an indirect surrogate marker to determine whether the antibody treatment was impacting systemic immune function.

Autoantibody Production

The presence of plasma anti-dsDNA autoantibodies (dsDNA), a clinical marker of SLE, was measured by ELISA (Alpha Diagnostics International, San Antonio, TX) and is presented as antibody activity index, as previously described by our laboratory[25].

Blood Pressure Measurement

At 34 weeks of age, blood pressure was recorded in conscious, unrestrained mice by carotid artery catheter as previously described by our laboratory[23, 24, 26–29].

Renal Injury and Inflammation

Albuminuria was measured by ELISA (Alpha Diagnostics International) in 24-hour urine samples at the conclusion of the study as previously published by our laboratory[23, 24,26–29]. Renal expression of tumor necrosis factor alpha (TNF-α) was assessed by immunoblot as previously reported in our laboratory[29, 30] and renal expression of the interleukin 17 receptor (IL-17RA) was assessed using a polyclonal goat anti mouse antibody (AF448, R&D Systems).

Statistical Analysis

Data are presented as mean ± standard error of means (SEM). Statistical analyses were performed using Sigmaplot 11.2 software (Systat, Richmond, CA). A two-way ANOVA was used to assess group and treatment effects followed by a one-way ANOVA with an appropriate post-hoc analysis to detect determine differences between groups. Values were considered statistically different at p values < 0.05.

RESULTS

Anti-CD3 treated animals have lower spleen weight

Spleen weight was assessed as a surrogate marker for the efficacy of the anti-CD3 treatment to reduce immune system hyperactivity. There was a trend for increased spleen weight in SLE mice relative to control animals; however, this did not reach statistical significance (Figure 1; 0.25 ± 0.06 vs. 0.16 ± 0.02 grams, p = 0.075) as it has in our previous studies[25]. However, spleen weight was significantly lower in SLE mice treated with anti-CD3 therapy (0.15 ± 0.02; p = 0.022) compared to SLE mice treated with IgG. Spleen weight was not altered in anti-CD3 treated control mice (0.14 ± 0.02).

Anti-CD3 treatment attenuates autoantibody production

Circulating levels of anti-dsDNA autoantibodies were greater in SLE compared to controls (Figure 2; 19.8 ± 7.3 vs. 0.7 ± 0.1 antibody units; p = 0.050, by two way ANOVA group effect) as previously reported[25]. Circulating anti-dsDNA autoantibodies were qualitatively lower in anti-CD3 treated SLE mice compared to vehicle treated SLE mice (8.4 ± 3.3), but the study was not sufficiently powered for this to reach statistical significance.

Anti-CD3 treatment attenuates the progression of hypertension in SLE mice

Mean arterial pressure was higher in SLE mice with established disease than controls (Figure 3; 156 ± 3 vs. 112 ± 4 mmHg; p < 0.001) as we previously reported[23, 24, 26–29]. Blood pressure was lower in anti-CD3 treated SLE mice (137 ± 4; p < 0.001) compared to vehicle treated SLE mice, but anti-CD3 did not change blood pressure in control mice (117 ± 2).

Anti-CD3 treatment does not impact renal injury and inflammation

Albuminuria was increased in SLE mice with established disease compared to control animals (Figure 4; 304679 ± 110518 vs. 52 ± 6 μg/mg creatinine; SLE vs control; p = 0.008, two way ANOVA group effect). However, urinary albumin was not altered in anti-CD3 treated SLE animals (272227± 59129 μg/mg creatinine) or control animals (74±5 μg/mg creatinine). Renal TNF-α expression (normalized to β-actin) was increased in female SLE mice compared to controls as we previously showed (12 ± 1 vs. 7 ± 3; p = 0.016, two way ANOVA group effect)[23, 25]; however, expression was not reduced in the treated animals (Figure 5A). Renal expression of the IL-17RA was increased in female SLE mice compared to controls, and its expression was lower in SLE mice treated with anti-CD3 antibodies (Figure 5B).

DISCUSSION

The prevalence of hypertension is much greater in women with SLE when compared to age matched healthy controls. Hypertension is a major cardiovascular risk factor and contributor to mortality in patients with SLE, and therefore should be considered as an important clinical endpoint that can improve care for this patient population. Previous studies have shown that anti-CD3 antibodies can attenuate the development of SLE and other autoimmune disorders; however, whether this treatment can reduce cardiovascular risk by attenuating the associated hypertension has not been tested. The major new finding of this study is that female SLE mice with established renal disease that are treated with an anti-CD3 antibody have lower blood pressure than vehicle treated animals. In addition, the attenuation of hypertension occurred independently of changes in renal injury and inflammation. Therefore, this study provides new insight into potential clinical benefits for patients with autoimmune disease that might arise from therapeutic approaches that target the immune system.

It is now widely recognized that abnormal immune system activation is associated with the pathogenesis of hypertension, both in humans and in experimental models. For example, numerous studies link inflammatory cytokines and blood pressure in humans[31–35] and a growing body of literature suggests an association between autoantibodies, consistent with systemic autoimmunity, and hypertension[36–40]. In experimental models of spontaneous hypertension, non-specific immunosuppressive therapies such as cyclophosphamide have been reported not only to prevent the development of hypertension, but also to reduce blood pressure in animals with already established hypertension[41]. Similarly, mycophenolate mofetil (MMF), an immunosuppressive therapy commonly used in patients with SLE that depletes proliferating T and B lymphocytes, effectively attenuates the development of hypertension in several experimental models and in humans[42–48]. More recently, our laboratory demonstrated that the development of hypertension associated with SLE could be prevented by treatment with a mouse monoclonal antibody to CD20 (equivalent of rituximab approved for use in humans) intended to specifically deplete B lymphocytes[25]. However, consistent with human literature showing variability in the efficacy of rituximab to treat SLE[49, 50], and in mouse models where efficacy of the anti-cd20 treatment of SLE was reduced with increasing age[51], prophylactic treatment was required to effectively impact SLE disease, and this early intervention impacted both B and T lymphocytes. The present study makes an important advance towards understanding the impact of immunotherapies on hypertension because of the interventional experimental design focused on a therapy (anti-CD3) that consistently attenuates autoimmune disease in experimental animal models.

In addition to assessing the impact of anti-CD3 therapy on blood pressure during SLE, we examined markers of renal disease and inflammation. Immune complex mediated glomerulonephritis is common in patients with SLE and urinary albumin is an important clinical marker of glomerular disease. Female NZBWF1 mice represent a widely established experimental model that progressively develops renal disease easily detectable by measuring albumin in the urine. Data from the present study show that once SLE disease is established, anti-CD3 treatment may not afford renal protection given that urinary albumin was unchanged in the treated group. This data, however, does help to address the important

experimental question of whether the albuminuria is simply driven by the hypertension. The fact that pressure is lower in SLE mice treated with anti-CD3, but urinary albumin is unchanged, suggests that these two characteristics are uncoupled in this model and that the renal disease is more likely to be driven by immune complex deposition rather than increased pressure. This is consistent with human studies suggesting that lupus nephritis and hypertension are not necessarily linked[52, 53].

The mechanism by which anti-CD3 therapy attenuated the hypertension during SLE remains uncertain. Previous work from our laboratory showed that treatment with etanercept to block the biological activity of TNF-α partially attenuated the hypertension[29]. The partial attenuation of the hypertension by etanercept mirrors the attenuation of hypertension reported here in the current study. However, renal TNF-α expression was not lower in the anti-CD3 treated animals, perhaps reflecting that that the current study design was interventional whereas our former work started treatment before evidence of albuminuria was present. IL-17, which is predominantly produced by T_H17 cells and serves as a strong inducer of inflammation, has been implicated as an important cytokine in the pathogenesis of autoimmune diseases including SLE, and in the development of hypertension[54, 55]. The data showing that expression of the IL-17A receptor is lower in the kidneys from anti-CD3 treated mice suggests that T_H17 cells, IL017, and downstream inflammation may be involved in the hypertension associated with this model. Another potential mechanism that could contribute to the attenuation of hypertension by anti-CD3 therapy is the expansion of the $CD4^+CD25^+FoxP3^+$ inducible T_{REG} (iT_{REG}) that mature from $CD4^+FoxP3^-$ conventional T_H cells in the periphery, leading to reduced inflammation and the induction of peripheral tolerance. This would be consistent with the mechanism by which anti-CD3 antibodies attenuated SLE disease in previous studies[17] and with our data suggesting that autoantibodies are reduced in anti-CD3 treated animals; however, direct measurement of this cell population is required for confirmation. T_{REG} dysfunction is recognized as an important contributor to the pathogenesis of SLE[56–61] and adoptive transfer of T_{REG} reduces blood pressure in non-autoimmune mediated models of hypertension[62–64]. It will be important for future studies to explore the possibility that directly expanding these cells can attenuate the pathogenesis of hypertension during autoimmune disease.

In conclusion, data from this study add to the current understanding of the potential clinical benefits that anti-CD3 treatment may afford to patients with autoimmune disease. As part of this benefit, this study highlights the potential interventional utility of this therapy to control a hypertension, a major cardiovascular risk factor and contributor to mortality, during SLE.

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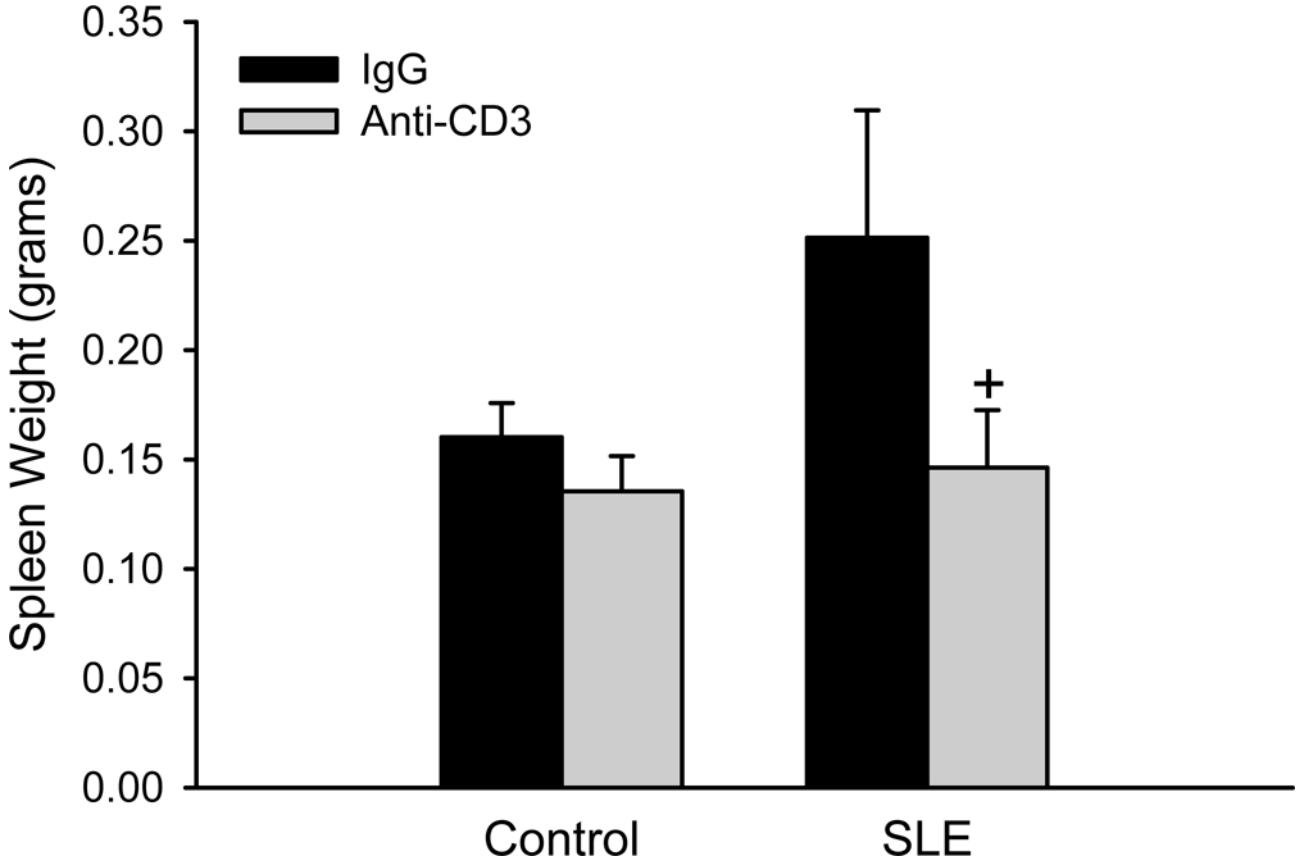


Figure 1. Anti-CD3 therapy reduces spleen weight in SLE mice

Spleen weight (g) in control and SLE mice administered anti-IgG or anti-CD3 antibodies (n = 6–11). +p <0.05 vs. SLE/IgG

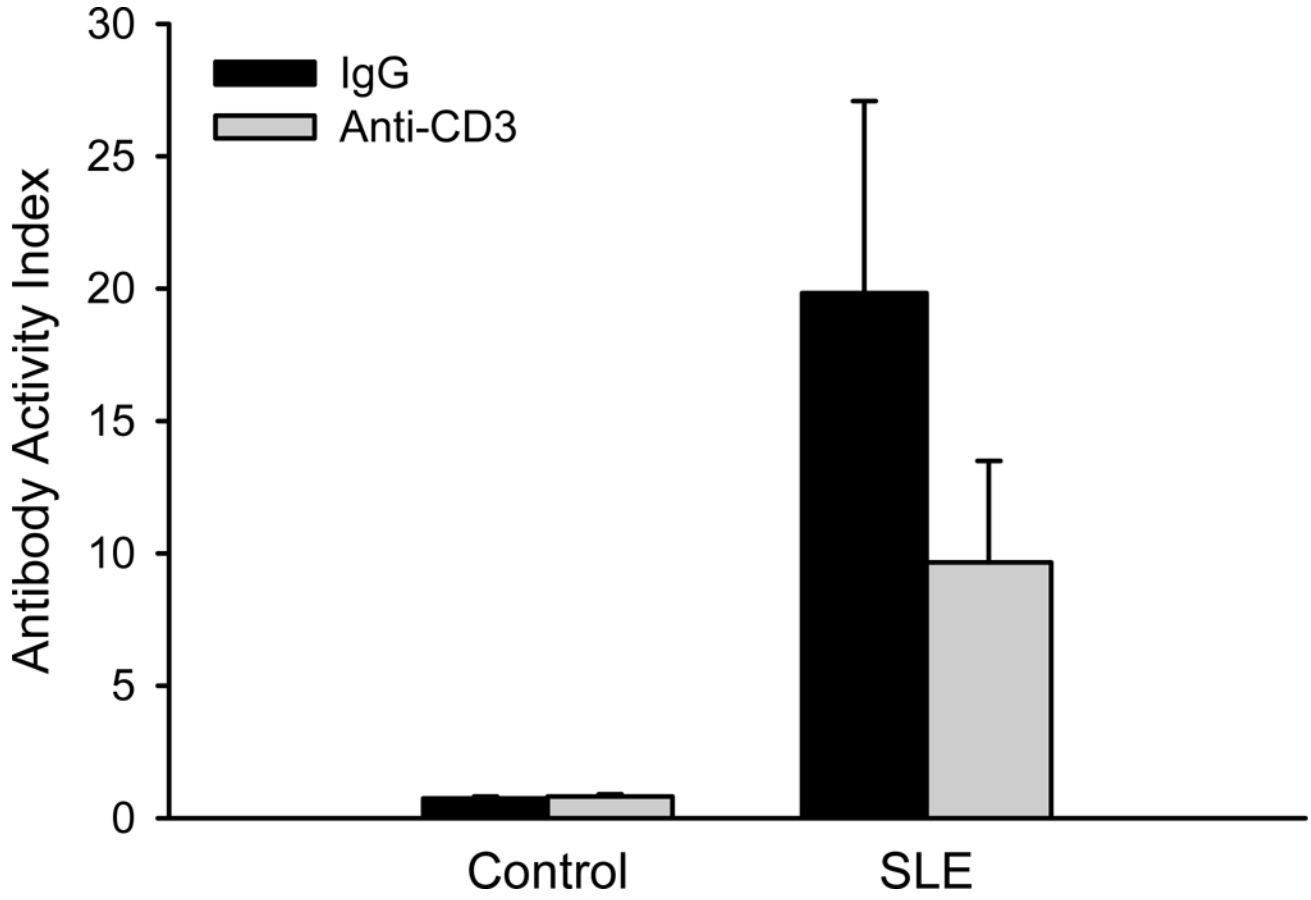


Figure 2. Anti-CD3 therapy attenuates autoantibody production in SLE mice

Circulating anti-dsDNA autoantibodies (presented as antibody activity index) measured in control and SLE mice administered anti-IgG or anti-CD3 (n = 3–12).

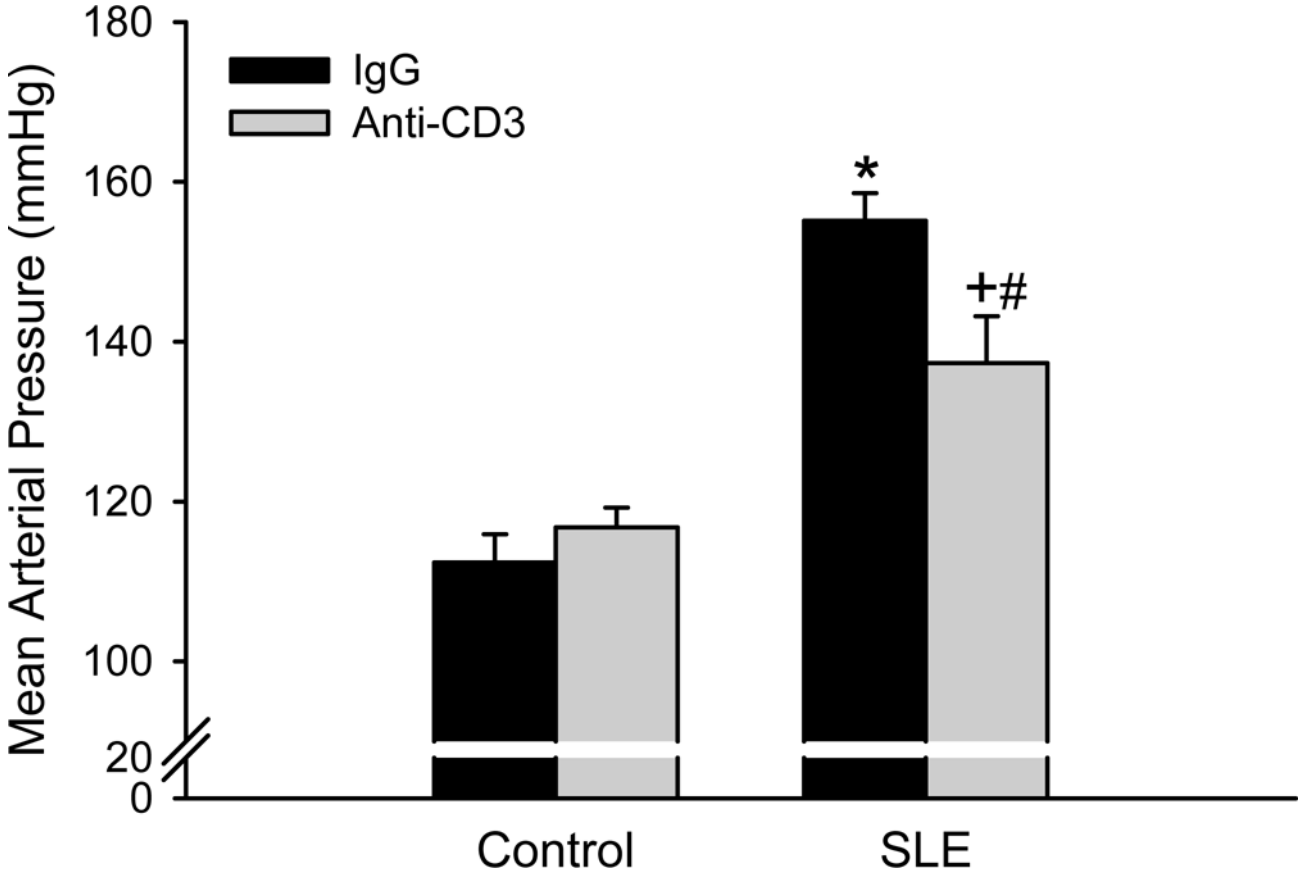


Figure 3. Anti-CD3 therapy attenuates the progression of hypertension in SLE mice

Mean arterial pressure measured in control and SLE mice administered anti-IgG or anti-CD3 (n = 6–7). *p<0.05 vs. Control/Anti-IgG; #p<0.05 vs. Control/Anti-CD3; +p<0.05 vs. SLE/Anti-IgG

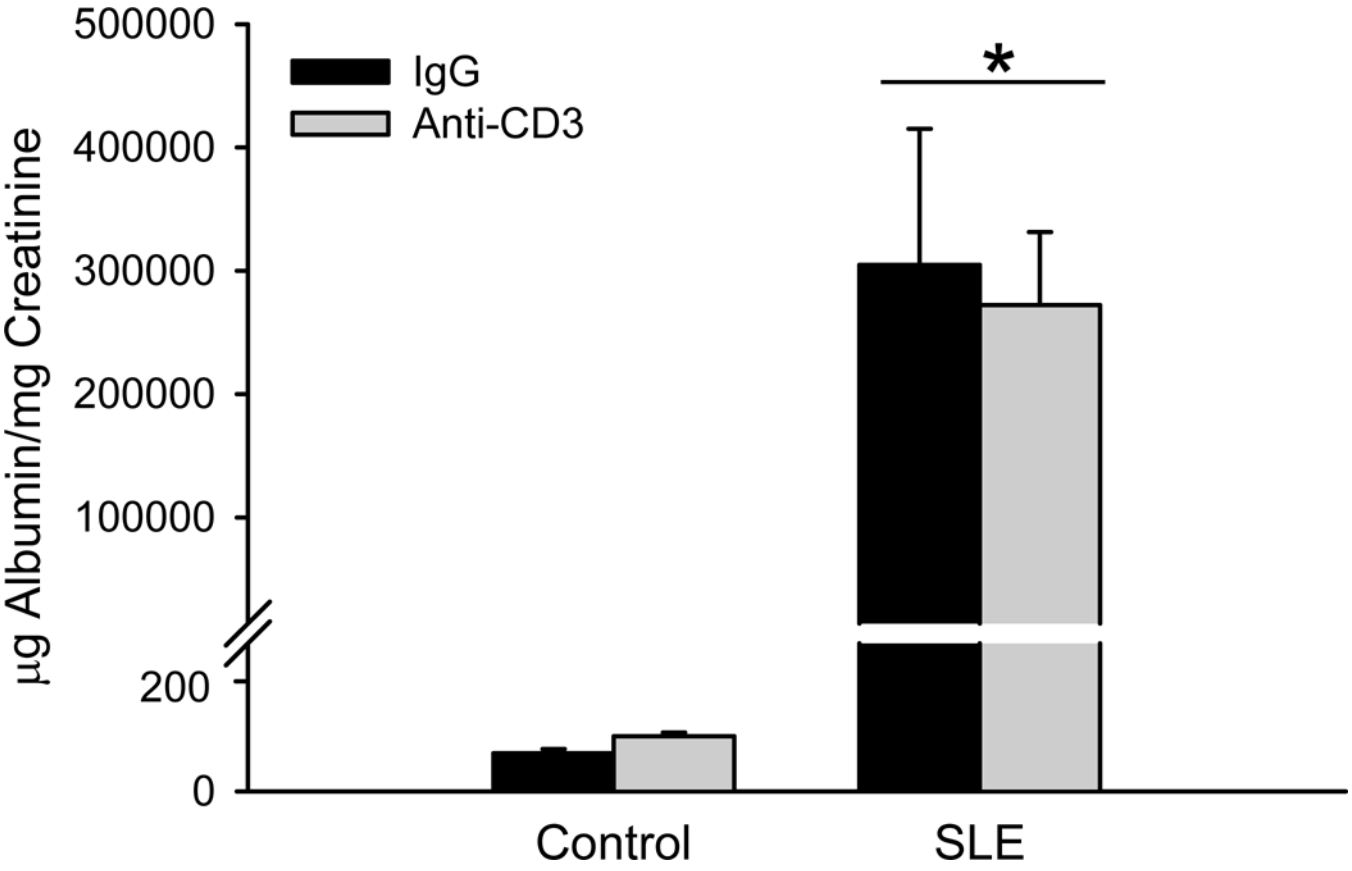
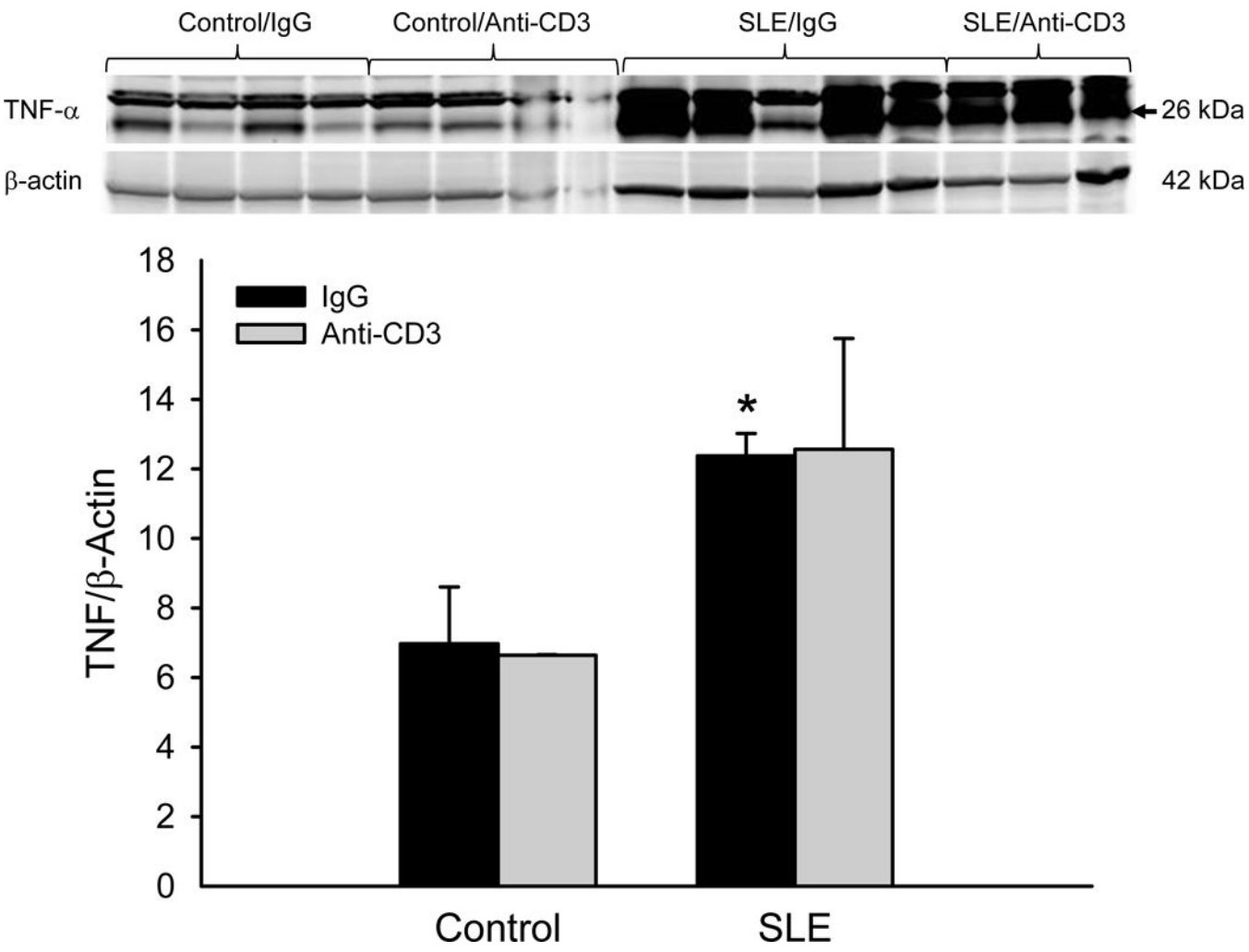


Figure 4. Anti-CD3 therapy does not alter renal injury in SLE mice

Urinary albumin excretion rate at 34 weeks measured by ELISA in control and SLE mice administered anti-IgG or anti-CD3 (n = 6–12). *p<0.05 vs. control.



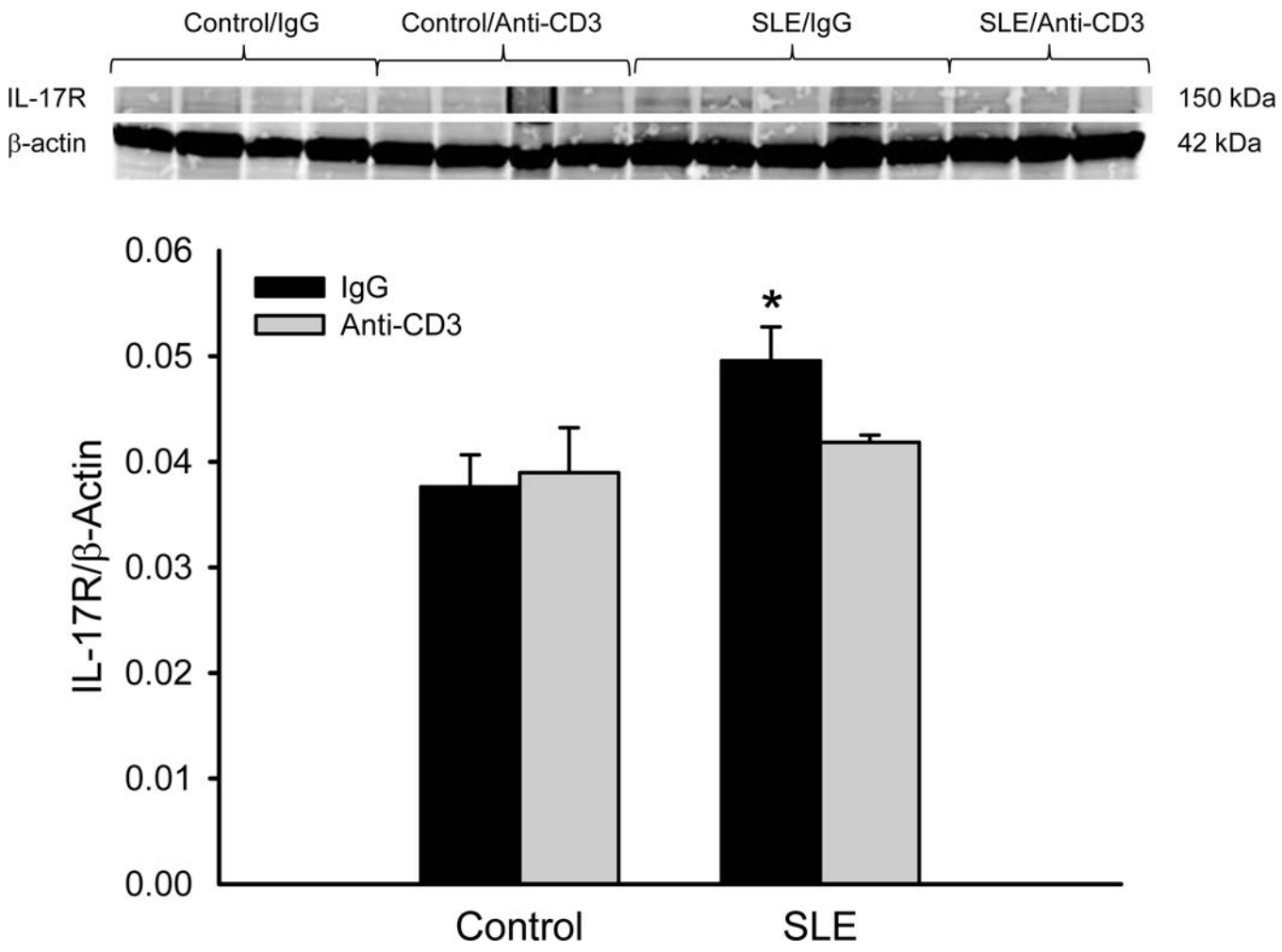


Figure 5.

(A) *Anti-CD3 therapy does not alter renal TNF-α protein expression in SLE mice.* Renal TNF-α was not altered in anti-CD3 therapy, as assessed by immunoblot. *p<0.05 vs. control IgG. (B) Renal IL-17RA expression is attenuated in female SLE mice treated with anti-CD3 therapy. *p<0.05 vs. control IgG and SLE anti-CD3.