Kimura's disease treated with an anti-interleukin-5 antibody, mepolizumab: Relevance for its efficacy for the treatment of immunoglobulin G4-related diseases

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Running head: Kimura's disease treated with mepolizumab

To the Editor,

Kimura's disease (KD) is a rare condition that manifests in young to middle-aged Asians as relatively large and poorly demarcated subcutaneous nodules composed of lymphoid follicles, fibrosis, and dense eosinophil infiltration.[1] The presence of eosinophilia, high immunoglobulin (Ig) E levels, and fibrosis is similar to the presentation of IgG4-related diseases (IgG4-RD).[2,3] Despite systemic administration and/or local injection of corticosteroids, surgical resection, or irradiation, KD is often intractable. Mepolizumab is a humanized IgG1κ monoclonal antibody (mAb) against Interleukin-5 (IL-5).[4] We herein report a case of intractable KD treated with mepolizumab and its efficacy for the reduction of IgG4-producing plasma cells (PCs).

A 42-year-old Japanese female already diagnosed with KD presented to our hospital with a 2-year history of pruriginous diffuse extensive indurations of bilateral upper limbs (Figure 1A). She underwent surgical resection, but soon relapsed. Oral prednisolone administration up to 0.5 mg/kg/day over a period of four years was ineffective. Consequently, we decided to administer mepolizumab after a washing-out period of prednisolone. Pre-treatment skin biopsy revealed prominent lymphoid aggregates with reactive germinal follicles, fibrosis, and dense eosinophil infiltration (Figure 1B). Interestingly, there was an infiltration of IgG- and IgG4-positive PCs (Figure 1C). The ratio of IgG4-positive PCs to IgG-positive PCs was 42.8%. Laboratory tests were as follows: a total white blood cell count of 6,300/μl with eosinophilia (32%), serum IgE 24,145.3 IU/ml (normal < 311.6 IU/ml), serum thymus and activation-regulated chemokine 7,030 pg/ml (normal < 450 pg/mL), serum IgG4 31 mg/dL (normal < 117 mg/dL), and undetectable serum IL-4. All other serum parameters were within normal limits. Fat-suppressed coronal T2-weighted magnetic resonance imaging (MRI) of the upper limb revealed diffuse subcutaneous masses (Figure 2A). Collectively, our case was consistent with KD. Moreover, when the diagnostic criteria of IgG4-RD were applied to our case, the diagnosis was "probable" IgG4-RD.

After providing a written informed consent, the patient received an intravenous

dose of 750 mg of anti-IL-5 humanized mAb (mepolizumab; GlaxoSmithKline, Harlow, U.K.) once a month for six months. After the treatment, there was a dramatic regression of the clinically indurated masses corroborating the reduced MRI intensity, whereas there was no improvement in the swelling and maximum circumference of both limbs (Figure 1A and 2A). Eosinophilia, but not high serum IgE levels, improved promptly (Figure 2B and C). In line with this observation, eosinophils were almost absent in the mass, meanwhile the mass was replaced with fibrosis (Figure 1B and S1A), suggesting that this fibrosis caused unaltered swelling and maximum circumference of both limbs. Interestingly, mepolizumab administration significantly reduced the number of IgG- and IgG4-positive PCs in situ (Figure 1C). Follicular helper T cells (T_{FH}) have been known to promote eosinophil recruitment[5] and fibrosis[6]. Prior to treatment, $CD4^+CXCR5^+$ T_{FH} consisted approximately half of $CD4^+$ T cells in lymphoid follicles. It is worth noting that the number of $CD4^+CXCR5^+$ T_{FH} did not reduce after treatment (Figure 2D, S1B, and S1C).

Given the preferential development of KD in the head and neck, bilateral upper limb involvement is quite rare.[1] We reported mepolizumab-mediated drastic eosinophil reduction in the circulation and subcutaneous mass of a patient with KD. Despite eosinophil disappearance in the mass, fibrosis was persistent. This may be because our case was a patient with chronic KD who spent 6 years before mepolizumab administration. Long-lasting local inflammation may result in persistent fibrosis. Conversely, early intervention with mepolizumab might change the result. T_{FH} facilitates B cell differentiation, leading to the increase of IgG1- and IgE-producing memory B cells and PCs.[7] We elucidated the presence of T_{FH} in KD and their unresponsiveness to mepolizumab. This observation was corroborated by stable serum IgE levels during treatment. Considering that T_{FH} promotes fibrosis, there is a possibility that the persistent fibrosis in our case may be mediated by the persistent T_{FH}. Moreover, given that T_{FH} promotes eosinophil recruitment, persistent T_{FH} may cause KD relapse after the discontinuation of mepolizumab.

In murine skin transplantation models, intraperitoneal injection of anti-IL-5 mAb has been reported to reduce the number of alloreactive PCs in the bone marrow by suppressing the production of eosinophil-derived a proliferation-inducing ligand (APRIL) and IL-6[8], both of which are crucial for long-term maintenance of PCs[9]. We, for the first time, confirmed this observation in humans.

Herein we report the efficacy of mepolizumab in a patient with KD, an eosinophil-associated skin disorder. Besides eosinophils, PCs, but not T_{FH}, were also reduced in situ. In this context, mepolizumab might be a promising option for the treatment of patients with eosinophil-associated autoimmune diseases, such as bullous pemphigoid, eosinophilic granulomatosis with polyangiitis, ulcerative colitis, eosinophilic myocarditis, neuromyelitis optica, primary biliary cirrhosis, and IgG4-RD.

KEYWORDS

Kimura's disease, IgG4-related diseases, anti-interleukin-5 antibody, mepolizumab, eosinophils, follicular helper T cells, plasma cells

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CONFLICT OF INTEREST

The authors have no financial conflicts of interest to disclose concerning the study.

ETHICAL APPROVAL

This study was approved by the Institutional Review Board of Yamanashi University Hospital.

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FIGURE LEGENDS

FIGURE 1 Clinical images of the upper limbs before (left panels) and after (right panels) treatment. Upper and lower panels are right and left upper limb, respectively (A). H&E staining (low and high magnification) of the mass taken before and after treatment (B). Upper panels are immunohistochemistry for IgG and IgG4 in the mass taken before and after treatment. Lower graph represents the number of IgG- or IgG4-positive cells in randomized ten areas (counted in magnification 100×). $^{*}p < 0.05$, $^{**}p < 0.01$ (C).

FIGURE 2 Left panels are images of fat-suppressed coronal T2-weighted MRI of the upper limb before and after treatment. The right graph represents the maximum circumference of both upper limbs during the course (A). Number and percentage of eosinophils (B) and serum IgE levels (C) in the peripheral blood during the course. Immunofluorescence images of CXCR5 (green), CD4 (red), and DAPI (blue). Left (low-power field) and middle (high-power field) are images before treatment, and right (high-power field) is an image after treatment (D).

SUPPLEMENTARY FIGURE LEGENDS

FIGURE S1 Eosinophil number in randomized ten areas (counted in magnification 100×) of the mass before and after treatment (A). Immunofluorescence images of isotype-matched control IgG for Figure 2D (mouse IgG1; green, rabbit IgG; red, and DAPI; blue) (B). Number of $CXCR5^{+}CD4^{+}$ cells in randomized ten areas (counted in magnification 100×) of the mass before and after treatment (C).

SUPPLEMENTARY MATERIALS AND METHODS

Immunofluorescence was performed on formalin-fixed, paraffin-embedded biopsies in 5 μm sections. The sections were dried, and subsequently dewaxed and rehydrated. Following antigen retrieval in 10-mmol/L citrate buffer (pH 9.0) and blocking with 5% goat serum for 1 h at room temperature, the sections were incubated overnight at 4°C with rabbit anti-CD4 (1:100, Abcam), mouse anti-CXCR5 (1:100, GeneTex), and each isotype-matched control IgG. Following washing, the sections were incubated for 3 h at room temperature with Alexa Fluor 488-conjugated anti-mouse IgG and Alexa Fluor 555-conjugated anti-rabbit IgG. All samples were mounted with VECTASHIELD Mounting Medium supplemented with DAPI (H-1200; Vector Lab). Immunofluorescent images were obtained using a Biorevo BZ-9000 fluorescence microscope (Keyence).

Statistical analysis was conducted using Unpaired Mann–Whitney U test. The differences were considered to be significant when the *p*-value was less than 5%.

Figure 1

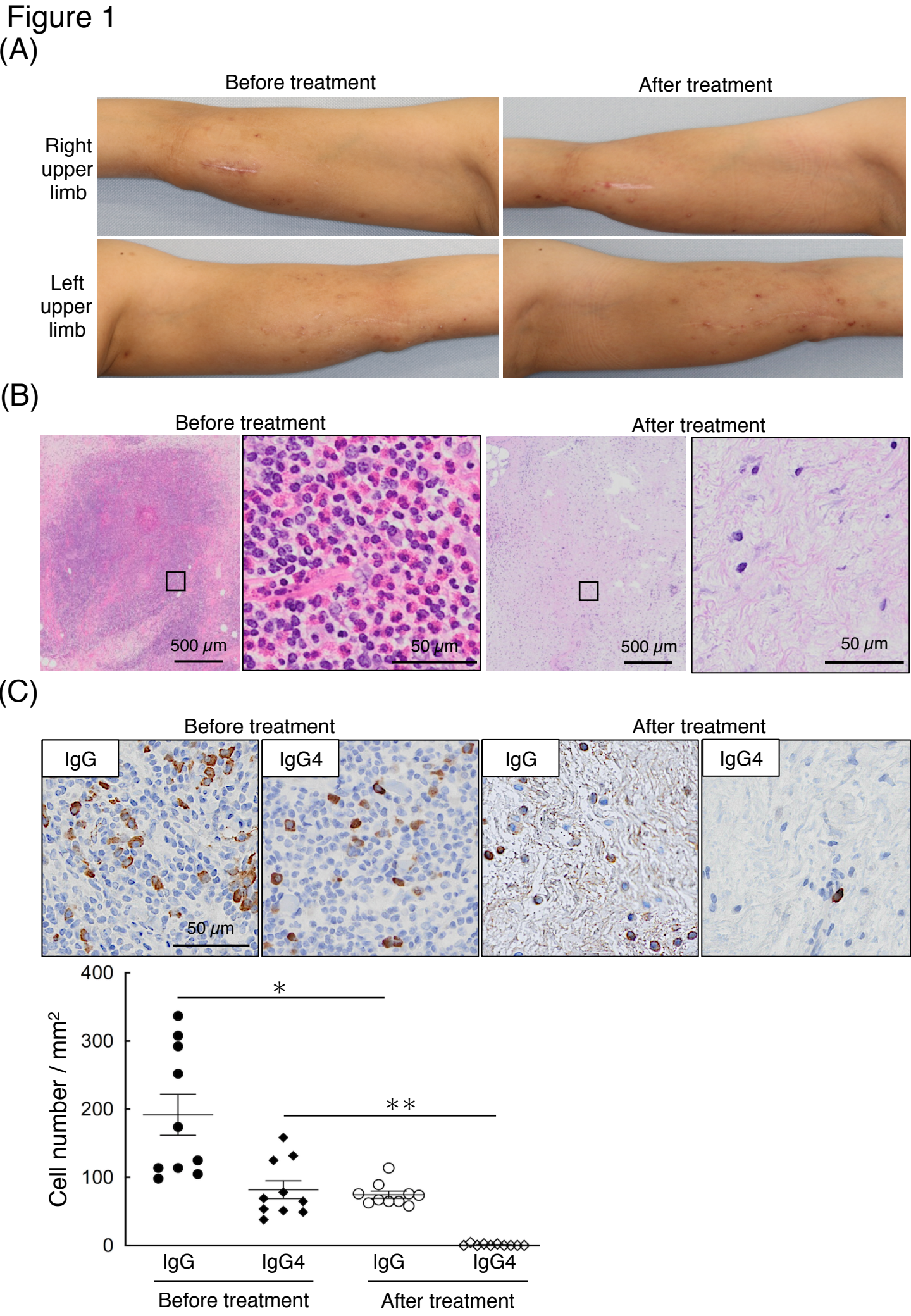
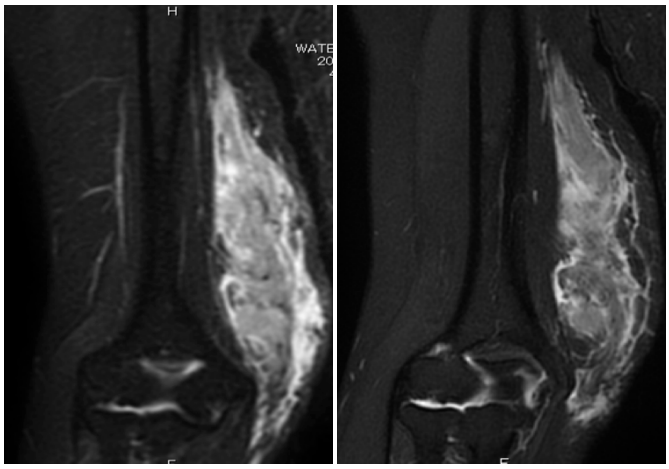
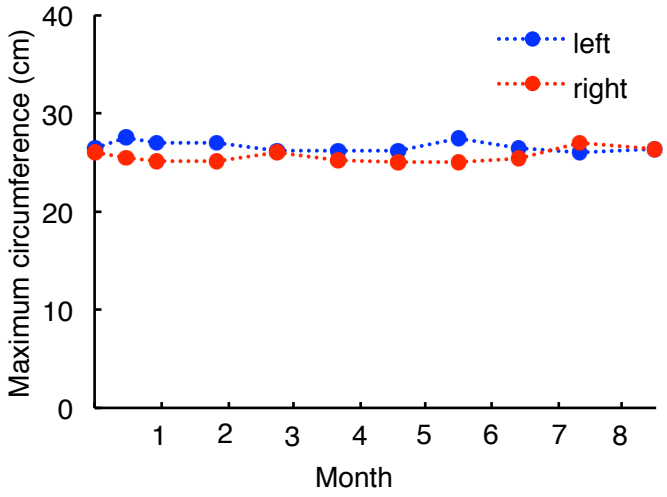

(A)
Before treatment
After treatment
Right upper limb
Left upper limb
(B)
Before treatment
After treatment
500 μm
50 μm
500 μm
50 μm
(C)
Before treatment
After treatment
IgG
IgG4
IgG
IgG4
50 μm
Cell number / mm²
400
300
200
100
0
*
**
IgG
IgG4
IgG
IgG4
Before treatment
After treatment

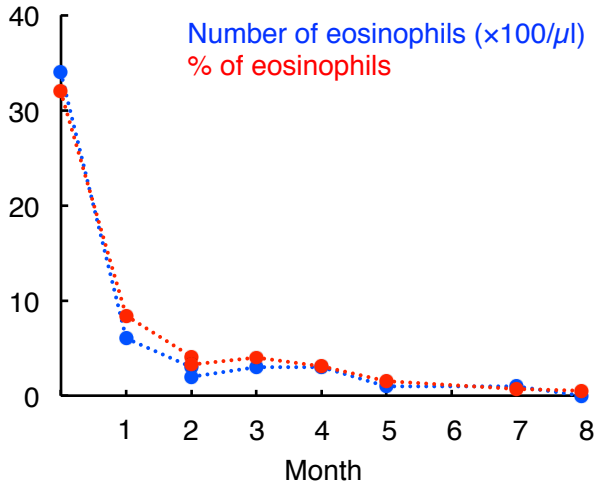
Figure 2

(A)

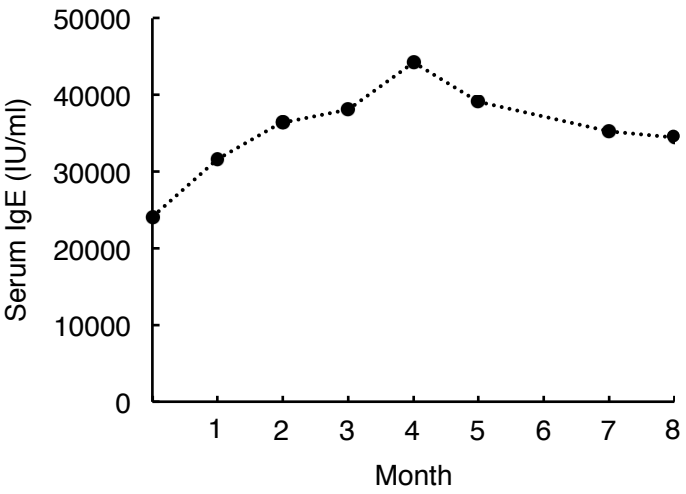




(B)



(C)



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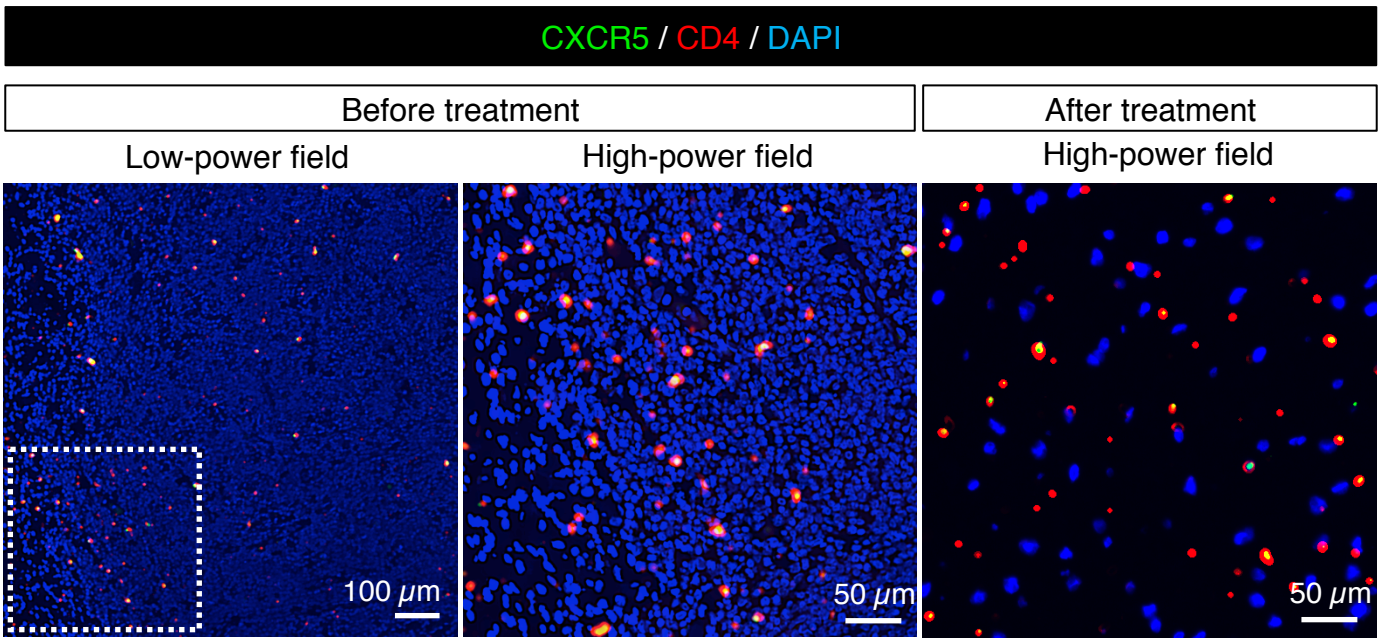
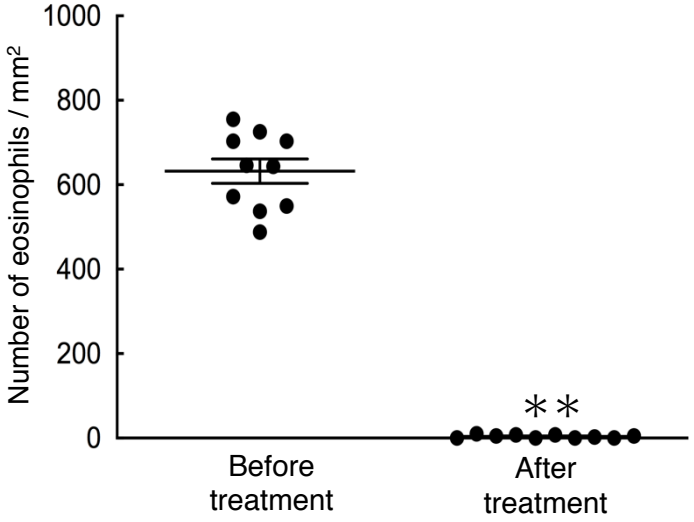
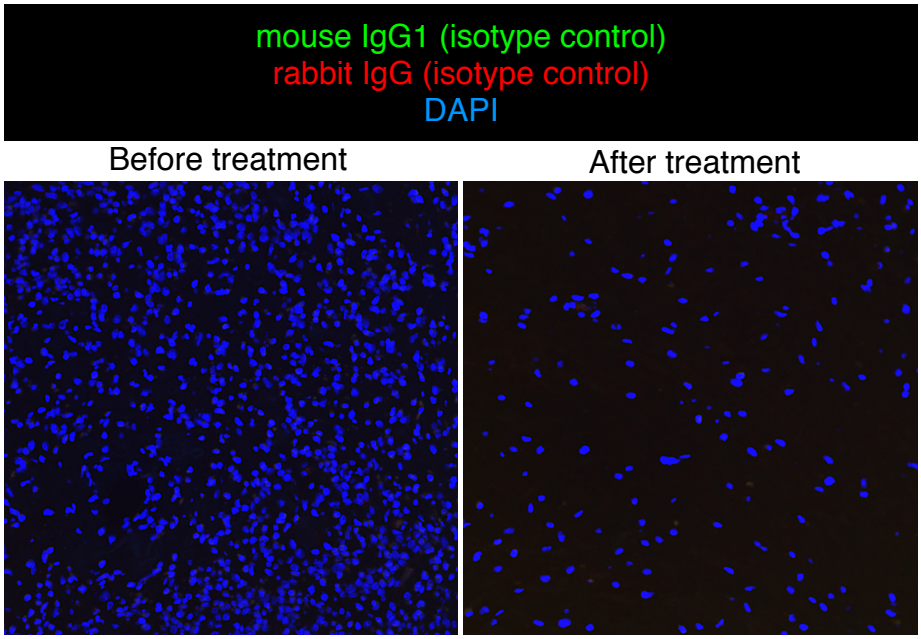


Supplementary Figure 1

(A)



(B)



(C)