

**Intravenous Immunoglobulin Expands Regulatory T Cells in Autoimmune Rheumatic Disease**

To the Editor:

Intravenous immunoglobulin (IVIG) therapy can benefit diverse autoimmune and inflammatory diseases through several mutually nonexclusive mechanisms<sup>1,2</sup>. *In vitro* and *in vivo* studies in experimental models have also demonstrated that IVIG can expand CD4+CD25<sup>+</sup> regulatory T cells (Treg), the cells that play a critical role in maintaining immune tolerance<sup>3,4</sup>. Treg maintain immune tolerance by suppressing the activation and function of both innate and adaptive immune cells, while deficiency of Treg is associated with autoimmune and inflammatory conditions<sup>5,6</sup>. Since IVIG therapy in autoimmune patients is associated with restoration of immune tolerance, we hypothesized that this effect of IVIG is in part through expansion of Treg in these patients, the bona fide immune regulators.

We analyzed Treg in paired blood samples of patients with autoimmune rheumatic disease before and 72 to 96 hours after high-dose IVIG therapy (human normal immunoglobulin; Tegeline, 2 g/kg per month)<sup>1</sup>. The patients broadly belonged to 2 groups: those with idiopathic inflammatory myopathy (8 patients, age range 22–57 yrs; 3 men) and those with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (3 patients, age range 61–68 yrs; 2 males). Patients' data are provided in Table 1. Local ethical committee approval was obtained for collecting blood samples, and patients provided informed consent.

Peripheral blood mononuclear cells were isolated from the blood samples by Ficoll-density gradient, and CD4+CD25<sup>high</sup> T cells were analyzed by flow cytometry using fluorescence-conjugated monoclonal antibodies (LSR II; BD Biosciences, Le Pont de Claix, France).

We found that 6 patients, including the 3 with ANCA-associated vasculitis, had substantial increases in the percentage of Treg following IVIG therapy (2.2% ± 0.3% before IVIG therapy and 7.9% ± 1.8% post-IVIG therapy); 3 patients with myopathies (Patients 7, 8, and 11) had marginal enhancement in Treg (1.1% ± 0.6% before IVIG therapy and 1.7% ± 0.7% post-IVIG therapy); and in 2 patients with dermatomyositis (Patients 2 and 6) the percentage of Treg did not change (1.95% ± 0.7% before IVIG therapy and 1.97% ± 0.6% post-IVIG therapy; Figure 1). These results indicate that the antiinflammatory effect of IVIG therapy is associated with enhancement of Treg in autoimmune patients and these Treg might help to restore immune tolerance.

Although several immunosuppressive drugs including steroids can enhance Treg<sup>7</sup>, IVIG has an added advantage in that this therapy is not an

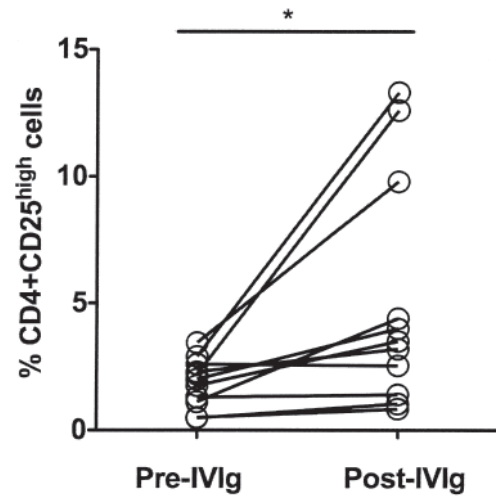


Figure 1. Changes in percentage of regulatory T cells in autoimmune patients before and after IVIG therapy. Peripheral blood mononuclear cells were isolated from heparinized blood samples and CD4+CD25<sup>high</sup> Treg were analyzed by flow cytometry using fluorescence-conjugated monoclonal antibodies. Circles represent patients. \*p < 0.05, paired Student t test.

immunosuppressor, but rather an immunomodulator. Hence adverse effects associated with immunosuppressive therapies can be avoided by IVIG therapy. The enhancement of Treg following IVIG therapy might implicate several mutually nonexclusive mechanisms<sup>8,9,10</sup>. It is known that inflammatory cytokines suppress Treg<sup>8</sup> and by neutralizing these inflammatory mediators, IVIG might favor Treg expansion. In addition, IVIG is known to modulate the maturation and function of innate immune cells, and these modulated innate cells may expand Treg. Alternatively, IVIG can reciprocally regulate pathogenic Th17 and Treg<sup>10</sup>.

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Table 1. Summary of data for patients with autoimmune rheumatic disease.

Patient	Disease	Sex/Age,	Associated Symptoms
1	Dermatomyositis	F 49	Proximal muscle weakness, rash
2	Dermatomyositis	M 35	Proximal muscle weakness, rash
3	Polymyositis	M 42	Proximal muscle weakness, polyarthritis, interstitial lung disease
4	Granulomatosis with polyangiitis	M 62	Polyarthritis, peripheral neuropathy, CNS involvement, pulmonary nodules, anti-proteinase 3 ANCA
5	Microscopic polyangiitis	F 61	Arthralgias, myalgias, peripheral neuropathy, antimyeloperoxidase ANCA
6	Dermatomyositis	F 22	Proximal muscle weakness, interstitial lung disease, typical skin involvement with Gottron papules
7	Inflammatory myopathy associated with diffuse systemic sclerosis	F 38	Proximal muscle weakness, severe gastrointestinal tract involvement with gastroparesis and colectasis
8	Inclusion body myositis	M 57	Myalgias and proximal and distal asymmetrical muscle weakness
9	Granulomatosis with polyangiitis	M 68	Skin, peripheral nerve, joint involvement, anti-proteinase 3 and antimyeloperoxidase ANCA, trituncular coronaropathy and dilatation
10	Polymyositis	F 43	Proximal muscle weakness and myocardial involvement
11	Dermatomyositis	F 45	Proximal muscle weakness, rash

CNS: central nervous system; ANCA: antineutrophil cytoplasmic antibody.

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## REFERENCES

1. Bayry J, Negi VS, Kaveri SV. Intravenous immunoglobulin therapy in rheumatic diseases. *Nat Rev Rheumatol* 2011;7:349-59.
2. Seite JF, Shoenfeld Y, Youinou P, Hillion S. What is the contents of the magic draft IVIG? *Autoimmun Rev* 2008;7:435-9.
3. Kessel A, Ammuri H, Peri R, Pavlotzky ER, Blank M, Shoenfeld Y, et al. Intravenous immunoglobulin therapy affects T regulatory cells by increasing their suppressive function. *J Immunol* 2007;179:5571-5.
4. Ephrem A, Chamat S, Miquel C, Fisson S, Mouthon L, Caligiuri G, et al. Expansion of CD4+CD25+ regulatory T cells by intravenous immunoglobulin: A critical factor in controlling experimental autoimmune encephalomyelitis. *Blood* 2008;111:715-22.
5. Sakaguchi S, Miyara M, Costantino CM, Hafler DA. FOXP3+ regulatory T cells in the human immune system. *Nat Rev Immunol* 2010;10:490-500.
6. Li X, Qian L, Wang G, Zhang H, Wang X, Chen K, et al. T regulatory cells are markedly diminished in diseased salivary glands of patients with primary Sjogren's syndrome. *J Rheumatol* 2007;34:2438-45.
7. de Paz B, Alperi-Lopez M, Ballina-Garcia FJ, Prado C, Gutierrez C, Suarez A. Cytokines and regulatory T cells in rheumatoid arthritis and their relationship with response to corticosteroids. *J Rheumatol* 2010;37:2502-10.
8. Bayry J, Siberil S, Triebel F, Tough DF, Kaveri SV. Rescuing CD4+CD25+ regulatory T-cell functions in rheumatoid arthritis by cytokine-targeted monoclonal antibody therapy. *Drug Discov Today* 2007;12:548-52.
9. De Groot AS, Moise L, McMurry JA, Wambre E, Van Overtvelt L, Moingeon P, et al. Activation of natural regulatory T cells by IgG Fc-derived peptide "Tregitopes". *Blood* 2008;112:3303-11.
10. Maddur MS, Vani J, Hegde P, Lacroix-Desmazes S, Kaveri SV, Bayry J. Inhibition of differentiation, amplification and function of human Th17 cells by intravenous immunoglobulin. *J Allergy Clin Immunol* 2011;127:823-30.

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## Correction

### **Intravenous Immunoglobulin Expands Regulatory T Cells in Autoimmune Rheumatic Disease (Letter)**

Bayry J, Mouthon L, Kaveri SV. Intravenous immunoglobulin expands regulatory T cells in autoimmune rheumatic disease (letter). *J Rheumatol* 2012;39:450-2. In the second paragraph, first sentence, 2 of the numbers given are incorrect. The sentence should read: We analyzed Treg in paired blood samples of patients with autoimmune rheumatic disease before and 48 to 96 hours after high-dose IVIG therapy (human normal immunoglobulin; Tegeline, 1–2 g/kg per month).

We regret the error.

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