Tsurikisawa et al. Clinical and Translational Allergy 2014, 4:38
http://www.ctajournal.com/content/4/1/38

Clinical and Translational Allergy

RESEARCH Open Access

High-dose intravenous immunoglobulin therapy for eosinophilic granulomatosis with polyangiitis

Naomi Tsurikisawa[1*], Hiroshi Saito[2], Chiyako Oshikata[1], Takahiro Tsuburai[1] and Kazuo Akiyama[1,2]

Abstract

Background: Regulatory T (T_{reg}) cells are implicated in the development and progression of eosinophilic granulomatosis with polyangiitis (EGPA). We previously showed beneficial effects of intravenous immunoglobulin (IVIG) therapy combined with corticosteroid and immunosuppressant treatment on clinical symptoms, including mononeuritis multiplex and cardiac dysfunction, and T_{reg} cell frequency, during EGPA. Whether the timing of administration (during initial treatment or at relapse after remission) or previous treatment affects the clinical and immunologic efficacy of IVIG is unknown. We evaluated whether the frequency of T_{reg} cells varied depending on when IVIG was provided relative to the start of conventional therapy for EGPA.

Methods: The patient population for this retrospective analysis comprised 17 patients with severe mononeuritis multiplex or heart failure whose EGPA did not respond to corticosteroids combined with immunosuppressant therapy. Ten patients first received IVIG during initial treatment, whereas the remaining 7 patients first received IVIG on relapse after remission. We measured the percentage of T_{reg} cells, defined as $FOXP3^+CD4^+$ T cells, present before the first round of IVIG and at 1 month after the last IVIG treatment.

Results: $FOXP3^+CD4^+$ T cells were increased in patients who required only a single course of IVIG to achieve remission compared with those who needed two or more courses. The dosage of prednisolone at initial IVIG was inversely correlated with the ratio of the number of $FOXP3^+CD4^+$ T cells before IVIG and that at 1 month thereafter.

Conclusion: Patients with severe EGPA who receive IVIG after nonresponse to high-dose prednisolone during initial treatment may need multiple courses of IVIG to achieve remission. An increase in the frequency of T_{reg} cells after IVIG may predict the need for additional IVIG in EGPA.

Keywords: Eosinophilic granulomatosis with polyangiitis, Churg–Strauss syndrome, Intravenous immunoglobulin, Regulatory T cells, IgG

Background

Eosinophilic granulomatosis with polyangiitis (EGPA; also known as Churg–Strauss syndrome) is a rare disease characterized by allergic granulomatosis and necrotizing vasculitis after peripheral and tissue eosinophilia [1]. The mortality and prognosis of EGPA are related to disease severity, as assessed by five-factor scores (FFSs) [2], and the survival rate at 5 years after myocardial involvement is reported to be one third of that without myocardial involvement [3]. The mainstay of treatment for EGPA is systemic corticosteroid therapy; some patients receive additional treatment with immunosuppressive agents, such as cyclophosphamide and azathioprine [4]. However, combined therapy with corticosteroids and cyclophosphamide afforded little benefit in some EGPA patients with mononeuritis multiplex, heart failure, or systemic vasculitis associated with antineutrophil cytoplasmic autoantibody [5,6]. We previously showed that intravenous immunoglobulin (IVIG) therapy was effective against severe mononeuritis multiplex or heart failure in patients with EGPA that did not respond to corticosteroid–cyclophosphamide treatment [7].

Regulatory T (T_{reg}) cells play a key role in balancing immune responses and in maintaining peripheral tolerance against antigens and allergens [8]. We previously reported a lower frequency of T_{reg} cells at the onset of

* Correspondence: n-tsurikisawa@sagamihara-hosp.gr.jp
[1]Departments of Allergy and Respirology, National Hospital Organization Sagamihara National Hospital, 18-1 Sakuradai, Minami-ku Sagamihara, Kanagawa 252-0392, Japan
Full list of author information is available at the end of the article

BioMed Central

© 2014 Tsurikisawa et al.; licensee BioMed Central. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

disease in patients with EGPA than in patients with asthma and that the frequency of T_{reg} cells increased at remission of EGPA [9]. Recent reports show that IVIG regulates the activation of $CD4^+CD25^+$ T_{reg} cells in autoimmune disease [10]. Possible mechanisms involved in the IVIG-mediated modulation of T_{reg} functions include the activation and induction of T_{reg} cells by the Fc region of IVIG and enhancement of T_{reg} function through increased expression of forkhead box P3 (FOXP 3), transforming growth factor-β, interleukin (IL)-10, and cytotoxic T-lymphocyte antigen 4 (CTLA-4) [11-13]; direct interaction of self-reactive natural autoantibodies with T-cell surface molecules [14,15]; and the suppression of allogeneic T-cell responses through direct activation of T_{reg} cells [16]. We found that prolonged IVIG treatment increased the frequencies of T_{reg} cells, defined as the $CD25^+$ subpopulation among $CD4^+$ T cells producing IL-10 and the $FOXP3^+$ subpopulation among $CD4^+$ T cells [17]. Several authors have reported that IVIG treatment may reduce the amount of corticosteroids needed for maintenance of remission of EGPA [17,18]. However, whether the clinical and immunologic efficacy of IVIG is affected by the timing of administration (e.g., during initial treatment of EGPA or at relapse after remission) is unknown. In addition, the characteristics of patients' disease condition that influence whether remission is achieved after single or multiple courses of IVIG have not previously been assessed. Here we evaluated whether the frequency of T_{reg} cells differed depending on when IVIG was provided relative to the start of conventional therapy for EGPA.

Methods

This study was a retrospective analysis for which we recruited patients given IVIG during initial treatment or at relapse after remission, to investigate the clinical and immunologic efficacy of IVIG therapy for EGPA patients.

Patients

Between March 2005 and November 2011, 17 patients with EGPA were diagnosed according to the classification criteria of the American College of Rheumatology at our hospital [19]. Two of these 17 patients were enrolled in the study reported in reference number 17; the remaining 15 patients were new patients. Multiple mononeuritis, a type of motor nerve dysfunction, was evaluated by using the manual muscle test (MMT); responses were scored (from 0 to 5) on the Medical Research Council scale, and sensory nerve dysfunction was evaluated through clinical examination. Lung involvement was considered to be present when any consolidation, ground-glass opacity, nodules within such opacity, interlobular septal thickening, bronchial wall thickening, lymph node enlargement, pleural effusion evident upon high-resolution computer tomography, or eosinophilic infiltration detected by lung biopsy was present. The heart was considered to be involved when any chest pain, chest discomfort, back pain, palpitations, echocardiographic abnormality, Holter electrocardiographic abnormality, elevation of B-type natriuretic peptide level, or [^{123}I]-meta-iodobenzylguanidine myocardial imaging abnormality was evident [20]. Gastrointestinal involvement was indicated by the presence of symptoms of upper or lower abdominal pain, diarrhea, constipation, or positive endoscopic signs combined with confirmation of eosinophilic infiltration by biopsy. Skin involvement was defined as the presence of purpura, erythema, livedo, ulceration, or acrocyanosis when a nodule, accompanied by eosinophilic infiltration, was detected by biopsy. Central nervous system involvement was defined as the presence of headache, visual disorder, abnormal visual sensation, cerebral infarction, bleeding, or cranial nerve dysfunction. Renal involvement was defined by any presence of eosinophils in urine, glomerular nephritis, nephrosis, renal dysfunction (i.e., the creatinine level was 20% or more higher than the baseline figure), or proteinuria (>0.5 g/dL). Disease severity in all EGPA patients was evaluated by using FFS 2009 [2].

All patients treated with IVIG had severe neuropathy (MMT score, <3) or cardiac involvement, including severe heart failure, myocarditis, or pericarditis, which did not improve or achieve remission after at least one month of treatment with conventional therapy (corticosteroids, immunosuppressants, or both; the initial dose of corticosteroid was approximately 1 mg/kg prednisolone daily for at least 1 month) [4]. Among our 17 patients with EPGA, 10 received IVIG during initial treatment with conventional therapy; the remaining 7 patients achieved first remission after conventional treatment without IVIG and therefore received their first IVIG on relapse after remission. Remission was defined as the absence of any clinical signs or symptoms of active vasculitis for at least 6 months. Relapse was defined as the presence of active disease combined with the recurrence, after initial remission, of vasculitis symptoms (with or without an increase in the percentage of eosinophils among white blood cells [WBCs]). Patients who relapsed required resumption of immunosuppressive therapy or increased doses of immunosuppressant.

Study design

Before treatment with IVIG (Venilon, Teijin, Tokyo, Japan; 400 mg/kg daily for 5 days), all patients received corticosteroids (initial dose, about 1 mg/kg prednisolone daily for at least 1 month) with or without immunosuppressants. Nine patients with treatment-refractory mononeuritis multiplex or heart failure received additional courses of IVIG at 2 to 12 months after the initial IVIG therapy until

they achieved remission. As in our previous study [17], we measured the percentage of $CD25^+CD4^+$ T_{reg} cells (that is, $CD25^+$ cells among $CD4^+$ T_{reg} cells) and $FOXP3^+CD4^+$ T cells (that is, $FOXP3^+$ cells among $CD4^+$ T cells), which we defined as T_{reg} cells, in the peripheral blood of all patients before and at 1 month after the initial IVIG treatment; the ratio between these values was used to represent the IVIG-associated change in the proportion of $FOXP3^+CD4^+$ T cells. The ethics committee of our hospital approved the study, and we obtained informed consent from each patient.

Immunologic analysis

The number of eosinophils in whole blood before and at the onset of IVIG therapy, and the serum IgG concentration before IVIG, were measured in all patients. Eosinophils and WBCs in the peripheral blood were counted by hemocytometry. The frequencies of $CD25^+CD4^+$ T cells and of $FOXP3^+CD4^+$ T cells were determined as described by Abdulahad et al. [21]. PE-conjugated anti-human FOXP3 and Peridinin chlorophyll conjugates of mouse IgG1 and an anti-CD4 antibody were purchased from BD Biosciences (Rikaken Co. Ltd., Tokyo, Japan). In brief, whole-blood lymphocytes were incubated with FITC-conjugated anti-CD4, and $FOXP3^+CD4^+$ T cells (defined as $FOXP3^+$ cells among $CD4^+$ T cells) were identified by incubating whole-blood lymphocytes with PE-conjugated anti-FOXP3 antibody after cell permeabilization with 4% (v/v) formaldehyde and 0.1% (w/v) saponin. The expression of surface and intracellular markers by $CD4^+$ T cells was analyzed by means of flow cytometry (FACSCalibur, Nippon Becton Dickinson, Tokyo, Japan).

Statistical analysis

All values are expressed as mean ± 1 SD unless otherwise specified. Statistical comparisons among groups were

Table 1 Patient characteristics

	EGPA patients who received IVIG during initial treatment ($n = 10$)	EGPA patients who received IVIG on relapse after remission ($n = 7$)	P
Age (y), mean ± 1 SD	59.1 ± 15.2	47.9 ± 18.3	NS†
Sex (M/F)	4/6	3/4	NS*
Age at onset EGPA (y), mean ± 1 SD	57.0 ± 42.6	42.6 ± 20.0	NS†
At onset of EGPA			
WBC (/μL), mean ± 1 SD	13,573 ± 4,647	16,930 ± 6,728	NS†
Blood eosinophils (/μL), mean ± 1 SD	6,681 ± 3,698	7,363 ± 6,686	NS†
MPO-ANCA (%) at onset	40	28.6	NS*
PR3-ANCA (%) at onset	0	0	NS*
At initial IVIG treatment			
WBC (/mL), mean ± 1 SD	9,912 ± 3,339	8,093 ± 2,752	NS†
Blood eosinophils (/μL), mean ± 1 SD	79.6 ± 69.2	252.3 ± 182.7	<0.05†
$FOXP3^+CD4^+$ T cells (%), mean ± 1 SD	2.4 ± 1.6	1.3 ± 1.1	<0.05†
Time from onset of EGPA to initial IVIG treatment (mo), median (range)	3.0 (1–3)	65.0 (10–122)	<0.01††
Number of IVIG treatments needed to achieve first remission (one/two or more)	3/7	5/2	NS*
Initial treatments at onset			
Prednisolone (mg), mean ± 1 SD	50.5 ± 10.5	48.6 ± 10.7	NS†
Patients taking an immunosuppressant (%)	90	42.9	< 0.05*
CYC/AZA/CSA	8/0/1	1/1/1	NS*
Other treatments at initial IVIG			
Prednisolone (mg), mean ± 1 SD	39.5 ± 11.2	12.9 ± 5.5	0.01†
Patients taking an immunosuppressant (%)	90	71.4	NS*
CYC/AZA/CSA	8/0/1	1/3/1	0.05*

AZA, azathioprine; CYC, cyclophosphamide; CSA, cyclosporin; EGPA, eosinophilic granulomatosis with polyangiitis; IVIG, intravenous immunoglobulin; MPO-ANCA, myeloperoxidase-specific antineutrophil cytoplasmic antibodies; NS, not significant; PR3, protein 3; WBC, white blood cells.
All values are expressed as means ± 1 SD.
Values of $P < 0.05$ were considered statistically significant.
†Two-way ANOVA with repeated measures between groups.
††Statistical comparisons made by using Mann–Whitney U-tests between groups.
*Chi-squared testing revealed no significant differences in frequencies between the two groups.

Table 2 Organ involvement at onset (%)

	EGPA patients treated with IVIG within the period of initial treatment ($n = 10$)	EGPA patients treated with IVIG on relapse after remission ($n = 7$)	*P*
Asthma	100	100	NS*
Paranasal sinusitis	90	85.7	NS*
Multiple polyneuropathy	100	100	NS*
Minimum MMT score, mean ± 1 SD	3.1 ± 0.9	4.1 ± 0.7	0.05†
Pulmonary infiltrates	80	85.7	NS*
Myocardial involvement	50	100	0.05*
Gastrointestinal tract	80	100	NS*
Liver, gall bladder, pancreas	16.7	30	NS*
Renal involvement‡	20	28.5	NS*
Proteinuria	50	42.8	NS*
Eosinophils in urine	28.6	40	NS*
Nephritis or nephrosis	10	14.3	NS*
Skin involvement	90	100	NS*
Arthritis	40	42.8	NS*
Myalgia	40	28.5	NS*
Central nervous system involvement	30	28.5	NS*
Number of organs involved per patient‡‡, mean ± 1 SD	5.7 ± 1.1	6.3 ± 2.1	NS†
FFS2009	1.5 ± 1.0	1.4 ± 1.0	NS†

EGPA, eosinophilic granulomatosis with polyangiitis; FFS, five-factor score; IVIG, intravenous immunoglobulin; MMT, manual muscle test; NS, not significant.
All values are expressed as means ± 1 SD.
Values of $P \leq 0.05$ were considered statistically significant.
†Two-way ANOVA with repeated measures between groups.
*Chi-squared testing revealed no significant differences between groups.
‡Renal involvement including proteinuria or eosinophils in urine or glomerular nephritis or nephrosis or renal dysfunction.
‡‡Cumulative organ involvement excluding asthma and sinusitis.

achieved by using two-way analysis of variance (ANOVA) according to a repeated-measures algorithm, followed by *post-hoc* comparisons by using the Newman–Keuls test. The two mean values obtained by this process were compared by using the Wilcoxon matched-pairs *t* test. Correlation coefficients were obtained by using Spearman's rank correlation test. *P* values less than 0.05 were considered statistically significant. Statistical analysis was performed by using SPSS for Windows, version 20 (SPSS Inc., Chicago, IL).

Table 3 Diagnosis by ACR criteria at onset

	EGPA patients who received IVIG during initial treatment ($n = 10$)	EGPA patients who received IVIG on relapse after remission ($n = 7$)	*P*
Asthma (yes/no)	10/0	7/0	NS*
Paranasal sinusitis (yes/no)	9/1	6/1	NS*
Multiple polyneuropathy (yes/no)	10/0	7/0	NS*
Pulmonary infiltrates (yes/no)	8/2	6/1	NS*
Extravascular eosinophils (pathology) (yes/no)	10/0	7/0	NS*
Eosinophilia in peripheral blood >10% (yes/no)	10/0	7/0	NS*
ACR 5/6 (%)	30	57.1	
ACR 6/6 (%)	70	42.9	

ACR, American College of Rheumatology, EGPA, eosinophilic granulomatosis with polyangiitis; IVIG, intravenous immunoglobulin; NS, not significant.
All values are expressed as means ± 1 SD.
Values of $P < 0.05$ were considered statistically significant.
*: Chi-squared testing revealed no significant differences between the two groups.

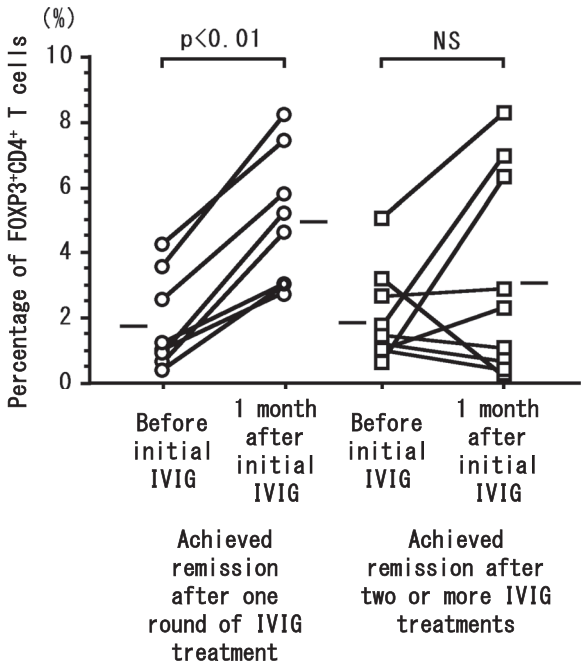

Figure 1 The percentage (mean ± 1 SD) of FOXP3$^+$CD4$^+$ T cells in 17 EGPA patients just prior to the initial intravenous immunoglobulin (IVIG) treatment and 1 month thereafter. Open circles represent patients with EGPA ($n = 8$) who achieved remission after a single round of IVIG treatment; open squares represent patients with EGPA ($n = 9$) that required multiple courses of IVIG to achieve remission. The mean values for each patient group were compared by using the Wilcoxon matched-pairs *t*-test; $P < 0.05$ was considered statistically significant. NS, not significant.

Results

A single course of IVIG after conventional corticosteroid-based therapy was sufficient to achieve remission of EGPA in 3 of the 10 patients who received IVIG during their initial treatment and in 5 of the 7 patients treated with IVIG after relapse of EGPA. The other nine patients required 3.6 ± 1.6 course of IVIG before remission was achieved. Overall, 8 patients that received a single round of IVIG treatment during initial therapy to achieve remission, and the remaining 9 patients needed two or more IVIG treatments after relapse to achieve a second remission. Although the dosage of prednisolone at initial treatment did not differ between the two groups, the proportion of patients who received immunosuppressants was greater ($P < 0.05$) for those given IVIG during initial therapy than for those treated with IVIG after relapse of EGPA (Table 1). The dosage of prednisolone at initial IVIG in patients with relapsed disease was lower ($P < 0.05$) than that for patients under initial treatment for EGPA. Whereas 9 of the 10 patients (90.0%) who received IVIG during their initial treatment received immunosuppressants in addition to corticosteroids, only 3 of the 7 patients (42.9%) with relapsed EGPA received immunosuppressants during their initial treatment ($P < 0.05$) (Table 1).

The number of eosinophils in peripheral blood at initial IVIG was higher ($P < 0.05$) and the percentage of FOXP3$^+$CD4$^+$ T cells was lower ($P < 0.05$) in patients with relapsed EGPA than in patients undergoing initial treatment (Table 1). The minimal MMT score at onset of treatment was lower ($P = 0.05$) in patients undergoing initial treatment than in patients treated for relapsed EGPA. The percentage of patients with myocardial involvement at initial diagnosis of EGPA was higher

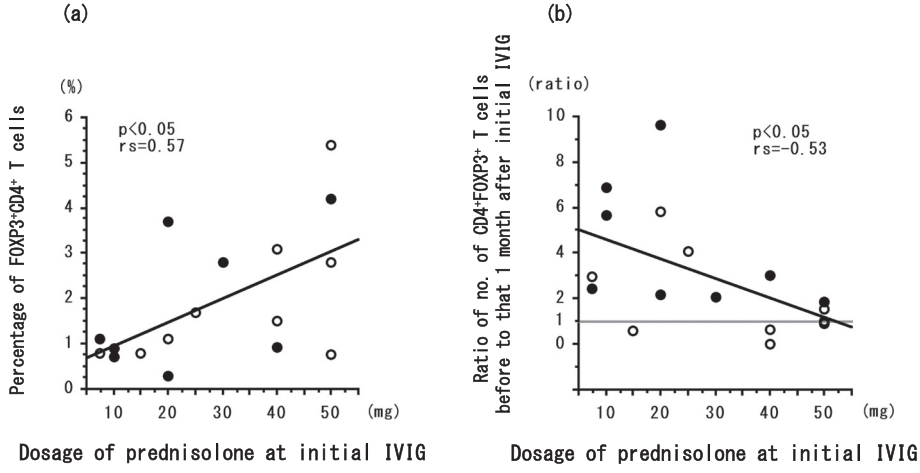

Figure 2 Statistical correlation between the dose of prednisolone given to patients during initial IVIG treatment and (a) the percentage of FOXP3$^+$CD4$^+$ T cells or (b) the ratio of the percentage of FOXP3$^+$CD4$^+$ T cells before the initial IVIG treatment to that at 1 month thereafter. Open circles represent patients with EGPA ($n = 9$) who needed two or more IVIG treatments to achieve remission; closed circles represent patients with EGPA ($n = 8$) who achieved remission after a single course of IVIG. Correlation coefficients (rs) were obtained by using Spearman's rank correlation test.

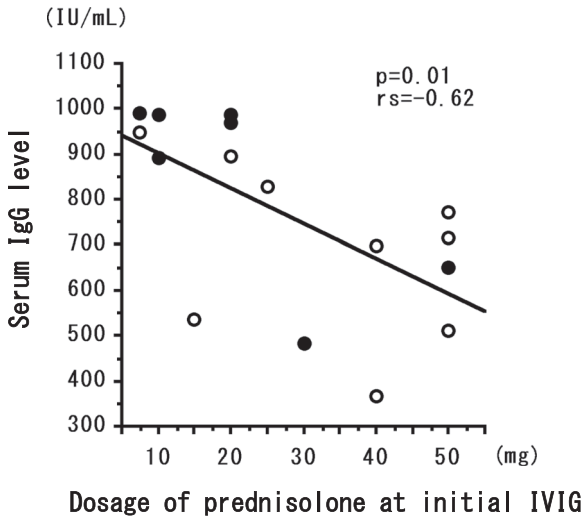

Figure 3 Statistical correlation between the dose of prednisolone during the initial IVIG treatment and the serum IgG level in 16 EGPA patients (one patient did not measure serum IgG). Open circles represent patients with EGPA ($n = 9$) who needed two or more IVIG treatments to achieve remission; closed circles represent patients with EGPA ($n = 7$) who achieved remission after a single course of IVIG. Correlation coefficients (rs) were obtained by using Spearman's rank correlation test.

($P = 0.05$) in those treated because of relapsed disease than in those who received their initial treatment for EGPA (Table 2). The diagnoses according to the criteria of the American College of Rheumatology are shown in Table 3.

The percentage of FOXP3$^+$CD4$^+$ T cells at initial IVIG was significantly ($P < 0.05$) greater in the 8 patients who achieved remission after a single round of IVIG compared with the 9 patients who needed two or more IVIG treatments for remission of EGPA (Figure 1). In all patients, the dosage of prednisolone at initial IVIG was significantly statistically correlated ($P < 0.05$, rs = 0.57) with percentage of FOXP3$^+$CD4$^+$ T cells (Figure 2a) and significantly inversely correlated ($P < 0.05$, rs = −0.53) with the ratio between the number of FOXP3$^+$CD4$^+$ T cells before to that at 1 month after the initial IVIG treatment (Figure 2b). The percentage of FOXP3$^+$CD4$^+$ T cells before the initial course of IVIG was greater than that at 1 month afterward in 5 of the 9 patients who needed two or more rounds of IVIG to achieve remission of EGPA (Figure 2b). In all patients, serum IgG concentration (IU/mL) before initial IVIG was significantly inversely correlated ($P < 0.01$, rs = −0.62) with the dosage of prednisolone at initial IVIG (Figure 3) but was not correlated with duration or the total dose of prednisolone taken during this study. The number of eosinophils in peripheral blood before IVIG was significantly inversely correlated ($P < 0.05$, rs = −0.56) with the percentage of FOXP3$^+$CD4$^+$ T cells (Figure 4a) but not with the ratio of FOXP3$^+$CD4$^+$ T cells before to that 1 month after initial IVIG (Figure 4b).

Discussion

Treatment with IVIG has shown efficacy in autoimmune and immune-mediated inflammatory diseases [14,15,22], including microscopic polyangiitis, granulomatosis with polyangiitis (that is, Wegener's granulomatosis), and antineutrophil cytoplasmic antibody-associated systemic vasculitis [5,23,24]. The phase at which IVIG is most effective in EGPA patients with neuropathy or cardiac failure is unknown, as are the optimal number and timing of courses of IVIG to induce remission. Among patients with systemic lupus erythematosis, responders and non-responders to IVIG treatment differed in their serum

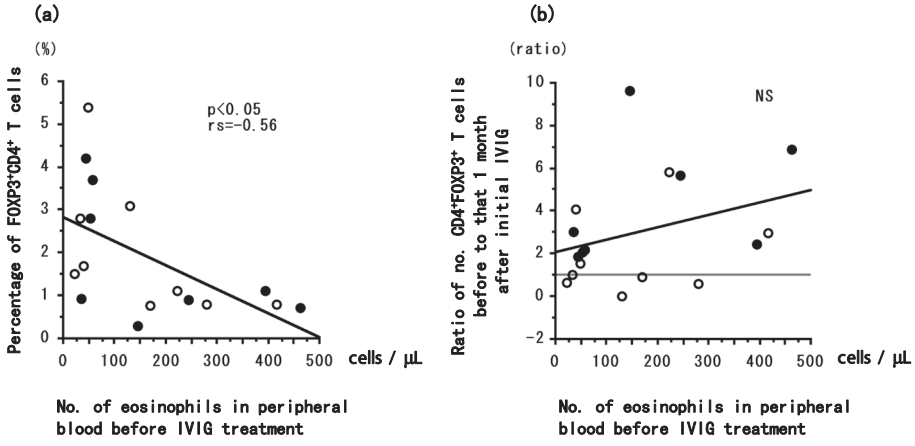

Figure 4 Statistical correlation between the number of eosinophils in the peripheral blood before IVIG treatment and (a) the percentage of FOXP3$^+$CD4$^+$ T cells or (b) the ratio of the percentage of FOXP3$^+$CD4$^+$ T cells before the initial IVIG treatment to that at 1 month thereafter. Open circles represent patients with EGPA ($n = 9$) who needed two or more courses of IVIG to achieve remission; closed circles represent patients with EGPA ($n = 8$) who achieved remission after a single round of IVIG. Correlation coefficients (r) were obtained by using Spearman's rank correlation test.

concentrations of C4, SS-A, and SS-B [22]. We previously reported that the number of courses of IVIG needed to induce remission was 2.6 ± 2.1 times greater to achieve first remission [17]. Whether differences in disease characteristics affect the need for one compared with multiple rounds of IVIG treatment to induce remission is unknown. We here show that patients with severe EGPA that receive IVIG during their initial treatment with high-dose systemic corticosteroids likely need multiple courses of IVIG to achieve remission. In addition, an increased percentage of $FOXP3^+CD4^+$ T cells before IVIG treatment may indicate an increased likelihood of induction of remission of EGPA. In patients receiving their initial treatment for EGPA, the percentage of $FOXP3^+CD4^+$ T cells was increased after conventional treatment comprising corticosteroids with or without immunosuppressants. However, the percentage of $FOXP3^+CD4^+$ T cells at one month after IVIG failed to increase in more than half of the patients given prednisolone doses exceeding 40 mg during IVIG treatment (Figure 2b), and high-dose prednisolone may suppress the serum IgG level (Figure 3). We consider that many inflammatory mediators are present in various quantities in serum during the acute disease phase associated with initial treatment of EGPA; these mediators might therefore out-compete IVIG and suppress the differentiation of T_{reg} ($FOXP3^+CD4^+$) cells.

The number of T_{reg} cells (i.e., $FOXP3^+CD4^+$ T cells) in patients with severe EGPA did not increase rapidly after IVIG, and this cell population was increased in patients requiring multiple courses of IVIG to achieve clinical remission (data not shown). We previously reported that the frequency of $CD25^+CD4^+$ T cells correlated with $FOXP3^+CD4^+$ T_{reg} cells in EGPA patients with severe mononeuritis multiplex or cardiac dysfunction and remained greater than that in EGPA patients without IVIG treatment for as long as 2 years after completion of IVIG therapy [17].

EGPA manifests as necrotizing vasculitis and eosinophilic tissue inflammation [25,26]. In both of our current patient groups, the number of eosinophils in peripheral blood decreased after conventional treatment and was significantly inversely correlated with the percentage of $FOXP3^+CD4^+$ T cells. However, the number of eosinophils at initiation of IVIG treatment was unrelated to any increase in the percentage of $FOXP3^+CD4^+$ T cells after IVIG. These results indicate that disease activity and response to IVIG likely are reflected not only in the number of peripheral eosinophils but also in levels of Th2 cytokines [27-29], Th17 [27,28,30,31], or other unknown mediators. Other possible mechanisms involved in IVIG-mediated inhibition are the differentiation and function of Th17 cells [32], the upregulation of T_{reg} cells by induction of cyclooxygenase-2-dependent prostaglandin E2 [33], or the suppression of inflammation by upregulating FcγRIIB on macrophages via IL-4 produced by basophils [34]. Although *in vitro* experiments have hinted at many novel findings regarding the mechanisms of IVIG, it is necessary to verify the clinical or immunologic effects of IVIG *in vivo*. It is useful clinically to determine optimal dose level, timing of initial dose, number of courses, and interdose interval for maximally effective IVIG therapy.

Conclusion

We conclude that most patients with otherwise uncomplicated non-severe EGPA (i.e., MMT score greater than 3, lack of cardiac involvement) who receive IVIG at relapse can achieve remission after a single round of IVIG therapy. However, many patients with severe EGPA (i.e., MMT score less than 3, cardiac abnormalities) who are undergoing initial treatment with conventional therapy including high-dose prednisolone will require multiple courses of IVIG to achieve remission of EGPA.

Abbreviations

CTLA-4: Cytotoxic T-lymphocyte antigen 4; EGPA: Eosinophilic granulomatosis with polyangiitis; FFS: Five-factor score; FOXP3: Forkhead box P3; IL: Interleukin; IVIG: Intravenous immunoglobulin; T_{reg} cells: Regulatory T cells; MMT: Manual muscle test; MPO-ANCA: Myeloperoxidase-specific antineutrophil cytoplasmic autoantibody; WBC: White blood cells.

Competing interests

All authors declare that they have no competing interests.

Authors' contributions

NT examined the patients, analyzed data and statistics, was the main contributor to manuscript preparation, and was involved in manuscript preparation and editing. CO examined the patients and contributed to discussions about the patients. HS assayed $FOXP3^+CD4^+$ T_{reg} cells in peripheral blood of patients. TT and KA contributed to discussions about the manuscript. All authors read and approved the final manuscript.

Author details

[1]Departments of Allergy and Respirology, National Hospital Organization Sagamihara National Hospital, 18-1 Sakuradai, Minami-ku Sagamihara, Kanagawa 252-0392, Japan. [2]Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagamihara National Hospital, 18-1 Sakuradai, Minami-ku Sagamihara, Kanagawa 252-0392, Japan.

Received: 12 February 2014 Accepted: 2 October 2014
Published: 12 December 2014

References

1. Churg J, Strauss L: **Allergic granulomatosis, allergic angiitis, and periarteritis nodosa.** *Am J Pathol* 1951, **27:**277–301.
2. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P, French Vasculitis Study Group (FVSG): **The five-factor score revisited. Assessment of prognosis of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) Cohort.** *Medicine* 2011, **90:**19–27.
3. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P: **Churg–Strauss syndrome. Clinical study and long-term follow-up of 96 patients.** *Medicine* 1999, **78:**26–37.
4. Abril A, Calamia KT, Cohen MD: **The Churg–Strauss syndrome (allergic granulomatous angiitis): review and update.** *Semin Arthritis Rheum* 2003, **33:**106–114.
5. Richter C, Schnabel A, Csernok E, De Groot K, Reinhold-Keller E, Gross WL: **Treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis with high-dose intravenous immunoglobulin.** *Clin Exp Immunol* 1995, **101:**2–7.

6. Renaldini E, Spandrio S, Cerudelli B, Affatato A, Balestrieri GP: **Cardiac involvement in Churg–Strauss syndrome: a follow-up of three cases.** *Eur Heart J* 1993, **14:**1712–1716.
7. Tsurikisawa N, Taniguchi T, Saito H, Himeno H, Ishibashi A, Suzuki S, Akiyama K: **Treatment of Churg–Strauss syndrome with high-dose intravenous immunoglobulin.** *Ann Allergy Asthma Immunol* 2004, **92:**80–87.
8. Roncarolo MG, Battaglia M: **Regulatory T-cell immunotherapy for tolerance to self antigens and alloantigens in humans.** *Nat Rev Immunol* 2007, **7:**585–598.
9. Tsurikisawa N, Saito H, Tsuburai T, Oshikata C, Ono E, Mitomi H, Akiyama K: **Differences in regulatory T cells between Churg–Strauss syndrome and chronic eosinophilic pneumonia with asthma.** *J Allergy Clin Immunol* 2008, **122:**610–616.
10. Tha-In T, Bayry J, Metselaar HJ, Kaveri SV, Kwekkeboom J: **Modulation of the cellular immune system by intravenous immunoglobulin.** *Trends Immunol* 2008, **29:**608–615.
11. Kessel A, Ammuri H, Peri R, Pavlotzky ER, Blank M, Shoenfeld Y, Toubi E: **Intravenous immunoglobulin therapy affects T regulatory cells by increasing their suppressive function.** *J Immunol* 2007, **179:**5571–5575.
12. Maddur MS, Othy S, Hegde P, Vani J, Lacroix-Desmazes S, Bayry J, Kaveri SV: **Immunomodulation by intravenous immunoglobulin: role of regulatory T cells.** *J Clin Immunol* 2010, **30**(Suppl 1)**:**S4–S8.
13. De Groot AS, Moise L, McMurry JA, Wambre E, Van Overtvelt L, Moingeon P, Scott DW, Martin W: **Activation of natural regulatory T cells by IgG Fc-derived peptide "Tergitopes".** *Blood* 2008, **112:**3303–3311.
14. Kazatchkine MD, Kaveri SV: **Immunomodulation of autoimmune and inflammatory disease with intravenous immune globulin.** *N Engl J Med* 2001, **345:**747–755.
15. Nimmerjahn F, Ravetch JV: **Anti-inflammatory actions of intravenous immunogloblin.** *Annu Rev Immunol* 2008, **26:**513–533.
16. Tha-In T, Metselaar HJ, Bushell AR, Kwekkeboom J, Wood KJ: **Intravenous immunoglobulins promote skin allograft acceptance by triggering functional activation of $CD4^+Foxp3^+$ T cells.** *Transplantation* 2010, **89:**1446–1455.
17. Tsurikisawa N, Saito H, Oshikata C, Tsuburai T, Akiyama K: **High-dose intravenous immunoglobulin treatment increases regulatory T cells in patients with eosinophilic granulomatosis with polyangiitis.** *J Rheumatol* 2012, **39:**1019–1025.
18. Danieli MG, Cappelli M, Malcangi G, Logullo F, Salvi A, Danieli G: **Long term effectiveness of intravenous immunoglobulin in Churg–Strauss syndrome.** *Ann Rheum Dis* 2004, **63:**1649–1654.
19. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY: **The American College of Rheumatology 1990 criteria for the classification of Churg–Strauss syndrome (allergic granulomatosis and angiitis).** *Arthritis Rheum* 1990, **33:**1094–1100.
20. Horiguchi Y, Morita Y, Tsurikisawa N, Akiyama K: **^{123}I-MIBG imaging detects cardiac involvement and predicts cardiac events in Churg-Strauss syndrome.** *Eur J Nucl Med Mol Imaging* 2011, **38:**211–219.
21. Abdulahad WH, Stegeman CA, van der Geld YM, Doornbos-van der Meer B, Limburg PC, Kallenberg CG: **Functional defect of circulating regulatory $CD4^+$ T cells in patients with Wegener's granulomatosis in remission.** *Arthritis Rheum* 2007, **56:**2080–2091.
22. Levy Y, Sherer Y, Ahmed A, Langevitz P, George J, Fabbrizzi F, Terryberry J, Meissner M, Lorber M, Peter JB, Shoenfeld Y: **A study of 20 SLE patients with intravenous immunoglobulin—clinical and serologic response.** *Lupus* 1999, **8:**705–712.
23. Lockwood CM: **New treatment strategies for systemic vasculitis: the role of intravenous immune globulin therapy.** *Clin Exp Immunol* 1996, **104**(Suppl 1)**:**77–82.
24. Jayne DR, Davies MJ, Fox CJ, Black CM, Lockwood CM: **Treatment of systemic vasculitis with pooled intravenous immunoglobulin.** *Lancet* 1991, **337:**1137–1139.
25. Kallenberg CG: **Churg–Strauss syndrome: just one disease entity?** *Arthritis Rheum* 2005, **52:**2589–2593.
26. Sinico RA, Bottero P: **Churg–Strauss angiitis.** *Best Pract Res Clin Rheumatol* 2009, **23:**355–366.
27. Jakiela B, Sanak M, Szczeklik W, Sokolowska B, Plutecka H, Mastalerz L, Musial J, Szczeklik A: **Both Th2 and Th17 responses are involved in the pathogenesis of Churg–Strauss syndrome.** *Clin Exp Rheumatol* 2011, **29**(Suppl.64)**:**S23–S34.
28. Terrier B, Bièche I, Maisonobe T, Laurendeau I, Rosenzwajg M, Kahn JE, Diemert MC, Musset L, Vidaud M, Sène D, Costedoat-Chalumeau N, Le Thi-Huong D, Amoura Z, Klatzmann D, Cacoub P, Saadoun D: **Interleukin-25: a cytokine linking eosinophils and adaptive immunity in Churg–Strauss syndrome.** *Blood* 2010, **116:**4523–4531.
29. Jakiela B, Szczeklik W, Plutecka H, Sokolowska B, Mastalerz L, Sanak M, Bazan-Socha S, Szczeklik A, Musial J: **Increased production of IL-5 and dominant Th2-type response in airways of Churg–Strauss syndrome patients.** *Rheumatology (Oxford)* 2012, **51:**1887–1893.
30. Vaglio A, Buzio C, Zwerina J: **Eosinophilic granulomatosis with polyangiitis (Churg–Strauss): state of the art.** *Allergy* 2013, **68:**261–273.
31. Saito H, Tsurikisawa N, Tsuburai T, Oshikata C, Akiyama K: **Cytokine production profile of $CD4^+$ T cells from patients with active Churg–Strauss syndrome tends toward Th17.** *Int Arch Allergy Immunol* 2009, **149:**61–65.
32. 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:**823–830.
33. Trinath J, Hegde P, Sharma M, Maddur MS, Rabin M, Vallat JM, Magy L, Balaji KN, Kaveri SV, Bayry J: **Intravenous immunoglobulin expands regulatory T cells via induction of cyclooxygenase-2-dependent prostaglandin E2 in human dendritic cells.** *Blood* 2013, doi:10.1182/blood-2012-11-468264.
34. Anthony RM, Kobayashi T, Wermeling F, Ravetch JV: **Intravenous gammaglobulin suppresses inflammation through a novel T(H)2 pathway.** *Nature* 2011, **475:**110–113.

doi:10.1186/2045-7022-4-38
Cite this article as: Tsurikisawa *et al.*: High-dose intravenous immunoglobulin therapy for eosinophilic granulomatosis with polyangiitis. *Clinical and Translational Allergy* 2014 **4**:38.

Submit your next manuscript to BioMed Central and take full advantage of:

- **Convenient online submission**
- **Thorough peer review**
- **No space constraints or color figure charges**
- **Immediate publication on acceptance**
- **Inclusion in PubMed, CAS, Scopus and Google Scholar**
- **Research which is freely available for redistribution**

Submit your manuscript at
www.biomedcentral.com/submit

BioMed Central