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PATHOGENESIS AND THERAPY IN AUTOIMMUNE DISEASES

Intravenous immunoglobulin exerts reciprocal regulation of Th1/Th17 cells and regulatory T cells in Guillain–Barré syndrome patients

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Abstract Guillain–Barré syndrome (GBS) is an acute, autoimmune inflammatory disorder of peripheral nervous system characterized by a severe functional motor weakness. Treatment with intravenous immunoglobulin (IVIg) is one of the approved and preferred therapeutic strategies for GBS. However, the mechanisms underlying the therapeutic benefit with IVIg in GBS are not completely understood. In the present study, we observed that GBS patients have increased frequencies of Th1 and Th17 cells, but reduced number of $Foxp3^+$ regulatory T cells (T_{reg} cells) with defective functions. We show that IVIg treatment in GBS patients results in a marked reduction in the frequency of Th1 and Th17 cells with a concomitant expansion of T_{reg} cells. Importantly, IVIg-expanded T_{reg} cells exhibited an increased T cell suppressive function. Together our results demonstrate that therapeutic benefit of IVIg in GBS patients implicates the reciprocal regulation of Th1/Th17 and T_{reg} cells.

Keywords Intravenous immunoglobulin · IVIg · Guillain–Barré syndrome · Th1 cells · Th17 cells · Regulatory T cells

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Introduction

Intravenous immunoglobulin (IVIg) is a therapeutic preparation, mainly of polyspecific IgG, obtained from the pooled plasma of several thousand healthy donors [1–3]. Although first used for immunoglobulin substitution in patients with immunodeficiencies, IVIg is now increasingly used in the treatment of several autoimmune and systemic inflammatory diseases [1, 4–7]. The therapeutic efficacy of IVIg in immunodeficiency as well as immune-mediated diseases is accomplished by bringing about homeostasis of dysregulated immune system, in addition to immunoglobulin replacement [8–14]. Although several mutually non-exclusive mechanisms are proposed [15–19], the cellular and molecular events underlying the therapeutic benefits of IVIg, particularly in autoimmune diseases, are still less understood.

Guillain–Barré syndrome (GBS) is an autoimmune, acute, inflammatory polyneuropathy of the peripheral nervous system. Despite an incidence rate of 0.6–4 per 100,000 per year throughout the world, GBS is considered to be a frequent cause of neuromuscular paralysis at all ages [20–22]. There are several subtypes of GBS described. The axonal subtypes, such as acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN), are relatively rare and are predominantly caused by antibodies to gangliosides [20, 21]. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) with predominant motor deficit is the most common subtype of GBS and resembles experimental autoimmune neuritis (EAN), which is mainly caused by T cells reactive to myelin proteins P0, P2 and PMP22 [20]. The role of T cell-mediated immunity in AIDP was unclear until recent studies revealed the increased frequency of Th1 as well as Th17 cells in the peripheral blood, and elevated levels of T cell effector cytokines, such as IFN-γ, IL-17 and IL-22 in the cerebrospinal fluid of GBS patients [23–26]. These findings are consistent with the observed pathogenic role of Th1 and Th17 cells in several autoimmune and inflammatory diseases [27–34]. Furthermore, $CD4^{+}Foxp3^{+}$ regulatory T (T_{reg}) cells, which play critical role in the maintenance of immune tolerance and prevention of autoimmunity [35–44], are significantly reduced in GBS patients as well as EAN models [25, 45, 46]. Therefore, similar to other autoimmune inflammatory disease, therapeutic molecules that target both T_{reg} cells and effector T (T_{eff}) cells (Th1 and Th17 cells) are being investigated for the treatment of GBS [24, 25].

In this context, IVIg is a proven effective treatment for GBS and is currently preferred over plasma exchange due to its similar efficacy, easier administration and more favourable side effect profile [21, 47–50]. Of particular interest, IVIg is found to induce expansion of T_{reg} cells in vitro as well as in autoimmune patients and experimental animal models [51–62]. Furthermore, in addition to Th1 cells, recent evidences from experimental animal models as well as in vitro studies have shown that IVIg inhibits the development of Th17 cells and production of their effector molecules, including IL-17, IL-22 and GM-CSF [30, 63–67]. However, it is not clear whether the beneficial effects of IVIg therapy in GBS and other autoimmune and inflammatory diseases are associated with the inhibition of Th1 and Th17 cells.

Since, the up-regulation of T_{reg} cells and inhibition of T_{eff} cells are important for the alleviation of autoimmune inflammatory conditions [28, 68], and IVIg treatment of autoimmune patients is associated with restoration of immune homeostasis, we hypothesized that the beneficial effect of IVIg therapy in GBS patients is associated with reciprocal regulation of T_{reg} cells and effector Th1 and Th17 cell populations.

Materials and methods

Patients and healthy donors

This is a multicentric study, consisting of 5 GBS patients and 4 healthy donors. Blood samples of control group were obtained from 4 healthy donors from Hôpital Hôtel Dieu, Etablissement Français du Sang, Paris, France, with an appropriate ethical approval (N°12/EFS/079). Patients with GBS were hospitalized between 15 January 2011 and 31 May 2011, in Neurological Department of Pitié-Salpétrière Hospital or Hôpital Universitaire of Limoges. Diagnosis of GBS was established according to criteria defined by Asbury and Cornblath [69]. Patients under the treatment of immunomodulatory or immunosuppressive drugs in 3 months prior to diagnosis of GBS and those who were associated with other autoimmune disease and lymphoid disorders (lymphopenia $< 1{,}000/mm^3$, lymphoma, or infection with HIV) were excluded from the study. Five patients with the mean age of 67.6 ± 4.2 years were included in the study who fulfilled the diagnostic criteria. Relevant ethical committee approval (84-2012-08, CHU Limoges) and the consent from patients were obtained. The average onset of the neurological diseases was 11.6 ± 2.8 days at the time of patient inclusion in the study. All the patients included in the study showed AIDP, which is classical form of GBS.

Clinical evaluation

Patients with GBS were examined prior to the IVIg treatment and 1, 2, and 4–5 weeks after the IVIg treatment, for their muscular weakness using Medical Research Council grading system (MRC), and for motor function disability

based on modified Rankin scale (mRS). Briefly, the MRC sum score is a summation of the MRC grades (range 0–5) given in full numbers for the muscle pairs in hands and legs and that of mRS assigns grades ranging from 0 (no symptoms at all) to 5 (severe disability, bedridden, incontinent, and requiring constant nursing care and attention) [70, 71].

Sample preparation and analyses of cellular populations by flow cytometry

Blood samples (40–50 mL in lithium heparin) were obtained by peripheral venous blood at prior to the start of the treatment (0 week) and 1, 2, and 4–5 weeks after the treatment of IVIg. All the analyses were performed within 24 h following blood collection.

Peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll-Paque (1.077 g/mL) density centrifugation. PBMCs were then labelled with fluorochrome-conjugated antibodies to surface markers CD4 and then fixed and permeabilized using Foxp3 intracellular staining kit (eBioscience, France) according to the manufacturer's instructions to determine the $CD4^+Foxp3^+$ T_{reg} cells.

For the intracellular detection of T cell cytokines (IFN-γ, TNF-α, IL-4, IL-17 and IL-22), PBMCs were suspended in X-VIVO 15 culture medium (Lonza, France) and stimulated using phorbol 12-myristate 13-acetate (at 50 ng/mL; PMA, Sigma, France) and ionomycin (at 500 ng/mL, Sigma, France) at 37 °C for 4 h, in the presence of GolgiStop (protein transport inhibitor; BD Biosciences, France). Different Th cell populations were identified by surface staining of CD4 and intracellular staining of T cell cytokines using Foxp3 staining kit (eBioscience). All fluorochrome-conjugated antibodies were obtained from BD Biosciences, except antibodies to IL-17A and Foxp3 (eBioscience). Around 50,000 cells/sample were acquired on flow cytometry (LSR II, BD Biosciences) using FACS DIVA™, and data were analysed using FlowJo software.

Functional analysis of T_{reg} cells by T cell suppression assay

Using the PBMCs, untouched $CD4^+$ T cells were isolated by negative selection using the $CD4^+$ T cell isolation kit II (Miltenyi Biotec, France). Further, naïve ($CD45RA^+$) and memory ($CD45RA^-$) $CD4^+$ T cells were separated using the CD45RA microbeads (Miltenyi Biotec) by positive selection. Finally, $CD45RA^-$ memory T cells were separated into $CD25^+$ and $CD25^-$ cells using CD25 microbeads (Miltenyi Biotec). $CD4^+CD45RA^-CD25^+$ cells were used as T_{reg} cells and total $CD4^+CD25^-$ cells were used as T_{eff} cells for the T cell suppression assay.

Ninety-six-well U-bottom plates were coated with 1.5 μg/mL anti-CD3 mAb (R&D systems, France) for 2 h at 37 °C. Plates were then rinsed once with serum-free RPMI-1640 medium. T_{reg} and T_{eff} cells were co-cultured at different ratios (T_{reg}:T_{eff} at 0:1, 1:4, 1:2, 1:1) in serum-free X-VIVO 15 medium in the presence of soluble anti-CD28 mAb (1.0 μg/mL, R&D systems) for 4 days at 37 °C. After 3 days, tritiated [^{3}H] thymidine was added and T cells were cultured for another 18 h. Subsequently, the cell culture plates were frozen at −20 °C for further analysis of [^{3}H] thymidine incorporation by liquid scintillation to assess the degree of proliferation of T_{eff} cells and to determine the T cell suppressive function of T_{reg} cells.

Results

Treatment with IVIg ameliorates the functional motor deficit in GBS patients

All GBS patients examined are elderly individuals, with a mean age of 67.6 years. The clinical examination scores for MRC and mRS of GBS patients before (0 week) and after (1, 2, and 4–5 weeks) IVIg treatment are depicted in Fig. 1. Notably, there was a wide variation in the degree of functional motor deficit prior to IVIg therapy among the GBS patients. Consistent with the previous studies [21, 47, 48], GBS patients treated with high dose IVIg (0.4 g/Kg body weight per day for 4 days) showed a clinical improvement as evidenced by the increase in MRC score and/or decrease in the modified Rankin scale. The clinical amelioration of GBS was observed as early as 1 week following initiation of IVIg therapy in the patients GBS-P1, -P2 and -P4, and from 2 weeks in GBS-P5 (Fig. 1). However, no improvement was observed in GBS-P3 following IVIg treatment. Of note, GBS-P3 showed mild form of disease and failed to respond to IVIg therapy. The maximal improvement was seen in patient 1, who had the most severe motor deficiency at the beginning. In summary, four out of five (80 %) patients responded to the IVIg therapy with a considerable improvement in their motor functions (Fig. 1). In fact, the efficacy of IVIg in the treatment of severe form of GBS is well established, but not the mild form of disease [20, 21, 47]. This might explain the variations observed in the response to IVIg therapy within the cohort of GBS patients.

IVIg decreases the circulating Th1 and Th17 cells in GBS patients

After establishing the therapeutic efficacy of IVIg in GBS patients, we next investigated the cellular mechanisms mediating the clinical amelioration of disease. The present cohort of GBS patients showed the classical AIDP subtype of GBS, which is primarily caused by self-reactive T_{eff}

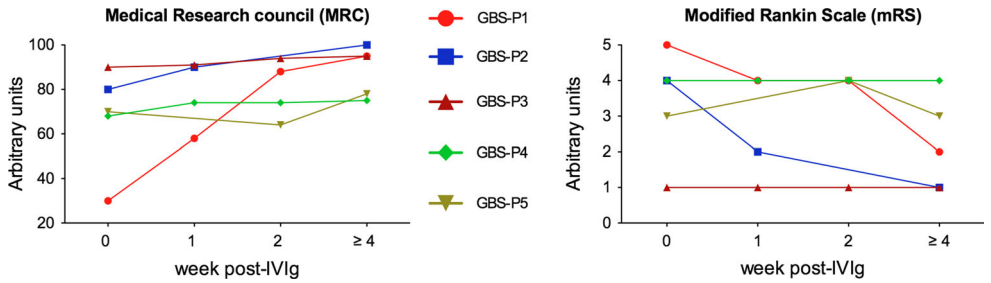

Fig. 1 Changes in the clinical evaluation score of GBS patients over time following IVIg therapy. Clinical examination of GBS patients was done before and after 1, 2, and 4–5 weeks of IVIg administration for assessing the muscular weakness by Medical Research council (MRC) sum score and the motor function disability by modified Rankin scale (mRS)

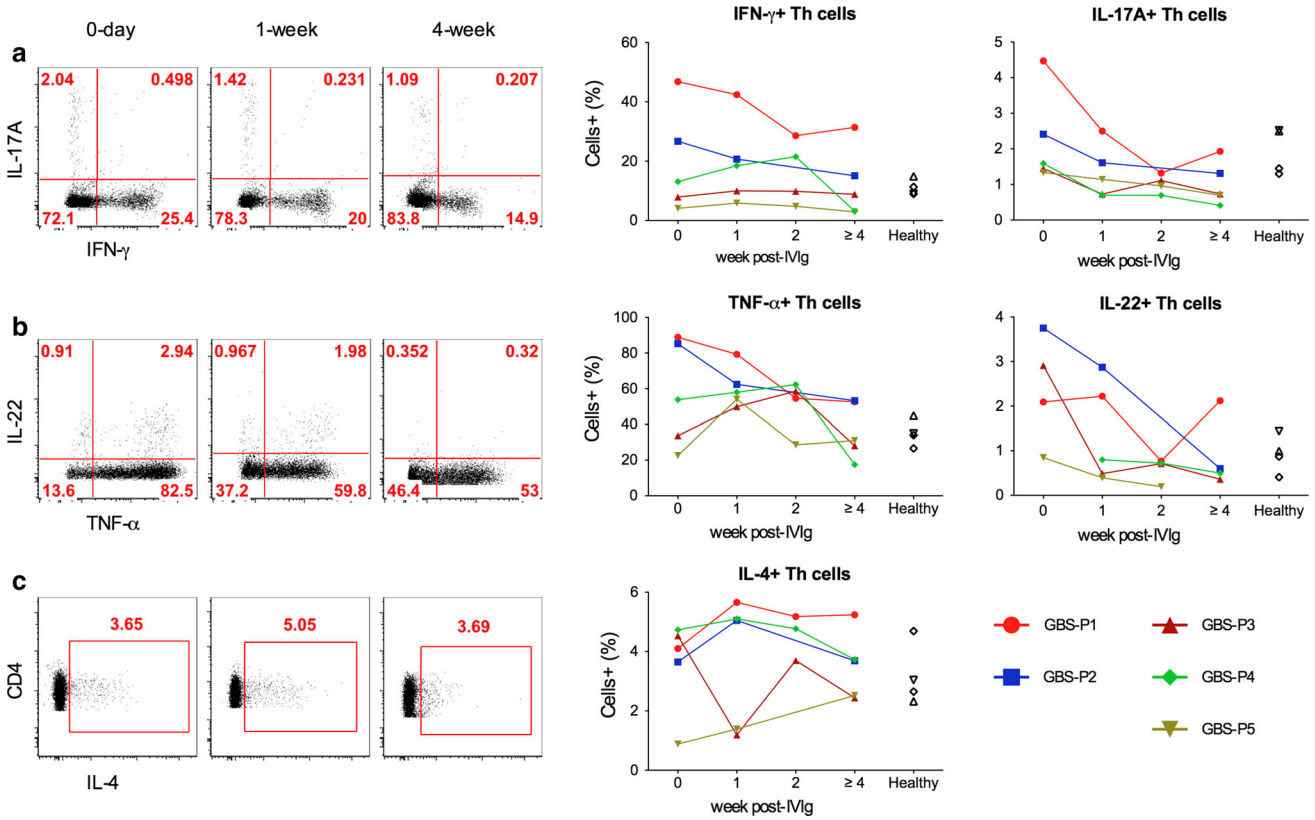

Fig. 2 Temporal changes in the frequency of circulating effector $CD4^+$ Th cell subsets in GBS patients following IVIg therapy. PBMCs from GBS patients were analysed by staining of surface CD4 and intracellular T cell cytokines. **a–c** The percentage of $CD4^+$ Th cells expressing IFN-γ, IL-17A, TNF-α, IL-22 and IL-4 was determined by flow cytometry at different time interval before and after IVIg treatment

cells. Since recent studies have indicated that Th1 and Th17 cells are associated with the severity of disease in GBS patients and EAN models [23–26], we evaluated the frequencies of different Th cell subsets in the blood of GBS patients.

Following the intracellular staining of PBMCs for T cell cytokines, such as IFN-γ, TNF-α, IL-4, IL-17 and IL-22, different Th cell subsets were identified within the $CD4^+$ T cells, including Th1 (IFN-γ^+), Th17 (IL-17^+), Th22 (IL-22^+) and Th2 (IL-4^+) (Fig. 2). Consistent with the previous reports [23–26], GBS patients showed increased frequencies of T_{eff} cell subsets, such as Th1, Th17 and Th22, compared with the healthy donors (Fig. 2a, b). TNF-α is a proinflammatory cytokine expressed mainly by inflammatory Th1 cells, but also Th17 and Th22 cells. Notably, the frequency of $CD4^+$ Th cells expressing TNF-α was also elevated in the blood of GBS patients compared with healthy donors (Fig. 2b). However, the frequency of Th2 cells, which are the primary T_{eff} cells implicated in allergic response, was similar to that of healthy donors (Fig. 2c).

Interestingly, there was a marked decrease in the frequencies of IFN-γ^+, TNF-α^+, IL-17^+ and IL-22^+ Th cells

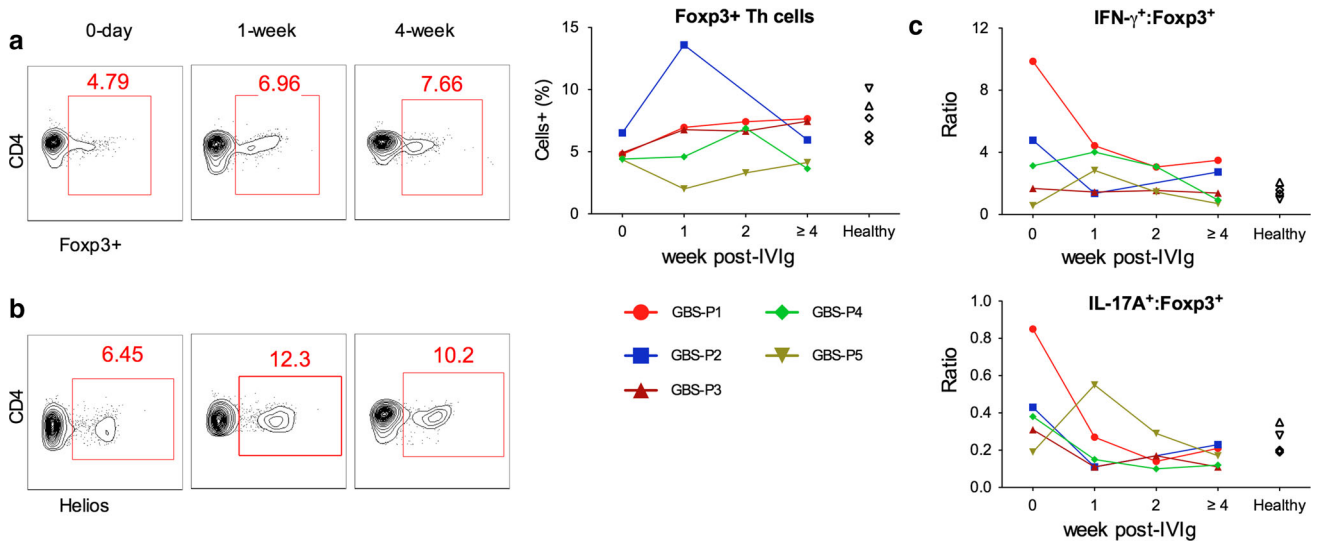

Fig. 3 Temporal changes in the frequency of circulating $Foxp3^+$ $CD4^+$ regulatory T (T_{reg}) cell population in GBS patients following IVIg therapy. PBMCs from GBS patients were analysed by staining of surface CD4 and intracellular Foxp3. **a**, **b** The percentage of $CD4^+$ Th cells expressing Foxp3 and Helios was determined by flow cytometry at different time interval before and after IVIg treatment. The T_{reg} frequency of day zero and 1 week is from the previous report[74]. **c** The ratio of $CD4^+$ Th cells expressing IFN-γ to that of Foxp3 and IL-17A to that of Foxp3

in the peripheral blood of GBS patients following IVIg therapy (Fig. 2a, b). Despite the wide difference in the frequencies of Th cells before IVIg treatment among GBS patients, T_{eff} cells were downregulated to a similar levels following 4–5 weeks of IVIg therapy (except for IFN-γ^+ Th cells). Further, the decline in the T_{eff} cells was drastic in GBS-P1, -P2 and -P4, who also had relatively severe form of disease (Figs. 1, 2). Notably, GBS-P3 and -P5 showed a moderate change in Th cells, which is consistent with their response to IVIg therapy (Figs. 1, 2). Despite a moderate change in the frequencies of IL-4^+ Th cells, IVIg therapy did not appear to alter Th2 cells in GBS patients. Taken together, these results suggest that IVIg treatment selectively downregulates the pathogenic T_{eff} cells involved in GBS.

IVIg therapy expands $CD4^+Foxp3^+$ T_{reg} cells in GBS patients

$CD4^+Foxp3^+$ T_{reg} cells play a critical role in sustaining immune homeostasis. While deficiency of T_{reg} cells is associated with autoimmune and inflammatory conditions, increased number of T_{reg} cells can lead to resolution of immune-mediated pathologies, which is associated with suppression of effector immune cells [35, 36, 38–40, 72, 73]. Therefore, we next explored whether the inhibition of T_{eff} cells by IVIg is associated with expansion of T_{reg} cells in GBS patients.

Compared with healthy donors, peripheral blood of GBS patients had lower frequency of $CD4^+Foxp3^+$ T_{reg} cells prior to IVIg therapy, supporting the significance of T_{reg} cells in controlling autoimmune response (Fig. 3a). Our recent report demonstrates that IVIg therapy leads to increase in the T_{reg} cell frequency 1-week following IVIg treatment in GBS patients P1, P2, P3 and P4 and was associated with an increased circulating prostaglandin E_2 [74]. In P4, the increase in T_{reg} cell was marginal. Here, we followed the evolution of T_{reg} cells up to 4–5 weeks post-IVIg infusion. We observed that GBS-P4 showed a delayed increase (2-week) in T_{reg} cells and that of GBS-P5 failed to upregulate T_{reg} cells. By fourth week, T_{reg} frequency returned to day-0 level in three patients. However, two patients (P1 and P3) still showed high frequency of T_{reg} cells even after 4 weeks. Furthermore, T cells expressing Helios were also increased following IVIg therapy (Fig. 3b). Notably, the ratio of T_{eff} to T_{reg} cell frequencies (IFN-γ^+:$Foxp3^+$ and IL-$17A^+$:$Foxp3^+$) showed a marked reduction in GBS patients (except P5) following IVIg treatment (Fig. 3c). These findings indicate that IVIg induces expansion of $Foxp3^+$ T_{reg} cells, which might be involved in suppression of T_{eff} cells to achieve amelioration of clinical disease.

T_{reg} cells expanded by IVIg are efficient in T cell suppression

Finally, we examined the inhibition of T cell proliferation by enriched T_{reg} cells to assess the functional status. Consistent with other autoimmune studies, T_{reg}-enriched cells of GBS patients prior to IVIg treatment were

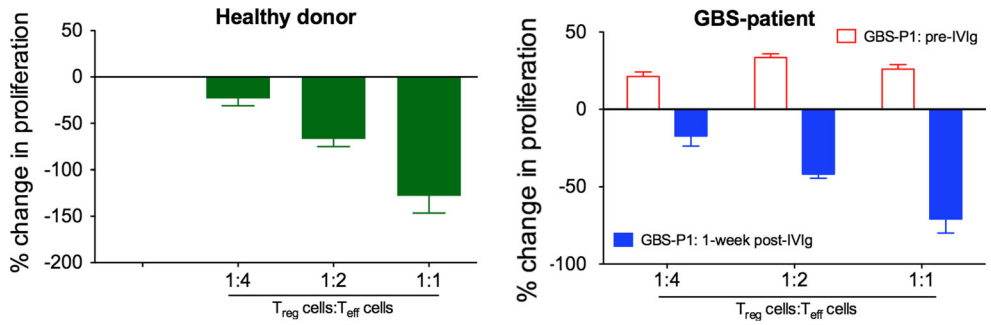

Fig. 4 T cell suppressive function of regulatory T (T_{reg}) cell population is restored in GBS patients following IVIg therapy. T_{reg}-enriched cells and effector T (T_{eff}) cells isolated from PBMCs of GBS patients were co-cultured in quadruplicates at different ratios (T_{regs}:T_{eff} at 1:4, 1:2, 1:1) in serum-free X-VIVO 15 medium in the presence of plate-bound anti-CD3 and soluble anti-CD28 mAb for 4 days at 37 °C. T cell proliferation (*upper panels*) was determined by [^{3}H] thymidine incorporation assay. Percentage change in proliferation of T_{eff} cells in the presence of increasing number of T_{reg} cells is presented

defective in suppression of T_{eff} cell proliferation, as compared to healthy donor (Fig. 4). In contrast to T_{reg} cell number-dependent reduction in T_{eff} cell proliferation in healthy donor, T_{reg}-enriched cells from GBS patients (GBS-P1: pre-IVIg) promoted T_{eff} cell proliferation (Fig. 4). Notably, following IVIg treatment, T_{reg}-enriched cells from GBS patients showed cell number-dependent reduction in T_{eff} cell proliferation (GBS-P1: 1-week post-IVIg), similar to healthy donors (Fig. 4). These results suggest that IVIg therapy induces expansion of T_{reg} cells with a restored T cell suppressive function in GBS patients.

Discussion

In the present study, we showed that beneficial effect of IVIg therapy in GBS patients with AIPD is characterized by selective decrease in the frequencies of pathogenic Th1 and Th17 cells with a concomitant enrichment of T_{reg} cells showing restored T cell suppressive function. In contrast to the ability of B cells to promote Th2 polarization [75], treatment with natural antibodies (IVIg) did not alter the frequencies of Th2 cells in GBS patients. Our results thus indicate that the reciprocal regulation of T_{reg} cells and T_{eff} cell subsets is the cellular mechanism responsible for the therapeutic efficacy of IVIg in GBS and other autoimmune disease. Notably, similar to GBS, the restoration of imbalance between pathogenic T (Th1 and Th17) cells and T_{reg} cells by IVIg therapy is also observed in patients with Kawasaki disease and also recurrent pregnancy loss [76, 77]. As size of GBS patient cohort was small, the present study results need to be validated with investigation of large cohort of patients.

Although the mechanistic events involved in the reciprocal regulation of T_{reg} cells and pathogenic Th1 and Th17 by IVIg in GBS patients are unclear, the findings of recent studies of in vitro cell culture as well as experimental mouse models have provided novel insights into mode of action of IVIg in autoimmune and inflammatory diseases. Interestingly, IVIg is found to inhibit the differentiation of naive $CD4^+$ T cells into pathogenic T (Th1 and Th17) cells and decreases the expression of effector molecules, such as IFN-γ, IL-17 and IL-22 in human T cell culture [63–65], and in experimental autoimmune encephalomyelitis (EAE) mouse model [66, 67]. Mechanistically, IVIg directly interacts with T cells to inhibit differentiation and function, mainly by interfering with the pathways involved in the induction of lineage-specific transcription factor, RORC [63]. Concomitantly, IVIg is shown to expand T_{reg} cells, mainly by inducing proliferation of pre-existing natural T_{reg} cells, rather than de novo generation from naive T cells [54, 63]. Notably, the reciprocal regulation of T_{reg} cells and Th17 in experimental autoimmune arthritis (EAA) mouse model by IVIg is found to be dependent on the up-regulation of IL-10 [78], which is an anti-inflammatory cytokine known to inhibit development and function of Th17 cells, but favour T_{reg} cells [29, 30]. It is possible that the direct interaction of IVIg with Th cell subsets in GBS patients mediates the reciprocal regulation.

Of particular relevance, IVIg is also known to modulate the maturation, function and cytokine production of dendritic cells (DCs) [11, 79–84], which are the principal antigen presenting cells involved in development of T_{reg} cells and T_{eff} cell subsets during autoimmune response [85–87]. Consistent with this, interaction of IVIg with DCs is found to promote the expansion of T_{reg} cells through different mechanisms, such as induction of cyclooxygenase-2-dependent prostaglandin E2 (PGE_2) [88], Treg-itopes [53, 89] and modulation of notch ligands [56, 88]. Interestingly, increased levels of PGE_2 were observed in the peripheral blood of GBS patients following IVIg therapy [74]. Therefore, in addition to direct effect on T cells, IVIg-mediated modulation of DCs might be involved in regulation of Th cell subsets in IVIg-treated GBS patients.

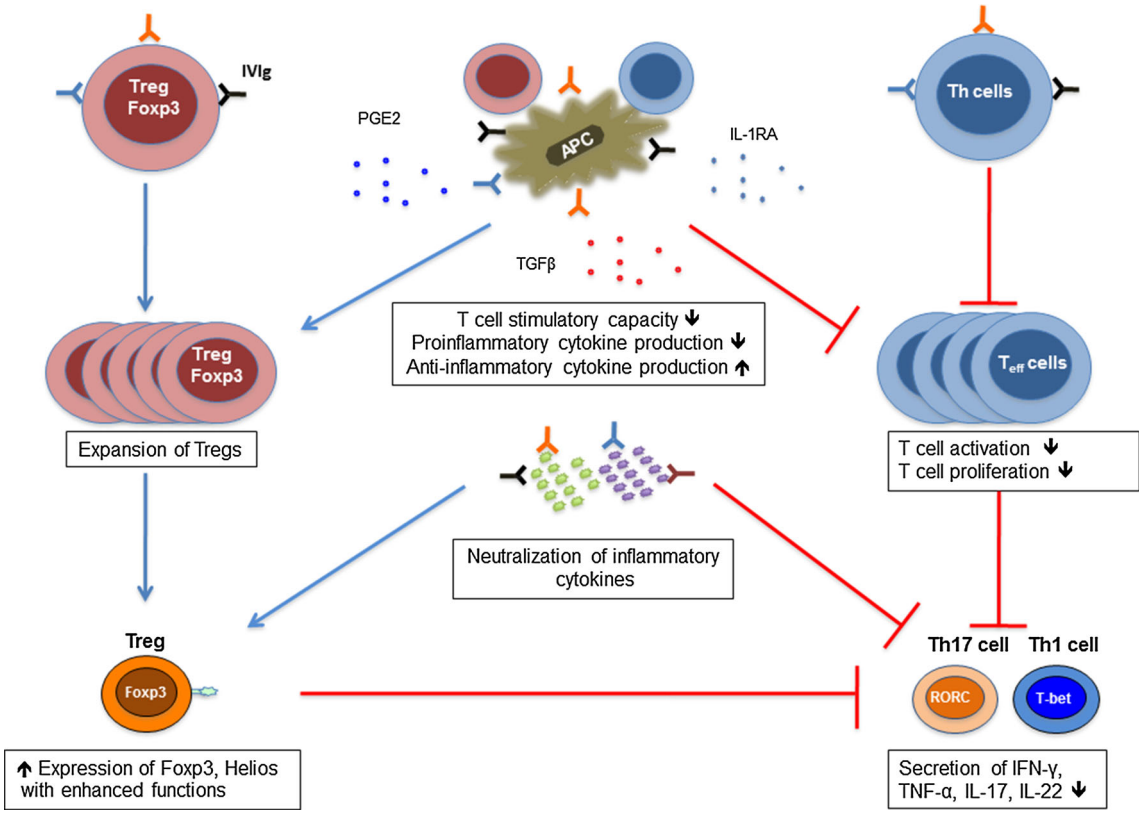

Fig. 5 The proposed mechanisms involved in the reciprocal regulation of Th1/Th17 cells and T_{regs} cells by IVIg. Exposure of effector T (T_{eff}) cells to IVIg results in inhibition of activation, differentiation and cytokine secretion. Parallel, interaction of T_{reg} cells with IVIg or IVIg-modulated antigen presenting cells (APCs) leads to expansion and enhanced suppressive function of T_{reg} cells. These IVIg-modulated T_{reg} cells exhibit an increased expression of Foxp3 and Helios. IVIg-modulated T_{reg} cells are efficient inhibitors of effector T_{eff} cells. In addition to these direct effects, IVIg-mediated modulation of cytokine network as a result of altered cytokine production from APCs and neutralization of inflammatory cytokines can create a microenvironment favourable for T_{reg} cell expansion, while inhibiting T_{eff} cells

The role of Fc-sialylation and Fcγ receptor IIb (FcγRIIB) in the anti-inflammatory effects of IVIg have also been proposed [17]. It is hypothesized that α2,6-sialylated Fc fragments interact with dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin-positive (DC-SIGN$^+$) innate cells to release IL-33, which in turn expands the IL-4-producing basophils to mediate the anti-inflammatory effects [90]. Interestingly, studies performed with $F(ab')_2$ and desialylated-IVIg have shown that both Fc fragment region of IVIg and FcγRIIB expression are dispensable for the expansion of Treg cells as well as suppression of pathogenic Th cells [63, 66, 67, 88], similar to IVIg-mediated modulation of human DCs [84, 88, 91] and experimental autoimmune mouse models [66, 67, 92]. Of relevance, IVIg treatment induced a significant increase in the plasma levels of IL-33 to a similar extent in GBS patients, irrespective of Th cell modulation and therapeutic outcome (data not shown). These results support our recent findings of lack of correlation between the plasma IL-33 levels and the basophil number in autoimmune patients treated with IVIg [93]. Furthermore, basophils and sialylation of IVIg were not required for the therapeutic efficacy of IVIg in arthritis mouse models [94].

Since IVIg is known to contain cytokine-specific antibodies [1], it is possible that treatment of GBS patients with IVIg results in neutralization of inflammatory cytokines, which can in turn favour T_{reg} cell expansion, while inhibiting inflammatory Th1 and Th17 cell subsets [95]. In addition, IVIg can also directly interact with B cells to inhibit their activation proliferation and functions through induction of anergy and apoptosis [96–98]. These features of IVIg might be relevant in the axonal forms of GBS, which are mainly caused by antibodies to gangliosides [20, 21, 99]. Furthermore, IVIg is also found to target neutrophils to downregulate their activation and functions to exert anti-inflammatory mechanisms [100, 101], which may indirectly influence the development and function of Th cells. In summary, multitude of cellular and molecular mechanisms might be involved in the reciprocal regulation of effector T (Th1 and Th17) cells and T_{reg} cells by IVg

therapy in GBS (Fig. 5). Thus, IVIg exhibits unique feature of pluripotency in order to achieve the therapeutic efficacy in diverse immune-mediated pathologies [102].

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