Title: A distinctive form of immune thrombocytopenia in a phase 2 study of alemtuzumab for the treatment of relapsing-remitting multiple sclerosis

Short title: Alemtuzumab-associated ITP

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Abstract
In a phase 2 clinical trial of annual alemtuzumab for the treatment of relapsing-remitting multiple sclerosis, 6/216 (2.8%) patients developed immune thrombocytopenia (ITP). Over a mean follow-up of 4.5 years, the incidence rate of ITP was 6.2 (95% CI 2.3-13.3) per 1000 person-years. The median times from initial and last alemtuzumab exposure to ITP diagnosis were 24.5 and 10.5 months, respectively. Five patients developed severe thrombocytopenia. Four were symptomatic, including fatal intracranial hemorrhage in the index case. Four patients received standard first-line ITP therapy, all of whom responded to treatment within 1 week. All 5 surviving patients achieved complete remission (CR) and remained in CR without need for ongoing ITP therapy for a median duration of 34 months at last follow-up. A monitoring plan for the early detection of ITP, implemented after presentation of the index case, identified all 5 subsequent cases before serious hemorrhagic morbidity or mortality occurred. In conclusion, we describe a distinctive form of ITP associated with alemtuzumab treatment characterized by delayed presentation after drug exposure, responsiveness to conventional ITP therapies, and prolonged remission. Clinicians should maintain a high level of vigilance and consider routine monitoring for ITP in patients treated with this agent. This study is registered at www.clinicaltrials.gov as NCT00050778.

Key words: alemtuzumab, immune thrombocytopenia, ITP
Introduction
Alemtuzumab, an anti-CD52 humanized monoclonal antibody that alters the circulating lymphocyte pool, is approved for the treatment of chronic lymphocytic leukemia (CLL) and is under investigation for the treatment of relapsing-remitting multiple sclerosis (RRMS). In a randomized controlled phase 2 efficacy and safety trial in patients with RRMS (CAMMS223, ClinicalTrials.gov number, NCT00050778), alemtuzumab was more effective than subcutaneous interferon beta-1a (SC IFNB-1a), significantly reducing the relapse rate, risk for sustained accumulation of disability (SAD), and mean Expanded Disability Status Scale (EDSS) score at Month 36 post-treatment.1 However, alemtuzumab use was associated with an increased occurrence of autoimmune disorders, which consisted of immune thrombocytopenia (ITP), thyroid disease, and one case of anti-glomerular basement membrane disease. Other notable adverse events included infusion-associated reactions and infections of predominantly mild to moderate severity.

Herein we provide a clinical description and follow-up of the cases of ITP noted in the original CAMMS223 study report1 and explore potential clinical and laboratory factors predictive of ITP occurrence. We also review the monitoring plan established for the early detection and treatment of ITP in studies of alemtuzumab in RRMS.

Methods
Participants, interventions, and outcomes
CAMMS223 methods have been published1 and are briefly reviewed here. From December 2002 through September 2004, 334 patients with RRMS from 49 centers in Europe and the United States were enrolled in the phase 2 study. Patients had received no previous disease-modifying MS therapy, had EDSS scores of 3.0 or less, had at least 2 relapses in the 2 years prior to study entry, and had evidence of at least one gadolinium-enhancing lesion on screening MRI. No patients had a history of ITP or other autoimmune cytopenias at the time of enrollment. The protocol was approved by the review boards of participating centers and all subjects provided written informed consent in accordance with the Declaration of Helsinki.

Patients were randomized in a 1:1:1 ratio to one of three treatment groups: 44 mcg 3 times/week SC IFNB-1a (Rebif®) or 12 mg/day or 24 mg/day intravenous alemtuzumab delivered during 2 or 3 annual cycles. The first cycle of alemtuzumab was administered over 5 days while subsequent cycles were delivered over 3 days. All patients received concurrent annual treatment with intravenous methylprednisolone sodium succinate 1 gm/day for 3 days. Infectious prophylaxis was not routinely administered. The initial study period lasted 36 months.

Co-primary efficacy endpoints were time to SAD and MS relapse rate. Safety was assessed through monitoring of treatment-emergent adverse events, changes in physical examination findings, vital signs, selected clinical laboratory results, and autoantibody monitoring.

ITP risk management program
In June 2005, one patient presented with fatal intracranial hemorrhage and was diagnosed with ITP. In retrospect, cutaneous signs of ITP had been evident for several weeks. Within 3 weeks of this fatality, investigators were instructed to contact patients and advise them to report abnormal bleeding, bruising, or petechial rash, and to perform monthly complete blood counts (CBCs) to...
identify thrombocytopenia or other hematologic abnormalities. In September 2005, alemtuzumab dosing was suspended after 2 additional patients notified their physicians of mucocutaneous bleeding and were diagnosed with ITP. During the suspension of alemtuzumab dosing, all safety and efficacy assessments continued and patients randomized to SC IFNB-1a continued to receive treatment. The study protocol was amended in December 2005 to include a formal monitoring plan to ensure timely detection and treatment of ITP. Dosing with alemtuzumab resumed in 2008.

The ITP monitoring plan included a monthly CBC and peripheral blood smear, a monthly questionnaire for signs and symptoms of ITP offset by 2 weeks from the monthly CBC, and education of subjects and investigators. Included among patient education materials were visual depictions of petechiae and ecchymoses. Alemtuzumab-treated patients were advised to continue safety monitoring for 4 years after their last dose. More intensive evaluation and monitoring were triggered by the development of thrombocytopenia, a large drop in the platelet count, or signs and symptoms of ITP (see Supplemental Table 1).

ITP was defined as either a single confirmed platelet count $<50 \times 10^9$/L or a platelet count $\geq 50 \times 10^9$/L but $<100 \times 10^9$/L on at least 2 consecutive occasions during a period of at least 1 month in the setting of a normal hemoglobin and neutrophil count; an absence of splenomegaly; and a normal peripheral blood smear (except for thrombocytopenia). Local hematologists participated in the diagnostic evaluation. Once a diagnosis of ITP was made, the patient received no further alemtuzumab treatment. Response to ITP therapy was defined as a rise in the platelet count to $\geq 30 \times 10^9$/L and at least a 2-fold increase from the nadir platelet count in the absence of bleeding. Complete remission (CR) of ITP was defined as a platelet count $\geq 100 \times 10^9$/L, absence of bleeding, and no ongoing ITP therapy.

**Laboratory assessments**

Serum antiplatelet antibodies were measured in retained and prospectively collected samples using an antigen-specific indirect assay for circulating antibodies to platelet surface glycoproteins IIb/IIIa, Ib/IX, Ia/IIa, IV, and HLA class I antigens (PAK-PLUS assay, GTI Diagnostics, Waukesha, WI). Platelet-bound antibodies to glycoprotein IIb/IIIa, Ib/IX, and Ia/IIa were measured using an antigen-specific direct assay in prospectively collected samples (PAK-AUTO assay, GTI Diagnostics, Waukesha, WI). Antiplatelet antibody testing was performed at the American Red Cross Platelet Serology Laboratory (Saint Paul, MN) according to the manufacturer’s instructions. To further explore potential markers of ITP, immature platelet fraction was measured using Sysmex XE-2100 (Sysmex America, Mundelein, IL), beginning in 2006. Lymphocyte subpopulations and titers of anti-TSH receptor and thyroid peroxidase antibodies were measured quarterly at central laboratories (Cirion Clinical Trial Services, Laval, QC, Canada; Charles River Laboratories, Edinburgh, UK).

**Statistical methods**

Clinical, demographic, and laboratory characteristics of subjects and autoantibody seroconversion were summarized with descriptive statistics for continuous variables and with frequency and percentages for categorical variables. Confidence intervals for incidence rates were calculated using the Exact method. Analyses were carried out using SAS 9.2 (Cary, NC).
Role of the funding source
Genzyme and Bayer Schering Pharma provided financial support and participated in the design of the CAMMS223 study as well as in the development of the ITP monitoring plan. Genzyme participated in the data analysis and interpretation and preparation of this report. The corresponding author had full access to all the data. The decision to submit for publication was made by the corresponding author and Genzyme.

Results
Incidence of ITP
Of the 334 patients that underwent randomization in CAMMS223, 6 of 216 (2.8%) alemtuzumab-treated patients and one of 107 (0.9%) SC IFNB-1a-treated patients developed protocol-defined ITP over a mean follow-up of 4.5 years. Of the alemtuzumab-associated cases, 2 of 108 (1.9%) occurred in the 12 mg/day group and 4 of 108 (3.7%) occurred in the 24 mg/day group. The overall incidence rate (95% CI) of ITP in alemtuzumab-treated subjects was 6.2 (2.3-13.3) per 1000 person-years. The incidence rate in the 12 mg/day and 24 mg/day dose cohorts was 4.2 (0.5-15.2) and 8.0 (2.2-20.5) per 1000 person-years, respectively. The incidence rate of ITP in the SC IFNB-1a group was 2.7 (<0.1-14.9) per 1000 person-years.

Description of cases
Demographic and clinical characteristics of the 7 cases of ITP in CAMMS223 are shown in Table 1 and individual platelet trends are depicted in Figure 1. The 2 patients in the alemtuzumab 12 mg/day cohort each received three dosing cycles. Three of the 4 patients in the alemtuzumab 24 mg/day cohort received 2 dosing cycles (including Subject 1, the fatal index case); the remaining patient received three dosing cycles. Among the 6 alemtuzumab-treated patients, onset of ITP was between 19 and 39 months following the first cycle and between 1 and 15 months from the last exposure to the drug. Five of the 6 patients developed severe thrombocytopenia (platelet count <10 × 10⁹/L) and 4 were symptomatic (Table 1).

Of the 5 surviving alemtuzumab-treated subjects, 4 received initial therapy with corticosteroids, intravenous immunoglobulin G (IVIG), anti-Rh(D) immunoglobulin, and/or platelet transfusion. All 4 responded to treatment with a median time to response of 2.5 days (range 1-7). Two patients (Subjects 3 and 6) had loss of response during tapering of their initial therapy and responded to re-induction with first-line agents. Both of these patients ultimately received rituximab and were subsequently weaned from first-line therapy. None of the surviving patients suffered serious bleeding during their disease course and no subject underwent splenectomy or treatment with thrombopoietic growth factor. One asymptomatic patient (Subject 5), who presented with mild thrombocytoenaia, did not receive ITP therapy and had spontaneous resolution of disease.

All of the 5 surviving alemtuzumab-treated subjects achieved CR during the monitoring period. The median time from diagnosis of ITP to CR was 4 months (range 1-8). At the time of last follow-up, all 5 patients remained in CR for a median duration of 34 (range 33-46) months without recurrence of thrombocytopenia or bleeding.

The one SC IFNB-1a-treated patient (Subject 7) had a normal baseline platelet count, but developed mild thrombocytoenaia within 3 months of study drug initiation that met protocol-
defined criteria for ITP. The drug was temporarily discontinued and the dose was subsequently reduced without clear improvement in the platelet count. Full-dose SC IFNB-1a was resumed at Month 6 and continued for the duration of the study. The patient remained asymptomatic throughout and did not require platelet-raising therapy. At Month 36, she had a platelet count of $119 \times 10^9/L$ and withdrew consent for further evaluation.

**Predictive and correlative factors**
Baseline demographic and MS disease characteristics were generally similar among patients that developed ITP and those that did not (Table 2). The results of serologic studies in alemtuzumab-treated subjects are shown in Table 3. One (16.7%) patient among the 6 ITP cases and 13 patients (6.5%) in the non-ITP group had circulating antiplatelet antibodies at baseline. Among those who tested negative at baseline, seroconversion occurred in 2 (40.0%) and 18 (9.6%) patients in the ITP and non-ITP groups, respectively. In the ITP cases (Subjects 1 and 3), seroconversion appeared to occur simultaneously with the onset of ITP. Moreover, Subject 3 became seronegative with attainment of CR (Figure 1). Anti-TSH receptor antibody and anti-thyroid peroxidase antibody seroconversion occurred with relatively high frequency in both the ITP and non-ITP groups. Platelet-bound antibody testing was not performed in the index case. Of the remaining 5 alemtuzumab-treated patients with ITP, 3 tested positive for platelet-bound antibodies. In 2 of these cases (Subjects 2 and 5), initial detection of platelet-bound antibody was concurrent with onset of ITP (Figure 1), though disappearance of antibody with CR was observed in only one of these individuals (Subject 5). Alterations in immature platelet fraction did not show a consistent temporal association with inception or resolution of ITP (data not shown).

**ITP monitoring program**
Investigator and patient education following the fatal index case (Subject 1) led to prompt identification of two additional cases (Subjects 3 and 6) upon onset of mucocutaneous manifestations of ITP. Following implementation of the formal monitoring plan, 3 additional cases of alemtuzumab-associated ITP were identified (Subjects 2, 4, and 5). All 3 of these cases were detected by monthly CBC. Two of the 3 were asymptomatic at the time of ITP diagnosis and the other presented with cutaneous petechiae. No patients were identified by clinical questionnaire and no patients presented with serious hemorrhagic morbidity or mortality after initiation of the monitoring plan.

**Discussion**
ITP is a syndrome of antibody- and cell-mediated platelet destruction and suppression of platelet production.\(^4\) It may occur in the absence of an evident predisposing etiology (primary ITP) or secondary to one of a variety of associated conditions including broader autoimmune disorders, lymphoproliferative neoplasms, congenital immune deficiencies, drugs, and infections.\(^5\) Here we report a distinctive form of secondary ITP associated with alemtuzumab treatment.

In our series, the incidence rate of alemtuzumab-associated ITP was 6.2 (95% CI 2.3-13.3) cases per 1000 person-years, strikingly higher than the incidence rate of ITP reported for the general adult population (0.016-0.039 per 1000 person-years).\(^6,7\) Two potential sources of bias may contribute to this disparity. First, it is conceivable that ITP occurs with greater frequency in patients with RRMS than in the general population, independent of MS therapy.\(^8-10\) However, the
rarity of reported incident ITP in the placebo groups of other clinical trials in RRMS speaks against this possibility. We conducted a pooled analysis of placebo-controlled clinical trials in RRMS in which the placebo arm consisted of at least 50 subjects. In this analysis, there were no published reports of ITP arising in 2015 placebo-treated subjects over a total exposure of 3115 person-years (unpublished data). Second, detection of new cases of ITP may have been enhanced by the frequent clinical and laboratory monitoring mandated by the CAMMS223 protocol. Nonetheless, the incidence of ITP following treatment with alemtuzumab, roughly 100-fold higher than that of the general adult population, is unlikely to be explained by ascertainment bias alone and suggests a potential etiologic role for alemtuzumab in the subsequent development of ITP.

Alemtuzumab may not be unique among disease-modifying MS therapies with respect to its association with ITP. Thrombocytopenia has been reported in clinical trials of Rebif® and Copaxone® and has been observed in the post-marketing surveillance of Betaseron®. Furthermore, ITP has been reported in the post-marketing surveillance of Avonex®, an intramuscular formulation of IFNB-1a, and natalizumab. One asymptomatic patient on the SC IFNB-1a arm of CAMMS223, who experienced mild intermittent thrombocytopenia during the study, met the protocol definition for ITP. She also had mild intermittent leucopenia, a finding atypical of ITP that may suggest an alternative process such as myelosuppression, rather than ITP, as the cause of her thrombocytopenia.

The natural history of alemtuzumab-associated ITP appears distinct from both typical drug-induced immune thrombocytopenia (DITP) and primary ITP. In contradistinction to other forms of DITP, which typically occur within days of exposure to the offending agent and resolve within days of its discontinuation, the 6 cases of alemtuzumab-associated ITP reported herein presented in a delayed fashion a median of 24.5 months after initial drug administration and 10.5 months after last exposure (Table 1).

Alemtuzumab-associated ITP proved highly responsive to conventional ITP therapies in our series. All 4 patients who received front-line corticosteroids, IVIG, anti-Rh(D), and/or platelet transfusion responded within the first week of treatment with rapid achievement of a hemostatic platelet count. Two patients had loss of response as initial therapy was tapered, but responded rapidly to re-induction with first-line agents. Both of these patients ultimately achieved durable CRs after treatment with rituximab.

As a rule, primary ITP in adults is a chronic disease. Only approximately 10% of patients experience long-term remission following first-line treatment. In contrast, all of the 5 surviving alemtuzumab-treated patients in our series achieved CR within 8 months of disease onset and remained in remission for a median of 34 months at the time of last follow-up without relapse or need for further ITP therapy (Table 1). In this regard, alemtuzumab-associated ITP resembles ITP of childhood, which assumes a self-limited course in 70-80% of cases. In view of this natural history, clinicians may wish to defer splenectomy in patients with alemtuzumab-associated ITP to allow time for platelet recovery. The role of thrombopoietic growth factors in the management of this disorder is unknown.
Few cases of severe thrombocytopenia arising as a complication of alemtuzumab therapy for disorders other than MS have been published despite its approval for the treatment of CLL a decade ago and its growing off-label use in a variety of settings such as hematopoietic and solid organ transplantation. Several reports even document the effective use of alemtuzumab for the treatment of ITP and other autoimmune cytopenias. The rarity of alemtuzumab-associated ITP in patients without MS may reflect differences in patient characteristics or in the dosing and schedule of the drug. Furthermore, alemtuzumab-associated ITP may be difficult to recognize in patients with CLL, who frequently suffer from other causes of thrombocytopenia including tumor infiltration of the marrow, the effects of myelosuppressive therapy, splenomegaly, and CLL-associated ITP.

The pathogenesis of alemtuzumab-associated ITP is incompletely understood. The delay in onset points to a mechanism distinct from typical DITP, which generally requires the presence of circulating drug, and suggests a possible disorder of lymphocyte repopulation. Indeed, the timing and spectrum of autoimmunity following alemtuzumab exposure is similar to that seen in the setting of other forms of immune reconstitution. Specifically, ITP, other autoimmune cytopenias, and thyroid disease have also been observed to occur with increased frequency months to years after autologous hematopoietic stem cell transplantation and initiation of antiretroviral therapy in HIV-infected individuals.

Cines and colleagues have proposed a classification scheme for various forms of secondary ITP on the basis of the site of impaired immune tolerance along a central-differentiation-peripheral immune response axis. We suggest that alemtuzumab-associated ITP may arise as a consequence of defects in central tolerance checkpoints during lymphocyte reconstitution. With immune recovery, resolution of these defects may contribute to the favorable natural history of the disorder. In contrast, other forms of ITP associated with impaired central tolerance such as autoimmune lymphoproliferative syndrome (ALPS)-associated ITP and Evan’s syndrome are characteristically poorly responsive to therapy and frequently assume a chronic course likely owing to the persistent nature of the checkpoint defects in these disorders.

A correlative study of patients in CAMMS223 showed that patients with autoimmunity following alemtuzumab therapy had higher rates of T cell apoptosis, but not more severe lymphopenia, than those without autoimmunity, suggesting increased cell cycling in this group. These perturbations in T cell cycling appeared to be driven by higher serum concentrations of IL-21, pre-treatment levels of which were associated with the subsequent development of autoimmune phenomena. Serial testing of additional immune markers implicated in ITP and immune reconstitution at baseline, during acute ITP, and in CR may shed further light on the mechanism of alemtuzumab-associated ITP as well as on ITP pathogenesis more broadly and may facilitate discovery of other predictive biomarkers that enable prospective identification of individuals at highest risk of developing autoimmunity.

Additional information on the incidence and natural history of alemtuzumab-associated ITP is also needed. Such information is likely to be provided by 2 large, ongoing, randomized phase 3 trials of alemtuzumab vs. SC IFNB-1a for the treatment of RRMS (ClinicalTrials.gov numbers NCT00530348 and NCT00548405) as well as an extension protocol for patients who participated in prior alemtuzumab studies (ClinicalTrials.gov number NCT00930553). These studies may
also elucidate clinical risk factors and biomarkers predictive of the development of alemtuzumab-associated ITP. Although our series was not adequately powered to detect such variables (Table 2), a recently reported prospective series of MS patients identified a family history of autoimmune disease and smoking as independent risk factors for the development of alemtuzumab-associated autoimmunity.35

As with other forms of ITP, our data suggest that circulating antiplatelet antibody and platelet-bound antibody assays are unlikely to have adequate predictive value for the diagnosis of alemtuzumab-associated ITP (Table 3). Prospective studies have demonstrated sensitivities and specificities for these assays of 49-66% and 78-92%, respectively.36 Test interpretation is further hampered by modest interlaboratory reproducibility.37

Ongoing studies of alemtuzumab in RRMS continue to utilize the monitoring plan described here for timely detection of ITP. Physician and patient education as well as monthly hematologic monitoring both appear to contribute to its effectiveness in reducing hemorrhagic morbidity and mortality. The monitoring plan continues to undergo prospective assessment.

In conclusion, we describe a unique form of ITP associated with alemtuzumab treatment and characterized by delayed presentation after drug exposure, responsiveness to conventional ITP therapies, and prolonged remission. Further investigation to understand the mechanism of and optimal surveillance for this potentially fatal disorder is ongoing. In the meantime, careful monitoring for signs and symptoms and a high index of suspicion for ITP is recommended in the growing number of patients treated with this agent.
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Authorship Contributions
D.H.M., M.G., and D.S.B. designed the ITP monitoring plan. A.P. and A.C. analyzed the data. A.C. wrote the manuscript and approved the final version. A.J.C., H.S., E.F., M.G., P.O., and D.H.M. reviewed and provided critical input into the manuscript.

Conflict-of-Interest Disclosure
A.C. reports receiving research support from Baxter, Bayer, and Novo Nordisk and consultancy fees from Bayer, Biogen-Idec, Canyon, CSL Behring, and Genzyme. A.J.C. reports receiving research grants and honoraria from Genzyme Corporation and travel and honoraria from Merck Serono and UCB Cell Tech. H.S. reports receiving research support from Genzyme; honoraria, consultancy and speaker’s bureau compensation from Teva; speaker’s bureau fees and compensation for travel from Novartis; and compensation for speaker’s bureau and commercial research support from Biogen-Idec. E.F. reports receiving consultancy fees, honoraria, travel, and research support from Bayer, Novartis, Ono, Sanofi, Biogen Idec, EMD Serono, Genzyme, Opexa Therapeutics, Pfizer, Teva Neuroscience, and Eli Lilly. M.G., A.P., P.O., and D.H.M. are employees of Genzyme, a Sanofi Company.
References


### Table 1. Demographic and clinical characteristics of ITP cases in CAMMS223

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Treatment group</th>
<th>Age at ITP onset (gender)</th>
<th>No. of alemtuzumab cycles (cumulative dose, mg)</th>
<th>Months from first dose (last dose) to ITP onset</th>
<th>Platelet count nadir (10^9/L)</th>
<th>Presenting signs or symptoms</th>
<th>ITP therapy</th>
<th>Months from ITP onset to CR</th>
<th>Duration of CR at last follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alemtuzumab 24 mg/day</td>
<td>39 (M)</td>
<td>2 (192)</td>
<td>19 (7)</td>
<td>4</td>
<td>Fatal ICH</td>
<td>None</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>Alemtuzumab 24 mg/day</td>
<td>37 (F)</td>
<td>3 (264)</td>
<td>36 (12)</td>
<td>4</td>
<td>Petechiae</td>
<td>PT, M</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>Alemtuzumab 24 mg/day</td>
<td>30 (M)</td>
<td>2 (192)</td>
<td>24 (12)</td>
<td>2</td>
<td>Ecchymoses</td>
<td>M, PT, IG, P, Da, De, Ri</td>
<td>4</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>Alemtuzumab 24 mg/day</td>
<td>34 (F)</td>
<td>2 (192)</td>
<td>21 (9)</td>
<td>3</td>
<td>None</td>
<td>P</td>
<td>6</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>Alemtuzumab 12 mg/day</td>
<td>34 (F)</td>
<td>3 (132)</td>
<td>39 (15)</td>
<td>41</td>
<td>None</td>
<td>None</td>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>SC IFNB-1a</td>
<td>49 (F)</td>
<td>3 (132)</td>
<td>25 (1)</td>
<td>1</td>
<td>Petechiae</td>
<td>De, PT, P, Rh, H, Ri</td>
<td>8</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>SC IFNB-1a</td>
<td>42 (F)</td>
<td>NA</td>
<td>3 (NA)</td>
<td>62</td>
<td>None</td>
<td>None</td>
<td>21</td>
<td>11</td>
</tr>
</tbody>
</table>

CR, complete remission; De, dexamethasone; PT, platelet transfusion; P, prednisone; Rh, anti-Rh(D) immune globulin; H, hydrocortisone; Ri, rituximab; ICH, intracranial hemorrhage; NA, not applicable; M, methylprednisolone; IG, intravenous immune globulin G; Da, danazol

*Patient died of ICH at presentation of ITP.
Table 2. Baseline characteristics between patients with and without ITP

<table>
<thead>
<tr>
<th></th>
<th>ITP (n=7)</th>
<th>Non-ITP (n=316)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>35.7 (6.52)</td>
<td>32.4 (8.61)</td>
</tr>
<tr>
<td>Sex, female (%)</td>
<td>71.4</td>
<td>64.6</td>
</tr>
<tr>
<td>Race, white (%)</td>
<td>85.7</td>
<td>89.6</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>26.2 (7.02)</td>
<td>25.8 (6.06)</td>
</tr>
<tr>
<td>MS disease duration since initial episode, median years (min, max)</td>
<td>0.6 (0.3, 2.3)</td>
<td>1.3 (0.1, 6.3)</td>
</tr>
<tr>
<td>Baseline EDSS, mean (SD)</td>
<td>1.8 (0.76)</td>
<td>1.9 (0.76)</td>
</tr>
<tr>
<td>Number of MS relapses in prior year, median (min, max)</td>
<td>2.0 (1.0, 2.0)</td>
<td>2.0 (1.0, 4.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of MS relapses in prior year, n (%)</th>
<th>ITP (n=6)</th>
<th>Non-ITP (n=210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 (28.6)</td>
<td>123 (38.9)</td>
</tr>
<tr>
<td>2</td>
<td>5 (71.4)</td>
<td>126 (39.9)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>49 (15.5)</td>
</tr>
</tbody>
</table>

MS, multiple sclerosis; EDSS, Extended Disability Status Scale

Table 3. Correlative serologic studies between alemtuzumab-treated patients with and without ITP

<table>
<thead>
<tr>
<th></th>
<th>ITP (n=6)</th>
<th>Non-ITP (n=210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable at baseline</td>
<td>Serum anti-platelet antibodies</td>
<td>6</td>
</tr>
<tr>
<td>Positive at baseline (%)</td>
<td>Anti-TSH receptor antibodies</td>
<td>6</td>
</tr>
<tr>
<td>Seroconversion* (%</td>
<td>Anti-thyroid peroxidase antibodies</td>
<td>6</td>
</tr>
</tbody>
</table>

*Defined as negative serology at baseline and positive serology on one or more occasions after alemtuzumab exposure.
Figure legends

**Figure 1. Platelet trends in ITP cases**
Platelet counts for the 7 ITP patients in CAMMS223 are shown in red in panels 1-7, respectively. For alemtuzumab-treated patients (panels 1-6), vertical lines represent alemtuzumab dosing. Green arrowheads represent onset of ITP. ITP treatments and the timing of their administration are shown for each patient in the area above the platelet counts. Results of serum antiplatelet antibody and platelet-bound antibody testing are noted at the bottom of each panel. Plt, platelet; AB, antibody; IVIG, intravenous immunoglobulin G.
A distinctive form of immune thrombocytopenia in a phase 2 study of alemtuzumab for the treatment of relapsing-remitting multiple sclerosis

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