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Efficiency of long-term treatment with intravenous immunoglobulins correlates with reduced autoreactive T cell responses in chronic inflammatory demyelinating polyneuropathy patients

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare disease of the peripheral nervous system, characterized by gradual increasing weakness of the limbs, with more than 50% of patients experiencing marked disability [1]. The underlying pathophysiological mechanism of CIDP remains unknown; however, studies have shown activated T cells in the circulation of CIDP patients [2–4]. In addition, patient studies suggest a key role for autoreactive T cell responses against peripheral myelin antigens such as P0, P1, P2 and peripheral myelin protein PMP-22 [5,6]. Mechanism-of-action studies in other chronic autoimmune diseases have shown that the T cell memory compartment influences antigen responses by showing up-regulation of $CD4^+$ or $CD8^+$ T effector memory (TEM) cells [7,8]. Recently, published data from a randomized, placebo-controlled clinical trial demonstrated the long-term efficacy and safety of intravenous immunoglobulin (IVIg) treatment in CIDP patients [9]. However, the underlying mechanism of action of IVIg in the treatment of CIDP remains unclear [10,11]. The aim of this study was to investigate the course of autoreactive T cell responses against the two peripheral myelin antigens P2 and PMP-22 in addition to the frequency of memory T cell subsets during IVIg treatment in CIDP patients [12].

In an observational trial of previously IVIg-treated patients (maintenance), previously untreated patients (treatment-naive) and controls ($n = 48$), IVIg treatment-naive patients ($n = 18$) were evaluated clinically prior to the first IVIg treatment (baseline) and at 4-week intervals after IVIg treatment initiation by using the adjusted Inflammatory Neuropathy Cause and Treatment (INCAT) disability score, the Medical Research Council (MRC) sum score and walking distance to assess the clinical status [12]. In addition, a blood sample was provided for analysis. Peripheral blood monocytes (PBMCs) were isolated from blood samples from treatment-naive patients ($n = 18$) at baseline and at follow-up (at least 6 months after IVIg treatment initiation, mean 20 months). For comparison, PBMCs were extracted from blood samples from CIDP patients ($n = 16$) receiving IVIg as a maintenance therapy (mean 33 months). Additionally, patients with non-immune neuropathy or healthy individuals acted as controls ($n = 14$). In order to quantify frequencies of interferon (IFN)-γ-producing T cells directed against the peripheral myelin antigens PMP-22 and P2 (autoreactive T cell response), cryopreserved (and subsequently thawed) PBMCs were assessed by enzyme-linked immunospot (ELISPOT) analysis. In addition, flow cytometric analysis was performed using freshly isolated PBMCs to quantify T memory subsets. Response to treatment was defined as an improvement of 2 or more points on the MRC sum score in two different muscle groups [13], an improvement of 1 point or more on INCAT disability score (except for the changes in upper limb function from 0 to 1) [9] or an improvement of the walking distance of more than 50% compared to baseline results to also cover patients with a dominant sensory atactic syndrome [12].

Baseline demographics were not significantly different between responders and non-responders, particularly with regard to sex, age, previous treatment, time since diagnosis, diagnosis or clinical severity. IVIg responders showed significantly higher autoantigen-specific T cell responses against peripheral myelin antigens PMP-22 and P2 (PMP-$22_{32–51}$ and PMP-$22_{120–133}$ as well as $P2_{14–25}$ and $P2_{61–70}$) at baseline compared to IVIg non-responders, maintenance therapy patients and controls. Maintenance therapy patients showed levels of IFN-γ responses similar to that of controls, those with other neuropathies and to non-responders. Analysing T memory compartments at baseline, IVIg responders ($n = 10$) showed increased frequencies of $CD4^+$ central memory T cells (TCM; $CD4^+45RA^-CCR7^+$) and effector/memory T cells (TEM; $CD4^+45RA^-CCR7^-$) compared to controls and to the maintenance group. In contrast, non-responders ($n = 8$) did not differ from control groups. $CD8^+$

memory T cells showed increased TEM frequencies in responders compared to non-responders and by trend to other groups. For $CD8^+$ TCM, non-responders differed significantly from other groups (maintenance and healthy control group) [12].

In order to investigate the long-term effect of IVIg on autoreactive T cell responses, treatment-naive CIDP patients were investigated longitudinally prior to treatment (baseline) and after repeated IVIg infusions (follow-up, mean 20 months). Data showed a significant reduction in IFN-γ-specific T cell responses for peripheral myelin antigens ($PMP\text{-}22_{32–51}$ and $PMP\text{-}22_{120–133}$ as well as for $P2_{61–70}$) over time in treatment responders. In contrast, treatment non-responders, who had no increased T cell response at baseline, did not differ in IFN-γ-specific T cell responses following IVIg treatment over time. Further analysis of T memory subsets found no statistical difference for $CD4^+$ T cell subsets between baseline and follow-up. In contrast, $CD8^+$ TEM were reduced significantly at follow-up [12].

Our data demonstrate that treatment with IVIg on a long-term basis reduces the autoreactive T cell response against peripheral myelin antigens which may be influenced by altered maintenance of $CD8^+$ and $CD4^+$ effector/memory T cell subsets towards a more anti-inflammatory immune status. Therefore, the assessment of such antigen-specific T cell responses may also serve as a biomarker to predict responsiveness to IVIg, warranting confirmation in a greater multi-centre cohort trial.

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