Chronic inflammatory demyelinating polyneuropathy (CIDP) denotes a spectrum of acquired, chronically progressive, or recurrent, immune-mediated disorders of the peripheral nervous system with variable pathology and pathogenesis. The estimated prevalence may be up to nine per 100,000 population. A universally accepted definition of disease does not exist. A variety of clinical and investigational criteria have been proposed and applied in attempts to include the various presentations of CIDP. Perhaps the future development of biological markers will help reliably identify patients with CIDP. The pathogenesis of CIDP is not fully understood. Cell-mediated and/or humoral immune mechanisms are involved in an attack against unidentified target antigen(s) of the myelin sheath and/or Schwann cells, at times leading also to secondary axonal injury.

The pathogenesis of CIDP is not fully understood. Cell-mediated and/or humoral immune mechanisms are involved in an attack against unidentified target antigen(s) of the myelin sheath and/or Schwann cells, at times leading also to secondary axonal injury.

Randomised controlled trials (class I evidence) showed that most (60–80%) patients respond at least to a degree to treatment with intravenous immunoglobulin (IVIG), plasmapheresis, or corticosteroids. ‘Conventional’ immunosuppressive drugs are of no proven benefit. Biological agents directed at key aspects of the CIDP immunopathogenic pathway have gained increasing attention due to the unpredictable efficacy and overall health risks of non-targeted immunosuppressive drugs. Presently, there exists insufficient clinical experience with biological therapy to allow specific treatment recommendations for CIDP. The challenge remains to identify drug-naïve or treatment-resistant CIDP patients who will most likely respond to targeted immunotherapy.

Biological therapy, CIDP, monoclonal antibodies, interferon, tumor necrosis factor alpha

Disclosure: The author has no conflicts of interest to declare.

Received: March 18, 2013 Accepted: April 22, 2013 Citation: US Neurology, 2014;10(1):38-43 DOI: 10.17925/USN.2014.10.01.38

Correspondence: Joerg-Patrick Stübgen, MB ChB, MD, Department of Neurology and Neuroscience, Weill Cornell Medical College/New York Presbyterian Hospital, 525 East 68th Street, New York NY 10065-4885, US. E: pstuebge@med.cornell.edu

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a term for a group of acquired, immune-mediated inflammatory demyelinating disorders of the peripheral nervous system. Most patients with CIDP respond to ‘first-line’ therapy with intravenous immunoglobulin (IVIG), plasmapheresis, and/or corticosteroids. ‘Conventional’ immunosuppressive drugs are of no proven benefit. Biological agents directed at key aspects of the CIDP immunopathogenic pathway have gained increasing attention due to the unpredictable efficacy and overall health risks of non-targeted immunosuppressive drugs. Presently, there exists insufficient clinical experience with biological therapy to allow specific treatment recommendations for CIDP. The challenge remains to identify drug-naïve or treatment-resistant CIDP patients who will most likely respond to targeted immunotherapy.

T-lymphocytes

Activated T-lymphocytes invade peripheral nerve and partake in the pathogenesis of CIDP. Natalizumab

Natalizumab (Tysabri®) is a monoclonal antibody (mAb) targeted at the α4 subunit of α4β1 (VLA4) and α4β7 integrins that are expressed on...
the surface of activated lymphocytes and thus blocks the \( \alpha_4 \)-mediated adhesion of lymphocytes to specific receptors (e.g., VCAM) on the luminal surface of activated vascular endothelium. Moreover, natalizumab perhaps acts in vivo by inhibiting the interaction of \( \alpha_4 \)-expressing leukocytes with corresponding ligand(s) in the extracellular matrix and on parenchymal cells, thus preventing additional recruitment and activity of stimulated immune cells.\(^{21}\) In a rat model of EAN, \( \alpha_4 \)-integrin-blockade led to apoptosis of peripheral nerve infiltrating T-lymphocytes and improvement of clinical disease.\(^{30}\) In the single literature report, a single 300 mg intravenous dose of natalizumab was ineffectual in a patient with refractive CIDP,\(^{31}\) despite demonstration of perivascular T cell activation (\( \alpha_4 \)-integrin-expression) on sural nerve biopsy and mAb attachment to target antigen on circulating T cells. Natalizumab is apparently planned for a CIDP trial,\(^{32}\) but no study is registered (www.clinicaltrials.gov). Optimum patient selection for T-cell-targeted therapy could potentially be based on the development and demonstration of indicators of T-cell activation e.g., (a) increased DR antigen expression in circulating T cells; (b) increased serum concentrations of soluble interleukin (IL)-2 and IL-2R; (c) increased concentrations of IL-6, IL-8, and IL-17, and percentage of IFN\( \gamma \)+ IL-4 T cells in cerebrospinal fluid (CSF), and (d) expression of \( \alpha_4 \) integrin on perivascular T cells.

**B-lymphocytes**

The concept of an aberrant B cell response is generally accepted as a major element in the pathogenesis of peripheral nerve immune-mediated demyelination.\(^{33,34}\)

**Rituximab**

Rituximab (Rituxan\textsuperscript{\textregistered}) is a chimeric mAb directed against the CD20 surface antigen of B cells. Rituximab (RTX) is an IgG1\( \kappa \) antibody created by attaching complementarity-determined regions of mouse anti-CD20 antibody (2B8) to human IgG1\( \kappa \) heavy-chain constant region sequences.\(^{35}\) In case reports, RTX ( Usually 4-weekly 375 mg/m\(^2\)) was offered to patients with CIDP that responded progressively less well to IVG or conventional immunosuppressants; two childhood-onset cases were described.\(^{36,37}\) CIDP variants occurred in patients with Morban syndrome and myasthenia gravis,\(^{38}\) sodium-losing nephropathy,\(^{39}\) lymphomas (Epstein-Barr virus [EBV]-associated,\(^{40}\) small lymphocytic B cell\(^{41}\) and marginal zone B cell\(^{42}\), idiopathic thrombocytopenic purpura,\(^{43}\) diabetes,\(^{44}\) Evans syndrome,\(^{45}\) or elevated anti-SGPG IgM antibody,\(^{46}\) one patient developed an IgM band (anti-disialosyl antibodies), cryoglobulins, and cold agglutinins, and fulfilled criteria for the CIDP subset, chronic ataxic neuropathy with ophthalmoplegia, M-protein, agglutinin, and anti-disialosyl antibodies (CANOMAD).\(^{47}\) Probable reporting bias of case histories selected for patients responsive to treatment. Some showed no benefit,\(^{48,49}\) or improved after transient worsening that coincided with a serum IgM flare-up.\(^{50}\) In one patient, the effect of RTX was difficult to assess because concurrent immunosuppressants were used.\(^{51}\) Explanations for the inconsistent treatment response may include: (1) possible differences in immunopathogenesis of CIDP patients with IVG-dependence versus IVG-resistance, e.g., CD20+ lymphocytes may play a variable role in different patients; (2) existence of concurrent diseases that may have confounded treatment response; (3) lack of ‘standard’ CIDP regimen so that some patients may require higher RTX doses; and (4) an undetermined element of secondary axonal damage unresponsive to treatment.

A retrospective email survey of all 105 members of the Inflammatory Neuropathy Consortium reported on the experience of 11 physicians with RTX on 20 more-or-less refractory CIDP patients.\(^{52}\) Treatment was considered beneficial (various outcome measures) in 12 of 20 patients, though two patients relapsed (one patient was re-treated). Of these 12 responsive patients, 11 suffered concomitant autoimmune or hematologic diseases. In a nationwide Italian retrospective analysis of various immunosuppressive/-modulatory drugs in 110 refractory CIDP patients,\(^{53}\) six of 18 patients responded to RTX treatment (defined as improvement by one point on the Rankin Scale). The percentage of patients responsive to RTX was similar to the other empirically chosen immune-altering drugs, so that RTX was not proven a superior treatment modality. Generally, only the presence of a serum monoclonal band predicted a less favorable therapeutic response.

A recent retrospective, observational multicenter study reported on RTX therapy (four doses of weekly 375 mg/m\(^2\)) in 13 refractory CIDP patients.\(^{31}\) Nine patients (seven patients with blood disorders) responded to treatment (i.e., improved >2 points on ‘standard’ clinical scales, or maintained improvement during ongoing IVG/plasma exchange). RTX benefit manifested after a mean of 2 months and lasted a mean of 1 year. From the above-mentioned information, it seems reasonable to consider RTX when treatment-resistant, active CIDP occurs in the context of other B cell-mediated diseases that might also respond to anti-B cell therapy. Treatment earlier in the course of disease seems to result in a better response. An unstated consensus implies that the lack of controlled trials and risk for adverse events presently preclude the generalized use of RTX in CIDP.

Conceivably, markers could provide useful information on any RTX-induced changes of B cell homeostatic regulation in patients with CIDP. For instance, measurements of serum B cell-activating factor (BAFF) proved a potential useful predictor of responsiveness after the administration of RTX to patients with anti-MAG polyneuropathy.\(^{54}\) Moreover, in treatment-naive CIDP patients, naïve B cells showed impaired expression of Fc\( \gamma \)-receptor IIb and failed to up-regulate as cells progressed to the memory compartment;\(^{55}\) this under-expression was partially restored by clinically effective IVIG treatment. Perhaps the application of Fc\( \gamma \)-RIIB expression could serve as a candidate prognostic marker for therapy directed at autoantibodies i.e., (B cells).

**B- and T-lymphocytes**

**Alemtuzumab**

Alemtuzumab (Campath 1H\textsuperscript{\textregistered}) is a recombinant humanized mAb (IgG1-\( \kappa \) isotype) directed at CD52 antigen that is present on the surface of most B- and T-lymphocytes, macrophages, and monocytes. After binding, alemtuzumab facilitates complement-dependent cytosis, antibody-dependent cellular cytotoxicity, and apoptosis.\(^{41}\) A single intravenous infusion results in rapid and marked lymphopenia. B-cell numbers return to/above normal in about 27 months, CD8+ T cells in 30 months, and CD4+ T cells in 60 months.\(^{56}\) It has been suggested that the efficacy of this mAb in autoimmune diseases rests on a rearrangement of the lymphocyte repertoire and not solely on T cell depletion. That said, CD52 expression on mononuclear cells in CIDP patients has not been specifically researched.

In a case report, alemtuzumab administration (30 mg/daily for 5 days) to a patient with IVG-dependent, relapsing CIDP induced a delayed (8 weeks), relatively long (16 months) clinical remission.\(^{57}\) It could not be established whether the clinical efficacy of alemtuzumab correlated with suppression of any particular lymphocyte subsets, because post-treatment counts...
Chronic Inflammatory Demyelinating Polyneuropathy

were too low. However, a return to normal lymphocyte levels correlated with return of neuropathy clinical activity.

In a small, multicenter, uncontrolled, retrospective study, alemtuzumab was offered to seven patients with refractory, IVIG-dependent CIDP. Patients received 1–2 infusions of alemtuzumab (12–30 mg/day; maximum 180 mg/course). Following treatment, the mean monthly IVIG requirement decreased by 26 %, and IVIG administration interval increased from a mean of 22 to 136 days. Response to treatment (or re-treatment) was inconsistent: prolonged remission was obtained in two patients; partial response was obtained in two patients; three patients showed no demonstrable benefit. Responding patients had a younger age at disease onset (teens), acute-onset illness (Guillain-Barré syndrome-like), and a shorter duration of disease (i.e., possibly less axonal injury). Secondary autoimmunity developed in three patients and may have been triggered by elevated serum IL-21 levels. In order to help improve the prediction of alemtuzumab treatment-response, any future CIDP trials should include a close study on depletion/reconstitution of lymphocyte subsets relative to clinical response. To help improve the benefit-risk ratio, it may be necessary to identify and exclude patients predisposed to autoimmunity e.g., genetically determined high levels of IL-21 secretion.

Interferons (IFNs) are extracellular protein molecules with antiviral, anti-proliferative, and immunomodulatory properties that are deemed important for maintaining homeostasis and in-host defense responses. If a molecule is capable of changing a pro-inflammatory cellular immune response (during active inflammation) into an anti-inflammatory response (during recovery), it should prove useful to treat autoimmune neuropathies; this was the logic behind the experimental use of IFNs type 1 in patients with CIDP.

Interferon-alpha

The method by which IFNα may improve CIDP theoretically rests on the complicated immunomodulating effect exerted via reduction of pro-inflammatory cytokines (e.g., IFNγ and tumor necrosis factor alpha [TNFα]) that take part in the process of inflammatory demyelination.

Case histories report on the benefit of IFNα therapy for refractory CIDP, including a 3-year-old child and a pregnant woman in an HCV-infected patient, CIDP responded well to an IFNα protocol aimed against the virus. The IFNα doses and schedules varied. Patients reported onset of improvement as soon as 2 days after the first infusion. Clinical recovery was documented as soon as 15 days after treatment onset. Nerve studies showed improved motor nerve conduction velocities and distal M-response amplitudes, and reduction of conduction blocks. Improvement persisted as long as 25 months after the last infusion. After exacerbation of CIDP, patients responded to IFNα dose increase or reintroduction, which suggested that improvement of neuropathy during IFNα therapy was not merely coincidental.

As a result of the positive experience in a single patient, an open-label, prospective, pilot study was launched to treat 16 patients with refractory CIDP with IFNα-2a (3 mU 3x/week) for 6 weeks. Nine patients improved with gains in the mean MRC and leg sensory scores, though without change of mean grip strength. Electrophysiologic measures did not improve. IFNβ1a therapy elevated baseline increased serum TNFα levels; therefore, it could not be proved that IFNβ1a exerts its immunomodulatory effects on inflammatory demyelination by down-regulating pro-inflammatory cytokines (i.e., TNFα). The limitations of this study included the unblinded, uncontrolled treatment of a small number of patients for only a relatively brief period.

Another open-label study hinted at the usefulness of IFNβ1a therapy in 12 patients with refractory CIDP. Follow-up periods ranged from 4 months to 8 years. Six patients showed marked and sustained improvement (Rankin scale). The onset of improvement was noted as soon as 2 to 4 days after initiating treatment. No improvement was measured in six other patients and further two patients with respiratory failure died. This small, uncontrolled study demonstrated a meaningful improvement in half the patients and suggested that IFNβ1a therapy could be considered a potentially effective therapeutic option for otherwise intractable CIDP. In the above-mentioned nationwide Italian retrospective analysis of various immunotherapy agents in 110 patients with refractory CIDP, four of 11 patients responded to IFNβ1a therapy. The presence of axonal injury, patient age at disease onset, and disease duration proved not to be predictors of poor therapeutic response. Based on existing information, it seems reasonable to carefully consider IFNβ1a therapy as a possible strategy in patients with CIDP who are resistant to, or intolerant of, current therapeutic strategies. IFNβ1a may newly induce or exacerbate pre-existing autoimmunity, but indicators of such a risk have not been determined; any future study must consider autoimmunity in a risk-benefit analysis.

Interferon-beta

IFN has shown success in the management of patients with multiple sclerosis. The interest in the use of IFNβ1 in CIDP patients was partly based on the apparent immune response similarities shared by this inflammatory neuropathy and multiple sclerosis, though the exact method of action in CIDP has not been established. Case histories report on the benefit of IFNβ1a therapy for refractory, relapsing-remitting and progressive pure motor CIDP improvement or stabilization of various measures was noted as early as 2 weeks after treatment onset. Patients suffered no relapses during long-term therapy (up to 40 months), regained or maintained functional independence and showed electrophysiologic improvement. Longer durations of treatment and follow-up periods were possible reasons for the observed efficacy of IFNβ1a therapy.

However, in the above-mentioned Italian nationwide retrospective analysis of the effects of various immunosuppressive drugs in 110 patients with refractory CIDP, none of three patients treated with IFNβ1a responded to therapy (defined as improvement by one point on the Rankin Scale). Open-label and randomized controlled studies also report on a less-than-impressive effect of IFNβ1a treatment in patients with refractory CIDP. In a 6-month prospective open study, four patients with refractory CIDP were treated with subcutaneous IFNβ1a (6 μg 3x/week for 1 week, then 12 μg 3x/week for 23 weeks). Overall, patients demonstrated no statistically significant benefit in the chosen primary outcome measures (Neurologic Disability Scale, a functional disability scale, timed 10-metre walk test, and the Hammersmith Motor Disability Test); electrophysiologic studies showed no improvement in summed motor responses. Yet, any potential therapeutic benefit was marred by poor prognostic indicators i.e., long-standing disease that proved refractory to other treatment and that axonal loss on electrophysiologic
Biological Agents for Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Tumor Necrosis Factor-alpha

TNF-α is a cytokine with pro-inflammatory and immune regulatory properties and thus plays significant roles in various aspects of immune system development, immune-response regulation, and T-cell-mediated tissue injury. The pathogenic role of TNF-α in the inflammatory demyelinating neuropathies was recently reviewed.

Tumor Necrosis Factor-alpha Antagonists

No individual case reports have been published on the treatment of CIDP with TNF-α antagonists. Limited available data have not proved that TNF-α is directly involved in the pathogenesis of CIDP; so that this cytokine may merely be marker of an activated immune system. A single retrospective, uncontrolled study reported on the possible efficacy of etanercept therapy in 10 patients with refractive CIDP. Patients received “standard” dose (25 mg subcutaneously twice weekly) etanercept. Significant improvement was determined in three patients and possible improvement in three patients, respectively, judged by manual muscle strength testing, sensory thresholds, and functional disabilities 4–6 months after starting treatment. Any benefit of treatment with etanercept was probably mediated by inhibition of the pro-inflammatory role of TNF-α in the pathogenesis of inflammatory demyelination neuropathies. This open-label, retrospective study has its inherent limitations and the full potential of anti-TNF-α treatment of immune-mediated neuropathies warrants further study preferably not confined only to treatment-resistant patients; however, no trials are registered. Theoretically, alteration of cytokine activity by TNF-α antagonists has a potential as an antigen-non-specific treatment approach to inflammatory demyelination of the peripheral nervous systems. Potential benefits of TNF-α blockade must be measured against drug side effects.

Complement

Data implicate complement activation in the pathogenesis of immune-mediated myelin damage. Moreover, in vitro and in vivo murine models of anti-GQ1b antibody-mediated demyelinating neuropathy showed significant neuroprotective effects by inhibiting the formation of the C5b-9 membrane attack complex.

Eculizumab

Eculizumab or hSG1.1-mAb (Soliris®) is a recombinant humanized IgG2/4 mAb that prevents cleavage of human complement component C5 and thus blocks the formation of C5b-9 and subsequent generation of pro-inflammatory molecules.

No reports on the use of this mAb in patients with CIDP exist. Of potential interest is a 14-week phase I study of eculizumab (three doses 600 mg weekly; five doses 900 mg twice-weekly) in 13 patients (10/13 with concomitant MG) with multifocal motor neuropathy. The mAb was deemed safe; there was no difference in the secondary outcome measure (IVIG dosing interval). A small treatment effect was noted in patients rated subjective scores and selected clinical and electrophysiologic measurements. To fully explore the potential of eculizumab, longer-term, placebo-controlled studies are necessary. Complement inhibition with eculizumab seems a theoretically attractive agent for therapeutic trials also in patients with CIDP because one proposed mechanism of effective IVIG treatment of CIDP includes complement binding. In an 8-month open-label study of eculizumab in patients with CD59 deficiency, primary outcome measures will assess (among other outcome measures) whether this mAb can improve the baseline neurologic deficits or reduce the relapse rate in patients with relapsing CIDP and alter the cumulative steroid and IVIG dosage before compared with after treatment (ClinicalTrials.gov identifier: NCT01579838). Provisional data are thus far unknown.

Conclusion

“Standard” randomized controlled trials are difficult to apply to CIDP because: (a) there is difficulty enrolling large patient numbers in a relatively rare disease; (b) there exists no universal agreement on disease definition; (c) CIDP may not be a single disease; (d) the natural disease course varies; (e) there exists no universal agreement on treatment outcome measures;
and (f) there is no universal agreement on the definition of therapeutic failure. Moreover, the full potential of investigational drugs will be unlikely realized if studies are restricted only to refractive patients (i.e., with indeterminate component of axonal injury), thus inadvertently creating a negative selection bias. The success rate of any future randomized controlled studies with biological agents could be potentially improved by: (a) enrolling sufficient patient numbers from multiple trial centers; (b) applying clear definitions of patient selection that are both disease specific and sensitive; (c) using validated outcome measures to establish therapeutic response; (d) ensuring studies reflect that the chronic nature of disease; (e) enrolling patients with earlier, perhaps more responsive phases of disease; and (f) developing and applying molecular biological techniques to discover ascertain biological markers that help specify appropriate targeted immunotherapy for specific CIDP patient subgroups. Finally, the viability of biological therapeutics in the modern health care environment will have to consider and apply risk–benefit and cost–benefit analyses.

Biological Agents for Chronic Inflammatory Demyelinating Polyradiculoneuropathy