CIDP: Current Treatments and Identification of Targets for Future Specific Therapeutic Intervention

Susana Brun 1, Jérôme de Sèze 2 and Sylviane Muller 1,3,4,*

1 CNRS-Strasbourg University Biotechnology and Cell Signaling UMR7242/Strasbourg Drug Discovery and Development Institute (IMS), 67000 Strasbourg, France; susanabrun@hotmail.com
2 Centre d’Investigation Clinique INSERM 1434, University Hospital of Strasbourg, and Biopathology of Myelin, Neuroprotection and Therapeutic Strategies, INSERM U1119, 67000 Strasbourg, France; jerome.deseze@chru-strasbourg.fr
3 Fédération Hospitalo-Universitaire OMICARE, Fédération de Médecine Translationnelle de Strasbourg, Strasbourg University, 67000 Strasbourg, France
4 University of Strasbourg Institute for Advanced Study (USIAS), University of Strasbourg, 67000 Strasbourg, France
* Correspondence: sylviane.muller@unistra.fr; Tel.: +33-(0)-640408725

Abstract: Chronic inflammatory demyelinating poly neuropathy (CIDP) is an acquired immune-mediated inflammatory disorder of the peripheral nervous system. This clinically heterogeneous neurological disorder is closely related to Guillain–Barré syndrome and is considered the chronic counterpart of that acute disease. Currently available treatments are mostly empirical; they include corticosteroids, intravenous immunoglobulins, plasma exchange and chronic immunosuppressive agents, either alone or in combination. Recent advances in the understanding of the underlying pathogenic mechanisms in CIDP have brought a number of novel ways of possible intervention for use in CIDP. This review summarizes selected pre-clinical and clinical findings, highlights the importance of using adapted animal models to evaluate the efficacy of novel treatments, and proposes the outlines of future directions to ameliorate the conditions of patients with CIDP.

Keywords: chronic inflammatory demyelinating polyneuropathy; peripheral nerves; pathogenesis; pathology; mechanisms; autophagy; treatments; intravenous immunoglobulin; animal models; experimental autoimmune neuritis

1. Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune-mediated inflammatory disease affecting the peripheral nerves and the nerve roots. This disorder is characterized by damage to the myelin sheath (the fatty covering that wraps around and protects nerve fibres) of the peripheral nerves and by immune infiltrates. The disorder causes progressive motor and sensory deficits that manifest as proximal and distal muscle weakness, numbness, paraesthesia, sensory ataxia, and often severe disability, which hallmark severe demyelination and secondary axonal loss of peripheral nerves [1] (Figure 1). CIDP has a slow onset with continued progression over more than two months and typically evolves as a relapsing, progressive or monophasic disorder.

CIDP presents prevalence rates that vary in different geographical regions, ranging from 0.8 to 8.9 cases per 100,000 persons [2–9]. The reasons for this apparent heterogeneity may be multiple, linked to genetic and environmental effects, and to diagnostic criteria that are applied. Onset may occur at any age but is more common in middle age (40–60 years) and twice as frequently in men than women.

The pathogenesis of CIDP remains largely unknown. Immuno-mediated inflammatory mechanisms have been recently postulated, with a pivotal involvement of macrophages and proteases, they secrete oxygen reactive species, cytokines, and T lymphocytes. The
implication of autoantibodies has also been proposed. Effectively, CIDP can follow various infections, including *Campylobacter jejuni*, which is, however, more frequently associated with Guillain–Barré syndrome (GBS), an inflammatory neuropathy sharing major features with CIDP [10–12]. Recent studies have demonstrated molecular similarity between a component of *Campylobacter jejuni* and GM1, one of the targets of the autoantibodies found in patients, suggesting a role of molecular mimicry by foreign epitopes in the pathogenesis of the disease [13–15]. The deposition of autoantibodies at peripheral nerve components could trigger the phagocytosis of myelin by macrophages via the recognition of immunoglobulin (Ig) fragment crystallizable receptor (FcR), for example, leading to the activation of complement cascade and resulting axonal damages [16–18]. Antibodies to LM1, a ganglioside localized in peripheral nerve myelin, and LM1-containing ganglioside complexes [19], or pathogenic IgG4 autoantibodies to nodal or paranodal junction proteins, such as neurofascin 155 and 186, gliomedin, and contactin 1 [17,20,21], have been described in CIDP. However, their low prevalence, in a minority only of patients with CIDP, precludes them from being considered as possible biomarkers and does not permit to elaborate pathophysiological consideration based on the antigens they target.

![Diagram of common manifestations in CIDP patients](image)

**Figure 1.** Common manifestations present in patients with CIDP.

### 2. Prognosis

The course of CIDP varies widely among individuals. The progression of CIDP can be subdivided into three principal categories even if other subcategories exist. The first category called “monophasic” is characterized for having a single bout of CIDP lasting for several months or years followed by spontaneous recovery. The second category called “chronic relapsing” is characterized for having many bouts in which symptoms continue to progress and worsen followed by a partial spontaneous improvement or remissions between relapses. This is the most common form of the disease with about two thirds of diagnosed patients. The last category called “chronic progressive” is characterized by constant worsening without improvement.

After a flare-up, mainly for the “chronic relapsing” form, some patients are left with some discomfort, weakness and residual numbness even if complete remission have also
been reported [22,23]. Although rarely observed, a disease that continues to progress and severe disability can occur [24].

It is known that several factors can impact the prognosis for CIDP, such as age at onset, clinical features, progression time, and initial response to treatment [24,25].

3. Current Treatments

The first-line treatments for CIDP includes corticosteroids, plasmapheresis (plasma exchange-PE) and intravenous Ig (IVIg). Randomized controlled studies have demonstrated that all these treatments have a similar level of clinical efficacy [26–31]; they differ however, in terms of cost, availability, and adverse effects (AEs). The main goal of these treatments is to reduce or suppress clinical symptoms by modulating or suppressing the immune system and it has been shown that 60–80% of patients that are treated with one of these standard treatments have improvements in their condition [26]. Physiotherapy treatment is also recommended to improve muscle strength and minimize muscle wasting even though evidence supporting this therapy is limited [32,33].

Corticosteroids such as prednisone, prednisolone, dexamethasone, and methylprednisolone, have demonstrated their efficacy when administered alone [34]. They are usually given initially in high daily doses to produce a rapid response, followed by decreasing over time to low dose daily to sustain remission [35]. However, it is known that high doses of corticosteroids or a long-term therapy are often accompanied by a large number of potentially serious AEs (SAEs) [36]. To overcome this problem, combined therapies with PE, IVIg or immunosuppressive drugs can be implemented, but this needs to be assessed [37–39].

Therapeutic PE is a process in which the liquid part of the whole blood from a patient (that is, the plasma which is supposed to contain the substances causing the disease such as antibodies, cytokines, and complement) is separated from the other components of the blood extra-corporeally. The plasma is then replaced by another fluid and re-infused back to the subject. Two controlled trials have demonstrated the efficiency of PE in CIDP [40]. In a limited comparison of cases, this strategy has been found superior to Ig immunoadsorption [41]. PE therapy is often used in the treatment of IVIg or corticosteroids-refractory patients as rescue therapy during exacerbations of CIDP or as a useful alternative for patients unable to receive any of the other first-line treatments due to contraindications or AE risk. The protocol is adapted according to the initial clinical response (favourable in two out of three cases) and relapses during withdrawal/weaning. The limits of this treatment are its high cost and the need to specialized centres. PE may cause AEs; in general, they are minor and resolved quickly, such as allergic reaction, nausea and vomiting, electrolyte imbalance, anemia, muscle cramps, and fatigue. The use of PE should be disregarded in CIDP patients with autonomic instability as the large shifts in fluids can induce hypotensive effects [12].

The last treatment introduced as a first-line treatment for CIDP was IVIg. IVIg is a mixture of normal polyclonal IgG extracted from thousands of healthy humans (typically containing more than 95% of unmodified IgG and only trace amounts of IgA or IgM). A variety of different mechanisms is thought to be responsible for the immunomodulatory effect of IVIgs, including neutralization of autoantibodies, inhibition, and abrogation of activated complement, alteration of FcR expression and redressing altered cytokine patterns [42,43] (Figure 2).

IVIgs have been shown to be effective in placebo-controlled studies with an estimated responder rate of nearly 80% [44–46]. Treating patients with IVIG showed short and also long-term benefit in patients with CIDP [47]. For 15% of these patients, one or two sessions of IVIg, one month apart, is sufficient to induce and maintain a stable remission. For the others, long-term treatment remains necessary to establish a normal or at least stable functional status. For non-responder patients, the priority is to re-evaluate the diagnosis before considering other treatments. The efficacy of IVIg has also been demonstrated in GBS [48,49]. Although the mechanisms of action of IVIg remain complex, the serum level of
IVLgs seems to be a good marker to follow the efficacy of this treatment in CIDP. In fact, for each patient, there is a serum threshold above which the therapeutic response appears and below which the patient relapses [50]. IVLgs are generally well tolerated and only minor AEs, such as headaches, flushing, fever, fatigue, chills, and diarrhea, are observed, which can be easily managed [51]. However, certain precautions should be taken in order to avoid the late and rare more serious side effects such as acute renal failure, thrombotic events and haemolysis.

Subcutaneous immunoglobulin (SCIg) was recently approved as a maintenance treatment for adult patients with CIDP [52]. The efficacy, safety and tolerability of SCIg seems to be preferred over IVIg with a better quality of life for some patients [53,54]. In term of efficacy, strength and motor functions remained stable or even improved during at least 7 years (the study time of a recent long-term follow-up) with benefits on walking capability and resistance, manual activity performances, and fatigue reduction [46].

CIDP is a heterogeneous disease with typical and various atypical variants characterized by a certain diversity in their clinical, pathological and electrophysiological features, and often in their different response to treatment and long-term prognosis. There are no good biomarkers to follow the course of the disease, but autoantibodies against nodal and paranodal proteins mentioned above have been associated with unique clinical phenotypes and poor response to IVIG treatment, for example [55–57]. Thus, especially in CIDP, it is central to consider these individual variabilities and develop personalized therapy for affected patients. Nowadays, precision medicine is becoming more common in the management of diseases. It takes into account the individual characteristics of each patient to tailor therapeutic strategies that are applied (right treatment, personalized timing of drug administration) to maximize drug efficacy, and if possible, reduce AEs [58–60]. In this context, the development of alternative strategies is of prime interest.

**Figure 2.** Immunomodulating effects of IVIg. Abbreviations: DC, dendritic cells; FcR, fragment crystallizable receptor; Mo, macrophages; NK, natural killer; PBMCs, peripheral blood mononuclear cells.
4. Animal Models

The use of animal models is essential to study CIDP in an attempt to understand its etiology and develop novel therapeutic strategies.

Experimental autoimmune neuritis (EAN) is the more used animal model of demyelinating peripheral neuropathies, mainly GBS and CIDP [21,61]. EAN can be induced in different species and in various animal strains by active immunization with peripheral nerve constituents. EAN has been induced in rabbits [62], mice [63–65], rats [66], and guinea pigs [67–69]. Various antigens related to the peripheral nervous system have been used, including peripheral nerve homogenate, P0, P2, or PMP22 protein, and synthetic peptides of the proteins mentioned above [63,70–73]. However, all these models, even if used to study CIDP, develop a pathology closely resembling that of acute inflammatory demyelinating polyneuropathy (AIDP), the most common form of GBS in western countries.

Tremendous progress has been made in the development and validation of rodent models mimicking human CIDP (Table 1). The first chronic EAN models were developed in guinea pigs [74], rabbits [75], mice [76], and dark Agouti rats [77]. However, none of these models are in common use. Spontaneous autoimmune polyneuropathy (SAP) in B7-2-deficient non-obese diabetic (NOD) mice has some similarities to the human disease and represents one model of CIDP: the mice are protected from diabetes, and all the female exhibit limb paralysis with histologic and electrophysiologic evidence of severe demyelination in the peripheral nerves without spontaneous recovery [78]. Although the SAP model has provided some important information about potential immunopathogenic mechanisms of CIDP [79,80], one drawback for its use in translational therapy strategies studies is its late onset (20 weeks) and slow progression.

Table 1. Experimental autoimmune neuritis models used to study CIDP.

| Animals                        | Antigen            | Model of Disease | Ref.  |
|--------------------------------|--------------------|------------------|-------|
| Adult guinea pigs              | MBP                | Acute            | [67]  |
| Rabbits                        | Sciatic nerve tissue| Acute            | [62]  |
| C57BL6 mice                    | P0(180–199)        | Acute            | [63,64]|
| C57BL6 mice                    | P0(106–125)        | Acute            | [70]  |
| SJL mice                       | P2 protein         | Acute            | [71]  |
| SJL mice                       | BPNM               | Acute            | [65]  |
| Lewis rats                     | P2(53–78)          | Acute            | [72]  |
| Lewis rats                     | P0(180–199)        | Acute            | [66]  |
| Lewis rats                     | PMP22              | Acute            | [73]  |
| Juvenile guinea pigs           | BPN homogenate     | Chronic          | [74]  |
| Rabbits                        | BPNM               | Chronic          | [75]  |
| Heterozygous KO (P0+/+) mice   | Inherited          | Chronic          | [76]  |
| Dark Agouti rats               | BPNM               | Chronic          | [77]  |
| B7-2 KO NOD mice               | Spontaneous        | Chronic          | [78]  |
| Lewis rats                     | S-palm P0(180–199) | Chronic          | [81]  |

MBP: myelin basic protein; BPN: bovine peripheral nerve; BPNM: bovine peripheral nerve myelin; P0: protein zero; P2: protein two; PMP22: peripheral myelin protein-22; KO: knockout; NOD: non-obese diabetic; S palm P0(180–199): P0(180–199) peptide thiopalmitoylated at cysteine residue 181.

We recently developed a new model of chronic EAN (c-EAN) that can be easily and reliably induced by active immunization of Lewis rats with the P0(180–199) peptide thiopalmitoylated at cysteine 181 [81,82] (Figure 3). In contrast to the classical acute monophasic EAN induced by P0(180–199) and mimicking GBS, 100% of rats immunized with the thiopalmitoylated P0(180–199) peptide develop an ongoing neuropathy, either
chronic or relapsing, that fulfills electrophysiological criteria of demyelination with axonal degeneration, confirmed by immunohistopathology. Interestingly, the late phase of the chronic disease is characterized by accumulation of interleukin-17+ (IL-17+) cells, macrophages, and T cells in sciatic nerves and by high IL-17 levels in the serum. This c-EAN model bears considerable similarity to CIDP and has proven useful in investigating new therapeutic strategies [83,84]. Furthermore, experiments performed in this rat model revealed hitherto unknown molecular alterations of autophagy occurring in sick animals, in both, immune and non-immune compartments [83,85,86].

Figure 3. Clinical scores in the c-EAN rat model mimicking CIDP. (a) Visualization of clinical scores from male Lewis rat aged nine weeks: (Left) Rat immunized with CFA and not developing clinical sign (clinical score of 0), (Right) Rat immunized with S-palm P0(180–199) peptide plus CFA and developing CIDP (clinical score of 3) (From [86]). (b) Clinical course of EAN and c-EAN in Lewis rats immunized with P0(180–199)/CFA (○), S-palm P0(180–199)/CFA (■) or CFA as control (△). Mean values and SEM are indicated (From [81]). Abbreviations: c-EAN, chronic experimental autoimmune neuritis; CIDP, chronic inflammatory demyelinating polyneuropathy; CFA, complete Freund’s adjuvant. n, number of rats included in the study.

5. Novel Therapeutic Options

As highlighted above, the current treatments applied to patients with CIDP show some limitations due to their cost, the difficulty to determine a correct therapeutic window to balance efficacy with AEs in the case of corticoids and immunosuppressive agents [87], the inherent heterogeneity of the disease and the fact that some patients are refractory to common medication or become non-responder with time. There is therefore a tremendous unmet need in drug development in CIDP.

CIDP is considered as a rare disease and novel immunotherapies are proposed either in using new approaches with original compounds or by repurposing existing drugs, a strategy that is less demanding in terms of cost and clinical trial time [88]. Some selected examples are described below.
5.1. IVIG and SCIg

New developments based on IVIg or SCIg are still in progress. Essentially, they concern the purity of preparation to eliminate all side compounds present in the origin blood (especially IgA and others). Among the IVIg products available, there are numerous differences in product-specific formulations and features, including clinical tolerability, volume load, osmolality, sodium content, sugar content, pH, and IgA content. Many efforts are focused on the quality of preparations. A higher incidence of thromboembolic complications has been associated with formulations with high sodium content. A high sugar concentration was associated to renal failure or insufficiency [89]. Hizentra (CSL Behring, Bern, Switzerland), which is the world’s most prescribed SCIg for primary immunodeficiency (PI), has a proven track record of safety, efficacy, and tolerability. It was first approved by the U.S. FDA for treating patients with PI (March 2010) and more recently for CIDP (March 2018) to prevent relapse of neuromuscular disability and impairment. A large trial including patients with CIDP showed that this product was efficacious and well tolerated [52]. Other preparations are known under the name Octagam, Tegeline, Privigen, or Clairyg, for example.

The ADVANCE-CIDPTM 1 study (NCT02955355), which is sponsored by Baxalta (a subsidiary of Takeda Pharmaceutical Company, Tokyo, Japan), is an open phase IIIb clinical trial mounted to assess the long-term safety, tolerability, and immunogenicity of the subcutaneous treatment with SCIg facilitated with recombinant human hyaluronidase (HYQVIA/HyQvia) in CIDP participants who have completed Baxalta Clinical Study Protocol 161403 Epoch 1 without CIDP worsening. It assesses if the investigational medication could help to prevent muscle weakness in the upper and lower limbs. The investigational medication is given as an infusion under the skin every 2, 3, or 4 weeks. The estimated study completion date is in September 2023.

5.2. B Cell-Targeted Strategies

In the case of CIDP, depleting antibody-producing cells have not shown long-term beneficial effects. For example, strategies based on anti-CD20 monoclonals (ofatumumab, ublituximab, obinutuzumab, and rituximab’s humanized version, ocrelizumab) were shown efficient in certain cases but at discontinuation, relapses generally occur indicating that immune checkpoints were not restored by the treatment and that B cells reoccur. Larger randomized clinical trials with long-term follow up would be required, especially in refractory patients to other treatments or in patients who develop anti-drug antibodies (ADA) [90,91].

5.3. T Cell-Targeted Strategies

Non-antibody mediated effects are present in CIDP, especially in the T cell compartment. Specific strategies include several immunotherapies that target Th17 cells and regulatory T cells (Treg). Experimental treatment with atorvastatin/Lipitor (an oral drug that is effective in lowering triglycerides) and fingolimod/FTY720 (a sphingosine-1-phosphate receptor modulator sold as Gilenya to treat the relapsing form of multiple sclerosis) reduced accumulation of IL-17-secreting cells in the peripheral nervous system of treated animals and ameliorated neuritis [92,93]. In c-EAN rats, FTY720 decreased the severity and abolished the chronicity of the disease. It reversed electrophysiological and histological anomalies, suggesting that myelinated fibers were subsequently preserved. It significantly reduced circulating pro-inflammatory cytokines [84]. IL-17, IL-6 (which induces IL-17), and IL-2 (that is required for Treg proliferation, survival, and activity) representing privileged targets in novel strategies.

Another strategy targeting cellular adhesion and T-cell migration with Natalizumab (brand name Tysabri, among others) was evaluated in a few CIDP patients after a failure of the validated treatments [94]. A long-term improvement in one patient, a dramatic improvement over a significant duration in another patient, and stabilization in the last patient were observed, leading authors to conclude that Natalizumab could be a second-line treatment.
for individual patients with a high dependency on waning efficacy of first-line therapies. In animal models, fibronectin connecting segment-1 (FNCS1) inhibited CIDP leukocyte trafficking at the human blood–nerve barrier (BNB) in vitro. FNCS1 peptide treatment resulted in significant improvements in disease severity, motor electrophysiological parameters of demyelination, and histological measures of inflammatory demyelination [95]. FNCS1 is an alternatively spliced fibronectin variant expressed by microvascular endothelial cells at sites of inflammation in vitro and in situ; it is a counter-ligand for leukocyte α4 integrin (also known as CD49d) implicated in pathogenic leukocyte trafficking. To the best of our knowledge, this compound is not being evaluated in the current clinical trials for CIDP. Other key molecules involved in leukocytes trafficking across the BNB are promising targets. They are difficult to investigate experimentally because no animal model really allows investigating trafficking of leukocytes at the BNB in real time [61]. Molecules such as selectins, chemokines (and their receptors), adhesion molecules and integrins might be exploited with success if adverse effects (AEs) do not hamper their clinical utility.

5.4. Ig-Targeted Strategies

The most recent developments in patients include Rozanoliximab or UCB7665 from UCB (ClinicalTrials.gov Identifier: NCT03861481) and Efgartigimod or ARGX-113 from Argex (NCT04281472). Rozanoliximab, an anti-neonatal Fc receptor humanized monoclonal antibody, has also been evaluated in patients with generalized myasthenia gravis (MG). In these patients, it was well-tolerated, but did not significantly improve the quantitative MG score [96]. Efgartigimod has been shown to display clear therapeutic effects in a mouse model of MG [97]. Following encouraging data generated in healthy volunteers [98], a phase 2 clinical trial to investigate the efficacy, safety, and tolerability of Efgartigimod in adult patients with CIDP has been launched. The results of these clinical investigations in CIDP are eagerly awaited.

5.5. Complement-Targeted Strategies

Several clinical studies that target the complement pathways are under way. Complement inhibitors and modulators have been shown to ameliorate axonal injury in murine GBS models. The monoclonal antibody Eculizumab which is directed against human component C5 was effective in a murine model for Miller Fisher syndrome, a variant of GBS and appeared to be partially efficacious in a patient with severe GBS [99]. Eculizumab is being investigated in patients with GBS in Japan (NCT04752566) and in a monocentric study in Scotland (NCT02029378). Japanese study is a phase 3, prospective, multicenter, placebo controlled, randomized study to investigate the efficacy and safety of Eculizumab in participants with severe GBS, defined using the Hughes Functional Grade (FG) scale as progressively deteriorating FG3 or FG4/FG5 within 2 weeks from onset of weakness due to GBS. We are not aware of current clinical trial in CIDP.

A phase 2, multicenter, open-label, proof-of-concept study evaluating the efficacy, safety, and tolerability of BIVV020 in adults with CIDP has also been recently launched (NCT04658472). BIVV020 is a complement C1s inhibitor. The study consists of two parts: an initial 24-week treatment period (Part A), followed by an optional extension period providing up to 52 additional weeks of treatment (Part B). In this trial sponsored by Sanofi, three subpopulations of CIDP patients are followed in part 1, namely standard of care (SOC)-treated, SOC-refractory, and SOC-naïve.

5.6. Antigen-Presenting Cells (APCs) and Autophagy-Targeted Strategies

In EAN, Quinpramine, a chimeric compound derived from the tricyclic antidepressant Imipramine and Quinacrine used for malaria ameliorated the clinical and histological severity with reduced immune cell infiltration and inflammatory myelin destruction in the PNS. Ex vivo in cell culture studies, Quinpramine showed effects on APCs by reducing the expression of MHC class II molecules at their surface, which lowered autoimmune cell activation [100].
Interestingly, a peptide known as P140, which is issued from the ribonucleoprotein U1-70K, also decreases expression of MHC-II molecules expressed at the surface of mouse and human B cell APCs in lupus [101–105]. P140 has been shown to be efficient in lupus (both in lupus-prone mice and lupus patients [106,107]) as well as in various murine models of inflammation, including primary and secondary Sjögren’s syndrome [104,108], chronic house dust mite-induced airway inflammation [109], and CIDP [83]. In the same way as Quinpramine, the P140 mechanism of action involves reducing the hyperactivation of autoreactive T-cells via its effect on MHC-self peptide presentation to the receptor of autoreactive T cells. In lupus, P140 has therefore the unparalleled capacity to modulate the overstimulated immune response at an upstream level with downstream effects in the immune cascade that is governed by autoreactive T cells, namely the sustain of autoreactive B cells, the differentiation of the latter into plasma cells and finally, the production of pathogenic antibodies with deleterious effects in the tissues where they deposit. In the case of P140, this impressive effect was seen to occur via autophagy regulation [101–103,110]. Dysregulation of autophagy has been observed in a number of pathologies, including cancer, pulmonary, metabolic, and neurodegenerative diseases, as well as immune-mediated diseases and senescence. In particular, we and others have shown that there are many defects that alter the autophagy process in inflammatory and autoimmune diseases [111–116]. Our previous findings in experimental CIDP showing defects of autophagy were novel and corroborated other results [117,118]. Several autophagy pathways are impacted in autoinflammatory diseases, especially macroautophagy, chaperone-mediated autophagy and mitophagy. In experimental CIDP, several markers of autophagy were abnormally expressed in sciatic nerves, especially MAP1LC3B, SQSTM1/p62, and LAMP2A, and P140 treatment corrected these alterations [83]. Of importance, P140 has no effect on cells that display a normally balanced autophagy activity. Apparently, it corrects alarming immune cells only, in which autophagy is hyperactivated, therefore acting rather as a selective immunomodulator and not as a global immunosuppressant. This peptide presented no safety concerns in the hundreds of patients included in phase 2 clinical trials that were completed for lupus [107]. As autophagy failures have been observed in the c-EAN rat model, we have developed [82,86] and that P140 efficacy at diminishing clinical symptoms was demonstrated [83], a repositioning of P140 in CIDP may constitute a potential future therapeutic option in this indication.

6. Conclusions

Chronic (and acute) inflammatory demyelinating polyneuropathy, CIDP and AIDP, are extremely complex autoimmune disorders, characterized by patient-to-patient heterogeneity, lack of valuable biological markers of diagnostic and evolution, and a poor knowledge of etiologic elements [9,119]. Animal models have greatly enhanced our understanding of some cellular and molecular mechanisms that occur in CIDP but at this stage, we have to recognize that the pathogenesis of CIDP remains elusive despite several decades of dedicated research. No novel treatments of CIDP have been developed in over 30 years. Several studies have, however, been carried out in the last few years that might contribute to the development of a new family of personalized, targeted treatments. The new options being considered are rather mechanism-driven and not merely disease-modifying strategies that reduce (for a while) the severity of symptoms. This aspect is crucial because CIDP is a typical example of an indication that cannot be considered as a single disease but rather as a group of diseases; even if the clinical signs are similar, the elements of pathogenesis are variable and therefore, therapy must also be variable. This observation encourages us to invest much more in the identification of underlying molecular and cellular mechanisms that occur in CIDP (and closely related diseases), to create more suitable tools able to ameliorate the quality of life of patients with CIDP and possibly halt the development of their disease.
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