International Journal of Pharmacological Research
ISSN: 2277-3312 (Online)
Journal DOI: https://doi.org/10.7439/ijpr **Review Article**

Immunotherapy on Neurodegenerative Diseases: Mini Review

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Abstract

Neurodegenerative disease is a range of conditions which primarily affect the neurons in the human brain. Neurons are the building blocks of the nervous system which includes the brain and spinal cord. Neurodegenerative diseases are incurable and debilitating conditions that result in progressive degeneration and / or death of nerve cells. This causes problems with movement or mental functioning. Neurodegenerative diseases (NDs) have a serious impact on global health with no effective treatments available to date. Vaccination has been proposed as a therapeutic approach for NDs, and clinical evaluations of some candidates for Alzheimer's disease and multiple sclerosis are ongoing. Moreover, monoclonal antibodies for passive immunotherapy are under evaluation for Common Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Prion disease, Motor neurone disease (MND). Neurodegenerative diseases affect millions of people worldwide. Alzheimer's disease and Parkinson's disease are the most common types, with more than five million Americans living with Alzheimer's disease, and at least 500,000 Americans living with Parkinson's disease, although some estimates are much higher.

Keywords: Alzheimer's disease, pathophysiology, Immunotherapy.

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***Article History:**
Received: 11/08/2019
Revised: 28/11/2019
Accepted: 29/11/2019
DOI: https://doi.org/10.7439/ijpr.v9i11.5340

QR Code

How to cite: Danao K, Jatwe K. and Mahajan U. Immunotherapy on Neurodegenerative Diseases: Mini Review. *International Journal of Pharmacological Research* 2019; 09(11): e5340. Doi: 10.7439/ijpr.v09i11.5340 Available from: https://ssjournals.com/index.php/ijpr/article/view/5340

1. Introduction

The lack of disease-modifying treatments for neurodegenerative diseases explains the need for developing new therapies that target the molecular origins of the pathology [1]. Interestingly, many of these neurodegenerative diseases are accompanied with an abnormal accumulation of soluble proteins in insoluble intracellular or extracellular aggregates [2], and it is yet to be determined whether the toxicity resides in the insoluble aggregates and/or their soluble oligomeric precursors [3]. A new era in development of immunotherapies for the clearance of these aggregates and oligomers, as these are critical factor in the neurodegeneration pathways [4].

Initially, immunotherapeutic approaches for neurodegenerative disorders were focused on targeting and clearing extracellular protein aggregates, the most relevant example being amyloid beta (Aβ) peptide accumulation in Alzheimer's disease [4,5]. However, intracellular accumulation of toxic proteins, a hallmark of numerous neurodegenerative diseases [6], is currently in the spotlight for the development of new immunotherapies after the discovery that these aggregates are accumulate in the plasma membrane and secreted to the extracellular environment [7]. Such is the case of α-synuclein (α-syn), tau, prion protein (PrP) and huntingtin, for which immunotherapeutic approaches are being developed for the clearance of aggregates and reversal of cognitive deficits associated with their accumulation [8]. Accordingly, immunotherapy might represent a plausible strategy for the management of several neurodegenerative disorders, specifically targeting membrane-bound or extracellular forms of aggregation-prone proteins [9].

Neurodegenerative disorders such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), prion's disease and Motor neuron disease (MND) are characterized by the deposition and aggregation

of different but misfolded proteins or peptides in the central nervous system [10]. Accumulation of insoluble filamentous aggregates of physiologically soluble proteins such as β-amyloid, tau, α- synuclein, protease-resistant prions, huntingtin, ataxin constitute the major aggregation products deposited in the aged central nervous system [11]. Recently, active and passive immunization approaches have been applied to neurodegenerative disorders which resulted in a quick and effective clearance or prevention of those deposits in the CNS [12].

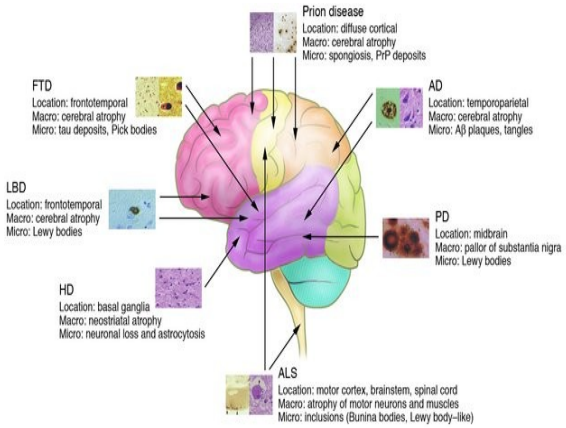

Figure 1: Types of Neurodegenerative Diseases with location

Neurodegenerative diseases include some processes whose pathogeneses present as the onset of conformational changes in certain proteins, without altering their biochemical composition (misfolded proteins), changes that are transmitted by a prion-like mechanism to normal cell proteins, thus spreading the disease's pathological alterations [13]. Alzheimer's disease (AD) is found among these proteinopathies, affecting around 20 million people worldwide, as well as Parkinson's disease (PD), with 6 million cases.

Neither disease has an effective treatment nor do they pose a significant burden for healthcare, both economically and socially. The outcomes of the action of specific monoclonal antibodies which could dissolve the aggregates of pathological amyloid peptide in vitro, considered the cause of the alterations observed in AD, as well as impede the formation of new aggregates, the possibility of acting specifically on certain neurodegenerative diseases has been contemplated, using antibodies that could recognise and neutralise the abnormal proteins [14]. In recent years, this possibility has led to several vaccine trials with the goal of stimulating the production of antibodies with the ability to act on the proteins causing the pathological alterations, that is, immunotherapy aimed at decreasing the modified protein load [15]. The trials are generally based on stimulating B cells, T cells and the immune response by activating the phagocytic capacity of the microglia [15,16].

AD is a complex and chronic neurodegenerative disease characterized clinically by a progressive deterioration of memory [17]. Pathologically, it is defined by the deposition of extracellular Aβ as senile neuritic plaque as well as intracellular hyperphosphorylated fibrillar tau accumulation in the form of NFTs [18]. Some of the known environmental risk factors for LOAD include level of physical activity, educational status, diabetes mellitus, hypertension, and head injury [19].

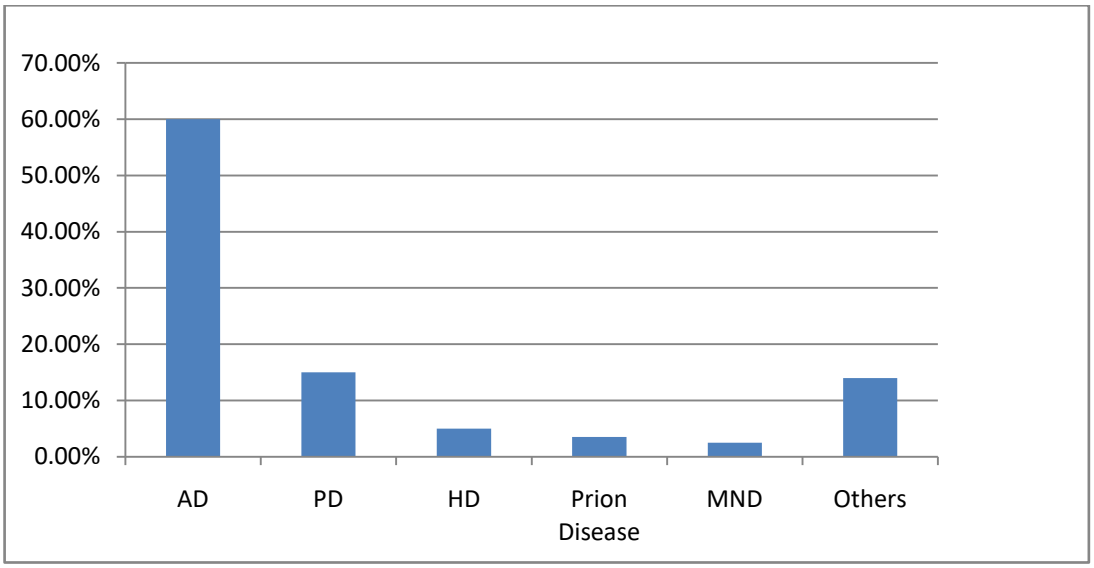

Figure 2: Percent Population of Neurodegenerative Diseases

The percent of world population are affected from the neurodegenerative diseases shown in figure 2. Lewy body diseases (LBD) are one of the most common pathologic types of dementia in the elderly, following AD and vascular dementia. LBD are a heterogeneous group of diseases characterized by motor and cognitive impairments [20], and the presence of intraneuronal eosinophilic cytoplasmic inclusions called Lewy bodies (LBs). The primary structural component of LBs is the protein α-synuclein (α-syn) [21, 22].

Huntington disease (HD) is a genetic autosomal dominant neurodegenerative condition caused by a CAG trinucleotide expansion in axon 1 of the huntingtin gene [23]. The clinical disease typically presents in a variable combination of a complex movement disorder, cognitive problems predominantly of the dysexecutive type and behavioural problems ranging from apathy, irritability to depression [24]. There is no cure for HD, and the disease progresses relentlessly with an expected survival of 15-20 years after the initial symptom presentation [25]. Variations in the clinical presentation of HD include Juvenile HD with onset before age 21 and a distinct clinical phenotype and late-onset HD after age 60.

This prion-like propagation is the principal molecular mechanism of these major neurodegenerative diseases with amyloid-like abnormal protein pathologies, and can account for the degeneration of subsets of neurons, the diverse but characteristic pathologies, and the disease progression [26]. Therefore, regulation of the propagation of abnormal proteins is an important goal for disease-modifying therapy of these major neurodegenerative disorders [27].

Motor neuron diseases are a heterogeneous group of disorders characterized pathologically by death of motor neuron cells [28]. They can be sporadic or genetic and are classified clinically according to whether they involve upper or lower motor neurons, or both [29]. Upper motor neuron involvement leads to positive neurological features including spasticity, brisk reflexes, clonus, and extensor plantar responses, as well as negative features such as weakness and loss of dexterity [30]. Spasticity is defined as the velocity-dependent increase in muscle tone as assessed by passive movement of the limbs [31].

2. Pathogenesis & Immunotherapy of Common Neurodegenerative Diseases

A. Alzheimer's disease (AD)

From Fig.2, showing (1-5) misfolded β amyloid proteins (1) APP undergoes normal cleavage by β and γ-secretase to produce the (2) normal soluble Aβ. Soluble Aβ can undergo a conformational change to (3) a β sheet-rich conformer that further aggregates to form (4) soluble, toxic Aβ oligomers. These also may precipitate to form (5) relatively inert fibrils in amyloid plaques and congophilic amyloid angiopathy [32].

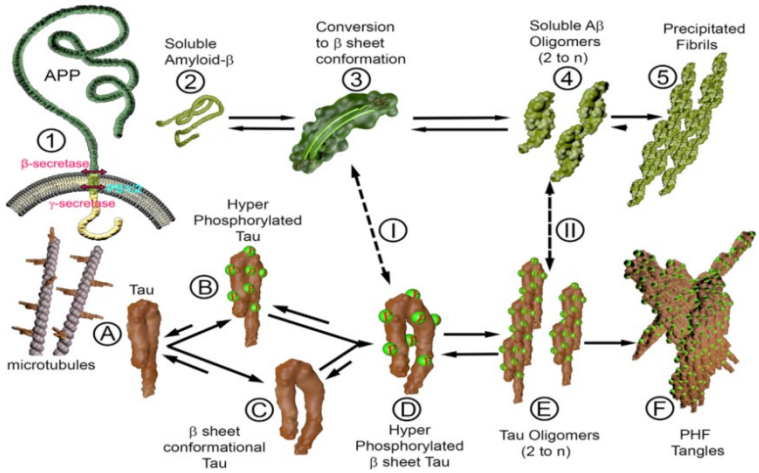

Figure 2: Ab and Tau Conformational Changes in AD

Also from, Fig.2 showing (A–F) misfolded Tau Protein(A) Tau is a microtubule-binding protein. Tau can undergo (B) hyperphosphorylation or (C) a conformational change to a β sheet conformer. These species can both further change to (D) hyperphosphorylated tau in a β sheet-rich form that is predisposed to further aggregation into (E) toxic, tau oligomers. These can precipitate to form (F) PHFs in the form of NFTs. (I and II) The Aβ , β sheet conformers and Aβ oligomers may cross-seed, under some circumstances, with intermediate tau species in a β sheet conformation and with tau oligomers, to synergistically exacerbate AD pathology. The most effective immunotherapeutic approaches for AD will need to be able to concurrently reduce levels of the toxic Ab and tau oligomeric species.

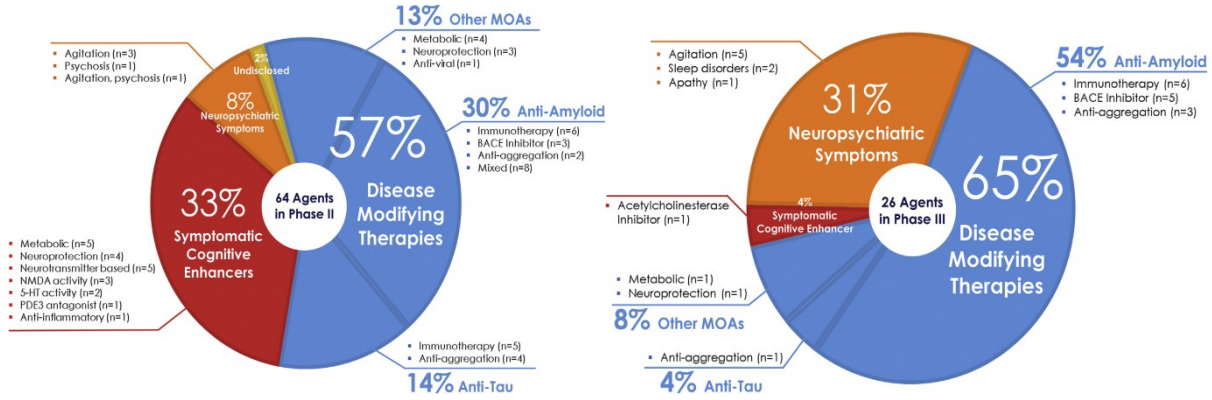

Figure 3: Mechanisms of action of Antialzheimer's Agents in phase II & III Immunotherapy (Diana *et al*., 2013).

1. Active: AN1792, Affitope AD02, ACC001, CAD106, ACI-24
2. Passive: Bapizumab, Solanezumab, Gantenerumab, Crenezumab, IVIG

B. Parkinson's disease (PD)

LBD include dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD) and idiopathic PD, all of which are characterized by specific patterns of neurodegeneration associated with the accumulation of α-syn. Which results in the death of dopaminergic neurons in the substantia nigra, while in DLB and PDD additional degeneration of cholinergic neurons in the basal forebrain is also observed [33]. PD involves grey matter loss in frontal areas, while in PDD and DLB this loss extends to temporal, occipital and subcortical areas, accompanied by significant occipital atrophy when compared to PD [34]. In addition to LBD, other neurodegenerative disorders are also associated with intracellular accumulation of α-syn, such as multiple system atrophy (MSA) and Gaucher disease [35].The occurrence of α-syn aggregates unveils a potential continuum between these conditions, which could be lumped together under the term of α-synucleinopathies [36].

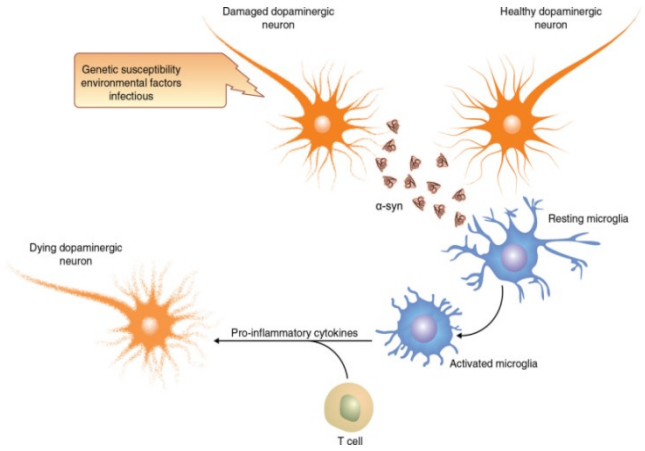

Figure 4: Neuroinflammation process in PD

3. Immunotherapy

The in vitro and in vivo preclinical data have provided sufficient evidence of target engagement to prompt several biotech companies, often partnering with big Pharma, to initiate clinical trials of active and passive immunotherapies in PD. In addition to monoclonal antibodies PRX002/RG7935 (Prothena/Roche) and MEDI1341 (MedImmune/Astra Zeneca), both of which bind the C-terminus region of α-synuclein, BIIB054 (Biogen) is a monoclonal antibody that specifically targets the N-terminus region of α-synuclein [37].

In a Phase IA single ascending dose study in healthy volunteers, PRX002, a humanized IgG1 monoclonal antibody designed to target aggregated forms of α-synuclein, was found to be safe in a dose of up to 30 mg/kg. Furthermore, PRX002 was associated with a robust reduction in serum-free α-synuclein in healthy individuals. In a Phase IB multicenter, randomized, double-blind, placebo-controlled, multiple ascending dose study, 80 subjects were randomized into six escalating dose cohorts to receive PRX002/RG7935 (0.3, 1.0, 3.0, 10, 30 or 60 mg/kg), or a placebo (clinicaltrials.gov Identifier: NCT02157714) [38].

C. Huntington's disease (HD)

The HD gene and mutation were identified in 1993. The gene is located on the short arm of chromosome 4 and encodes a large protein called huntingtin that contains more than 3000 residues [39]. Exon 1 of the wild-type gene contains a stretch of uninterrupted CAG trinucleotide repeats, which is translated into a series of consecutive glutamine residues, a polyglutamine (polyQ) tract. Asymptomatic individuals have 35 or fewer CAG repeats and HD is caused by expansions of 36 or more repeats [40].

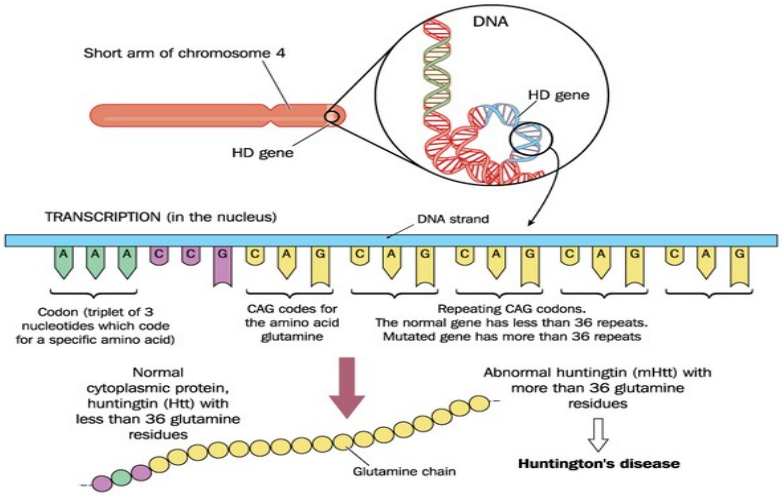

Figure 5: Pathogenesis of Huntington's disease

There is an inverse relationship between CAG repeat number and the age of onset of symptoms; the greater the number of CAG repeats, the earlier the age of onset [41]. Most adult onset cases have 40-50 CAG repeats, whereas expansions of >55 repeats frequently cause juvenile-onset disease. Incomplete penetrate has been observed in individuals with 36-39 repeats - some individuals in their 9th and 10th decades with alleles in this size range have no signs, symptoms or gross neuropathological features of HD About 70% of the variance in the age at onset of HD can be accounted for by CAG repeat number. Family studies suggest that a component of the residual variance not associated with the CAG repeat number, may be accounted for by additional genetic factors. One possible candidate modifying gene is the GluR6 kinase receptor. The effect that we reported of genotypes at this locus on age-at-onset of HD, after accounting for the CAG repeat length [42].

Immunotherapy

Some immunotherapies have been tested in clinical trials in patients. Miraxion (ethyl- EPA), developed by Amarin Corporation, was the only one till date to show some positive results – although a separate Phase 3 trial did not find relevant clinical benefits. Two ongoing Phase 2 clinical trials are evaluating the efficacy and safety of laquinimod (NCT02215616) and VX15/2503 (NCT02481674) in Huntington's patients [43,44]. Preclinical data in mice models of the disease has shown that laquinimod improved motor impairment and extended survival, and that VX15/2503 could reduce brain atrophy – a characteristic of this disease – and rescue cognitive defectsEHP-102 (previously called VCE-003.2), a molecule known to suppress immune responses, reduced the loss of nerve cells and improved motor function in mice models of Huntington's disease. LM22A-4 is a small molecule that binds to a receptor involved in the development and survival of brain cells. Another promising approach in suppressing inflammation is XPro1595, an inhibitor of a proinflammatory molecule known to be present at high levels in Huntington's disease patients. Preclinical data supports XPro1595 potential neuroprotective effects and ability to delay disease progression [45].

D. Prion disease

Transmissible spongiform encephalopathies represent a novel paradigm of infection in which infectivity is independent of an agent-derived nucleic acid component [46]. At this point, it is thought that infectivity resides in the misfolding of the normal cellular prion protein (PrPC) into a pathological and infectious conformation (PrPSc) [47]. Propagation of TSEs, both within individual animals as well as within populations of animals, is believed to occur through the ability of PrPSc to function as a template to promote misfolding of PrPC in an autocatalytic process [47,48]. Supportive of this hypothesis is the experimental finding that PrPC is generally converted to a protease-resistant conformation, a characteristic molecular signature of PrPSc, by contact with PrPSc in vitro, in a manner that is highly dependent upon species and prion strain. Other human protein misfolding disorders, such as Alzheimer's disease (AD), share many neuropathological characteristics with prion diseases, but lack this distinctive and titratable infectivity. PrPC, a glycosylphosphatidylinositol-linked cell-surface protein of approximately 35 kDa, is widely expressed throughout the body but at highest levels in brain neurons, as well as follicular dendritic cells (FDCs) of the immune system. PrPC from a variety of species has been characterized as rich in α-helices, soluble in mild detergent and sensitive to proteolytic degradation [49]. By contrast, PrPSc is rich in b-sheet content, insoluble in nondenaturing detergents, resists proteolytic degradation and is capable of forming amyloid deposits [50].

Immunotherapy

The demonstrated role of the immune system in prion disease progression and pathology suggests that modulation of immune responses may be of therapeutic value in the treatment and prevention of prion diseases. Specifically, antibodies directed against PrP may impair the interaction between PrPC and PrPSc [51]. SAF34 recognizes an epitope in the octa-repeat region of PrP, and does not interact with N-terminally cleaved PrPSc (which represents the majority of PrPSc in cells), and SAF61 (epitope 144–152) recognizes both PrP isoforms. These antibodies decrease the levels of both PrPSc in infected cells and PrPC in uninfected cells, with SAF61 showing the more marked effect, and an enhanced. No significant effect was observed after treatment with mAb 8F9 (epitope 205–233).The antibodies ICSM 18 and ICSM 35 were raised to recombinant mouse PrP folded in a- or b-conformation [52]. Montanide, TitreMax, CpG oligodeoxynucleotides. For induction of responses against either full-length PrPC or specific peptide regions [53].

E. Motor neurone diseases (MND)

The term is used to define the stiffness and other features seen due to damage to descending motor pathways in the central nervous system [54]. This damage, frequently in the spinal cord, leads to abnormal hyperexcitability of the tonic stretch reflex. In practical terms the patient with spastic legs complains of difficulty walking, stiffness or heaviness of the legs, weakness, fatigue, and reduced exercise tolerance [55]. They may also have cramps or ‘‘bounciness’’ of the legs due to spontaneous clonus. Lower motor neuron loss, on the other hand, leads to muscle wasting with fasciculation, weakness, and reduced or loss of reflexes [56].

Immunotherapy

First-line Treatment	Second-line Treatment	Treatment proven to be ineffective
Intravenous immunoglobulin (IVIg)	Rituximab Cyclophosphamide Methotrexate IFN b-1a (intramuscular) Subcutaneous immunoglobulin (Azathioprine) (Cyclosporine A)	Mycophenolate mofetil

The mode by which IVIg exerts its immunomodulatory effect is complex. Several mechanisms affecting different immune system pathways have been suggested, although none has conclusively been identified to be the dominant pathway [57]. IVIg neutralizes pathogenic antibodies and super antigens, inhibits antibody production by B-cells and accelerates catabolism of antibodies, suppresses pro-inflammatory mediators produced by T cells, inhibits complement-mediated inflammation and damage, induces blockade of Fc-receptors on macrophages and regulates proliferation and adhesion of T cells [58].

Other immunosuppressive and immunomodulating agents

Cyclophosphamide is an alkylating agent, which inhibits cell replication and is primarily used in haematological malignancies and some autoimmune disorders. Following the recognition of MMN as a separate entity, reported successful cyclophosphamide treatment in two patients [59]. Mycophenolate mofetil (MMF) inhibits more specifically the DNA synthesis and proliferation in lymphocytes. It is used primarily after organ transplantation to prevent rejection and in some immune-mediated diseases. There is one high quality randomised double-blind placebo-controlled trial including 28 MMN patients treated with IVIg in which oral MMF (1000 mg twice daily) was studied as add-on therapy. Primary outcome was defined as a reduction of the IVIg dose by 50% or more after 1 year of treatment. Only one patient using MMF reached this primary endpoint. There was no significant difference in mean IVIg dose reduction between patients using MMF or placebo [60]. Rituximab is a monoclonal antibody that targets the CD-20 antigen on B lymphocytes. More recently, three patients with MMN were treated with rituximab because of declining efficacy of IVIg [61]. Methotrexate inhibits DNA synthesis in proliferating cells and is used in a variety of immune-mediated disorders [62].

Azathioprine is a widely used immunosuppressive agent thatinhibits DNA synthesis in proliferating cells. However, in MND experience with the use of azathioprine is limited. Only two patients have been reported to respond to azathioprine monotherapy, one did not respond to corticosteroids previously and the other failed to respond to IVIg [63].

4. Conclusions

The immunotherapy for the treatment of neurodegenerative diseases support the view that this approach might have therapeutic potential for disease modification, although many questions remain unanswered including how exactly immunotherapy works. Promising results have been obtained for both active and passive immunization in preclinical studies, but caution must be exercised when advancing from mouse models to clinical trials in order to maximize efficacy and minimize autoimmune and vascular adverse effects. One example comes from passive immunotherapy against Aβ, where effector functions appear not to be critical for the clearance of Aβ aggregates by passive immunization in mice and are suspected to be responsible for Fc-mediated responses that result in vasogenic edema in humans. Another question that

needs to be addressed is whether immunotherapy can only be useful as preventive treatment or it could also be effective once the disease becomes symptomatic.

In conclusion, numerous preclinical studies and current Phase III clinical trials suggest that immunotherapy might constitute a potentially effective disease modifying treatment for several neurodegenerative disorders, as it targets the molecular origin of the disease.

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