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Biosimilars as Therapeutic Agents against Neurodegenerative Diseases - A Focus on Multiple Sclerosis

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Abstract

The following review deals with the possible use of biosimilars in the treatment of neurodegenerative diseases with a focus on Multiple Sclerosis. It discusses the possible use of Interferon-β (INF-β) biosimilars as a therapeutic agent against multiple sclerosis. There are a number of drawbacks associated with the use of such biosimilars against multiple sclerosis including the formation of neutralizing antibodies which are discussed as well. There are possible modifications which could be made to the agent in order to increase its efficiency. The various IFN-β biosimilars under clinical trial are also discussed with future implications.

Keywords: Biosimilars; Neurodegeneration; Multiple sclerosis; IFN-β

Introduction

The current health scenario of the world has seen the up rise of many diseases. With increasing number of people being affected by these diseases, there is great interest in developing drugs to fight against these. Great emphasis has been laid also on reducing the cost of medication by attempting to develop newer and cheaper methods for the production of these drugs. Development of biosimilars is one such approach.

Neurodegeneration and Biosimilars

Neurodegeneration refers to any pathological condition primarily affecting the neurons. It mainly involves loss of neuronal function and degeneration of neurons. However, edema, hemorrhage and trauma of the nervous system are not considered to be neurodegenerative disorders [1].

There is not much clarity on the cause of neurodegenerative disorders. However, there are certain factors which may accelerate the development of these disorders such as age [1]. It has been a field of great interest and a lot of emphasis is being laid on the treatment of neurodegenerative conditions. Although a complete cure for many of these diseases are not known, there are certain drugs which are prescribed to slow down the progression of few of these diseases. For example, five drugs are prescribed by FDA for the treatment of Alzheimer's disease, namely-acetyl cholinesterase inhibitors such like donepezil (aricept), galantamine (razadyne), rivastigmine (exelon) and drugs such as tacrine and memantine [2].

Many of these drugs are expensive and also have considerable side effects. This includes hepatotoxicity with use of tacrine [2]. Hence this limits the practical availability of drug options available to us for treating these diseases. A biopharmaceutical is a pharmaceutical manufactured using biotechnology (living organisms such as cells, microbes) [3]. A biosimilar on the other hand is a biopharmaceutical similar to the reference product's active agent and indications, which has been approved or is on track for regulatory approval following defined biosimilar approval mechanisms [3].

There are many protein characteristics which are assessed when comparison of the biosimilar and the reference product are done. These include composition or high order structure determined by amino acid sequencing and spectroscopy respectively. Post translational modifications such as glycosylation are determined by mass spectroscopy. Size and detection of aggregates may be done by use of electrophoresis and analytical ultracentrifugation. Finally, the bioactivity is compared by means of bioassays and animal models [4]. If biosimilar drugs are developed for such neurodegenerative diseases, it may result

in cutting down of costs and at the same time may bypass many of the side effects associated with contemporary drugs.

What is Multiple Sclerosis?

Multiple sclerosis (MS) is a genetic disease involving inflammation of the white matter in the (CNS), which is presumed to be mediated by auto reactive T cells. Clonal expansion of B cells, their antibody products, and T cells, hallmarks of inflammation in the CNS, are found in MS [5]. Brain tissue of individuals with MS reveals multiple sharply demarcated plaques in the CNS white matter [5].

The onset of multiple sclerosis is usually in the adult life from about 20 to 40 years of age. It is generally rare before the age of 15 [6].

The pathophysiology associated with MS is described as follows:

a) In a genetically susceptible host, common microbes activate the Antigen Presenting Cells (APCs) through Toll-Like Receptors (TLRs), generally TLR2 and TLR4 .

b) These microbes contain protein sequences cross-reactive with self- myelin antigens.

c) The activated APCs then present processed antigen to T cells for their activation.

d) This leads to induction of an autoimmune, inflammatory CNS disease in mammals.

e) Activated myelin-reactive T cells migrate into the CNS and recognize antigen presented by microglia, local APCs. Th1 cytokines are secreted and an inflammatory cascade is initiated [5].

Interaction of the microbial cell surface components with the TLR2 and TLR4 causes eventual differentiation of naïve T cells to Th17 and Th1 cells which in turn leads to increased production of IL-17 and IFN gamma causing CNS damage. There is also suppression of induced regulatory T cells and hence a state of increased autoimmunity [7]. Multiple sclerosis may be of many types. Relapsing-remitting MS (RRMS) is characterized by clearly defined attacks of worsening neurologic function. These attacks or relapses, flare-ups or exacerbations are followed by partial or complete recovery periods (remissions), during which symptoms improve partially or completely and there is no apparent progression of disease.

In secondary progressive MS, the disease progresses more steadily with or without relapses. Primary progressive MS is characterized by steadily worsening neurologic function from the beginning. In case of Progressive relapsing MS which is the least common of the 4, there is steady progression of the disease from the beginning and occasional worsenings along the way [8].

The prevalence of MS has shown to vary among populations across the globe, with cases ranging from around 90-150/100,000 in US and UK to about 10/100,000 in India. Obviously, the figure is bound to be higher than the noted statistical figure in India since a large section of the Indian population does not have access to medical facilities which would be able to accurately diagnose the disease [9].

Treatment Options - A Biosimilar Approach

Interferons were first identified as antiviral agents. Interferons are considered to be a part of cytokine family of proteins. They bind to their respective heterodimeric receptors which in turn signal through distinct JAK/STAT phosphorylation cascades, ultimately resulting in the transcriptional regulation of several hundred genes. Interferon beta is widely used as first-line treatment for relapsing remitting multiple sclerosis (RRMS).

Biosimilar products for IFN-β are newly emerging. The relapse rates with such biosimilar products are found to reduce by about 1/3 and also there is considerable reduction in the appearance of new lesions. There are also studies indicating reduction in brain atrophy [10]. IFN-β is thought toact on multiple pathways and inhibit the proliferation of leukocytes and antigen presentation, cytokine production and T-cell migration across the blood-brain barrier.

Several studies have been and are being conducted in relation to developing biosimilar forms of Interferon beta (INF-β) for treatment of Multiple sclerosis. In one such study the safety and efficacy of two biosimilar forms of IFNβ-1a were compared in the treatment of MS. These were Avonex and Cinnovex. IFNβ-1a was produced recombinantly in a Chinese hamster ovary cell line and was successfully marketed as Avonex.

CinnoVex is a biosimilar form of intramuscular IFNβ-1amanufactured by Cinna Gen Co., Iran. It is produced in the same cell line that produce Avonex. The process of production and purification were also similar. PK/PD studies were conducted to establish the similarity of CinnoVex to the original drug branded by BiogenIdec, Iran [11].

The results showed positive relapse control for patients. Disability was well controlled. Side effects of the two biosimilars included flu-like symptoms and leucopenia. Overall Avonex was shown to be a better biosimilar recombinant protein in terms of safety and efficacy [11].

Other studies compared Pharmacodynamic and pharmacologic effects of Betaseron (Interferon β-1b) and Avonex. The results of the study demonstrated that the approved dosing regimen of Betaseron provided a greater and more consistently elevated biological response compared with Avonex. Also it was found that when administered with ibuprofen, the intensity and duration of side effects such as fever and chills were comparable to that observed with administration of Avonex [12].

IFN-β therapy discontinuation studies conducted provide an insight into the “acceptedness” of this treatment. The studies showed that IFN-β discontinuation occurred primarily earlier in

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the treatment course due to side effects mainly. Stopping of IFN-β therapy was more common in case of Secondary progressive multiple sclerosis (SPMS) and was more often due to failure of treatment than the side effects [13]. SPMS is a stage of multiple sclerosis which usually comes after relapsing remitting multiple sclerosis. There is a sustained buildup of disability [14].

Bioassay for IFN-β

Agar diffusion method has been used for the bioassay of anti-viral agents. A procedure was developed whereby chick embryo cell monolayers were grown in baking dishes, infected with virus and overlaid with agar. Disks containing the anti-viral agent were placed on the agar surface. Post incubation, plaques were formed on the cell sheet except around the area where the disk was placed. Plaque-free zone size was found to be proportional to concentration of anti-viral agent present in disc [15].

Bioassays for interferons are primarily based on their anti-viral activity but in case of anti-tumor and immune modulatory therapies, their biological activity can't be predicted. Hence anti-cytokine based bioassays are more effective in this case. In case of IFN-β this is based on its ability to inhibit Granulocyte-macrophage- colony stimulating factor (GM-CSF) induced proliferation of erythroleukemic cell line TF-1. These anti-cytokine based bioassays are more sensitive and can be made specific to IFNs by inclusion of neutralizing antibodies in the bioassay [16].

Drawbacks

A neutralizing antibody (NAb) is an antibody that defends a cell from an antigen or infectious body by neutralizing any effect it has biologically. Many of MS patients are non-responsive to Beta interferon. One of the factors related to non-respondanceor failure of treatment is the presence of high levels of interferon beta neutralizing antibodies. Interferon therapy, and specially interferon beta 1b, induces the production of neutralizing antibodies [17].

Nabs can affect IFN beta therapy by binding directly to the epitope of the IFN-β molecule that binds to the IFN Beta receptor, neutralizing the effect of IFN-β on target cells. A real time PCR based bioassay exists for the quantification of neutralizing antibodies against human interferon beta. It is based on the real time PCR measurement of mRNA that results from the induction, in cultured human cells, of the MxA gene by IFN-β [18].

The problem of neutralizing antibodies may be solved by development of new less immunogenic IFN-β products [19]. Immunogenicity may be reduced by PE Gylation, involving covalent binding of polyethylene glycol (PEG) to the protein [20]. This basically helps to increase the size of the protein and also provide a hydrophilic coat. The increased size of the protein helps enhance its circulatory lifetime by reducing clearance of the drug. Also the increased steric hindrance helps prevent detection by the immune system. Two of such PEGylated drugs undergoing clinical trials are Idec's PEGylated IFN-b-1a (BIIB017) and Allozyne's PEGylated IFN-b-1b (AZ01) [19].

Other Monoclonal Antibodies

Natalizumab is a recombinant monoclonal antibody against α4 integrins. It was shown to produce significant reduction in progression of disability by 2 years and also reduced the time for clinical relapse. However the marketing of it was stopped when cases of progressive multifocal leukoencephalopathy began to be reported in patients who were administered the drug [21].

Monoclonal antibodies such as alemtuzumab were seen to show promising results against multiple sclerosis. However they also had the disadvantage that they could further heighten the inflammatory response as well [22].

Glatiramer acetate is composed of glutamic acid, lysine and tyrosine. It acts by mimicking peptide fragments of myelin basic protein, a putative auto-antigen in Multiple Sclerosis which acts as an altered peptide ligand, blocks T cell activation. Studies showed that administration of GA reduced the relapse rate significantly over a period of 2 years. Subjects reported skin reactions. Prolonged administration of GA was seen to be associated with development of focal lip atrophy at the site of injection [23].

Conclusion and Discussion

Multiple sclerosis has long been the cause of concern for doctors and researchers. While no permanent solution to the problem has been found yet, the biosimilar drugs launched or about to be launched against this deadly disease surely holds promise for the future. Many of these drugs would work to slow down the progression of the disease. As noted, modifications to the IFN-β are being utilized to produce drugs less liable to induce an immune response against the biosimilar itself. Recently, Russia's ministry of health has awarded Biocad marketing the authorization for a biosimilar version of the drug Rebif (Interferon beta-1a) for the treatment of MS [24].

IFN-β brands for multiple sclerosis among other IFNs are the highest sellers with almost 60% of the cytokine market. Biogen's Avonex had been the leading IFN-beta in the US market for several years. However, Serono's Rebif soon joined the race with a benefit of lower relapse rate.

Betaseron sales lagged behind since it was made in *E.coli* compared to the other two brands made in mammalian cell cultures. Some carbohydrate moieties were missing, leading to a higher incidence of neutralizing antibodies and hence reduced efficacy [25].

With the patents of many biopharmaceuticals expiring soon, there is great interest in developing biosimilar drugs with the ultimate hope that the drugs to treat neuro degeneration would be available to the general public at affordable costs and hence benefit mankind.

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