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ALZHEIMER'S - A PHARMACOLOGICAL APPROACH

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ABSTRACT

Objective: To study the various pharmacological evaluative parameters towards cognitive, functional and characteristic manifestations of AD. Methods: The critical analysis of recent advancement in pharmacological approach was analysed by literature work. **Results:** This approach was done to justify for the pharmacological AD approach on the basis of therapeutic, prevention and symptomatic with the study of cholinesterase inhibitor with the combination of meantime antagonist. The results generated are symptomatic, dose dependent and stability studies should be analysed at regular intervals which should not have the tendency to alter the drug course of action. According to the previous studies, it showed the only significant way in order to reduce the AD effect. Eventually, the following factors would be discussed, such as, realistic expectations, side effect management, switching agonist action, acceptance of discontinue treatments. The results got after the clinical studies also play a major role in the study of the formulation of the AD preventive drug will be reviewed. But according to this study, clinical trials did not generate accurate results for the pharmacological action. **Conclusion**: Pharmacological surveys have been recently available for the symptomatic AD treatment which renders sustained effect.

INTRODUCTION

AD is the most common neurodegenerative disorder. Accordance to The World Alzheimer Report, in turn that was published in 2009,it showed a certain figures of estimated 35.6 million people were living with dementia, worldwide, it would increase of about 65.7 million by 2030 and gradually increase to 115.4 million by 2050. According to this report, September 1 usually is celebrated as, Alzheimer's Day 2010. According to this review, the effect of vascular prevention, cholinesterase enzyme, memantine and the NMDA agonist, would play an important role in the pharmacological action of AD. The results of the AD will also be discussed(Wimo and Prince, 2010).

MECHANISM OF THE DISEASE

The main reason for this disease to form is the action of amyloid cascade hypothesis. According to the study of this hypothesis, the main reason for this AD to grow is the Aβ protein action in the receptor site of action, as a result amyloid plaque deposition occurs which in turn leads to secondary factors such as the hyper - phosphorylation of the protein membrane, inflammation, exit-toxicity, and then eventually leads to cell death, these are caused due to deficits generated by the neuro-transmitters(Canada, 2010). Usually, the APP undergoes 2 pathways as shown in fig. 1. The cleavage is done by alpha secretase enzyme that results in the formation of soluble particle by the

formation of The APP undergoes cleavage by 2 pathways (Figure 1). The sequential cleavage of APP by alpha-secretase and gamma-secretase leads to the formation of a soluble particle (p3 protein) that does not deposit abnormally. Recent analysis data suggests that the soluble Aβ may be toxic in nature before it results into plaque syndrome. They lead to the disruption of axonal transport and then gradually to cell death(Selkoe, 2001).

MATERIALS AND METHODS

Vascular Prevention: The vascular risk factors are studied based on the study of cognition effect and hypertension that leads to dis- lipid-anaemia.The studies have shown results in high blood pressure, with cognitive outcomes. HYVET analysis was done in order to study impact on incidence of dementia in aged people of about 80 years(Lee, 1995). The results from the HVET analysis include, mental analysis of 4 prevention studies, hyper-tension and the dementia incidence. The relative risk analysed was in the range of the following area of significance, (RR 0.87; 95% CI 0.76 to 1.00, P = 0.04). The CCCDTD analysis gave an end result of grade b hypertension that is the primary cognitive prevention for the cardio vascular and cerebrovascular outcomes from the treated people(Deschaintre et al., 2009).

Cholinesterase Inhibitors:

There are 3 types of cholinesterase available: they are donepezil, rivastigmine, and galantamine. The usage of these studies for the compounds are based on the the individual deficits of of Ach in the patients(Blesa et al., 2007). These esterase usually exists in 2 forms: BuChE and AChE, degrades of ACh. The cholinesterase acts by the action and optimization of acetyl choline enzyme but they do not alter any clinical phase.Usually the cholinesterase improves the symptoms of AD(Risner et al., 2006). Donepezil belongs from the piperidine derivative that inhibits acetyl choline esterase enzyme.(Erkinjuntti et al., 2002)Usually pooled analysis for this drug generally shows positive significant benefits on cognition systems and also the behaviour outcomes. According to the other studies, the most suitable drug dose is 5-10mg for effective statistics. It was found that there were dose dependent side effects for those patients treated with donepezil like the nausea, vomiting, diarrhoea, muscle cramps etc(Landreth et al., 2008).

Rivastigmine: Generally falls from carbamate derivative which has the tendency to inhibit both the acetyl choline derivative. A transdermal type of formulation using rivastigmine as the drug is currently available on the Canadian market that solely is stressed on the study of cholinergic side effects with subsequent highest doses of regimen at the site. According to the other studies, the most suitable drug dose is 5-10mg for effective statistics. It was found that there were dose dependent side effects for those patients treated with donepezil like the nausea, vomiting, diarrhoea, muscle cramps etc(Nourhashemi et al., 2010).

Galantamine: Galantamine is from a tertiary alkaloid derivative. It reverses the acetyl-cholinesterase enzyme for initiating the action at the specific site. It effectively binds at the nicotinic site in order to enhance the cholinergic transmission.The dose of this drug is usually based in the range of 16-24 mg. It's dose release characteristics is based on placebo analysis(Qaseem et al., 2008).

Practical Issues in the current study of Pharmacological Management in the treatment of AD:

According to the review, the issues that were studied were the choline- esterase, memantine, for the treatment of AD: different treatment expected strategies, side effects managements and discontinuation of therapy.

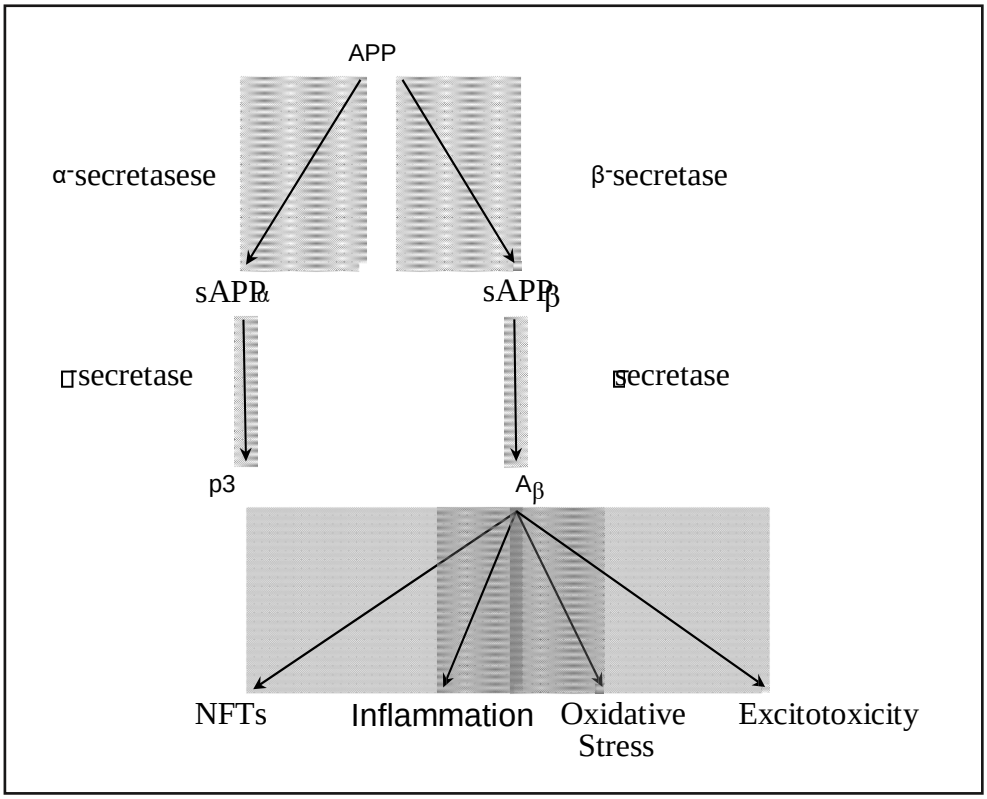

Figure 1 - Amyloidal cascade hypothesis in AD

Table 1 Pharmacological properties of ChEIs and memantine

Name	Metabolism	Starting dose	Minimal effective dose	Maximal dose
Donepezil	Hepatic CYP, CYP2D6, CYP3A4	5 mg/sid	5 mg/sid	10 mg/sid
Rivastigmine	Renal	1.5 mg/bid (Oral)	3 mg/bid	6 mg/bid
Rivastigmine	Renal	5 cm^2/sid (Transdermal)	10 cm^2/sid	10 cm^2/sid
Galantamine ER	Hepatic CYP, CYP2D6, CYP3A4	8 mg/sid	16 mg/sid	24 mg/sid
Memantine	Renal	5 mg in 1 or 2 daily doses	10 mg in 1 or 2 daily doses	20 mg in 1 or 2 daily doses[a]

a) Treatment Expectations: As reviewed from the before studies, the required pharmacological treatments were symptomatic that do not alter any progressive neuro-degenerative phases. In the case of clinical studies, the patient that is kept under study acts as the placebo comparator.Based on the type of patient, the treatments are adjusted towards the AD prevention(Hooper and Turner, 2002). The RCT is done in order to convert the severity of the disease, from mild to moderate that show improvement in cognitive measures in the range of 9-14 months of the study, whereas in some cases the severity may lead from moderate to severe as a result lead to symptoms and side effects such as depression, apathy, anxiety etc. From the moderate to severe stages of AD, mamantine has the ability to stabilize cognitive manifestations towards the progressive AD. As a result, the CCCDTD concluded that, all the three enzymes under the action were modestly efficacious for the treatment of mild to moderate AD(Zachariasse, 1978).

b) Amyloid-Based Therapies

Based on this specific hypothesis, it suggested that the accumulation of Aβ during the initial stages of the AD pathophysiological process, the side effects, with other downstream events in the neuro-degenerative region have highly complex consequences. The action of Aβ helps to increase the removal of the complex with removal of the putative toxicity are the goals(Haass and Selkoe, 2007).

c) Reducing Aβ Production.

The shifting of the APP is processed away from amyloid-genic b- secretase towards the Nano-myloid genic secretase pathway by blocking the BACE receptor. The inhibition of this type of enzyme may cause problems because it also cleaves numerous other substrates which also includes the one used for myelination process in the phase 1 trial(Aisen et al., 2006). Indirect modulation of BACE1 activity can also be possible via other complex mechanisms that involve the enzyme called the PPARg, which when initiated reduce the expression of BACE1 that leads to the reduction of APP concentrations. Such type of functions are also responsible of type 2 diabetes milletus(Pratap et al., 2012).

d) g- Secretase- as shown from the first fig. depicts that both the SAPPs completed the amyloid-genic pathway. It also involves other processes in the critical cell differentiation. Not all Abs formulated are of equal functions and capabilities. Longer the Ab42 drug moieties, aggregation at the site increases gradually. Certain NSDDS are also used for the critical aggregation process. The amyloid- genic pathway collectively inhibits the lowering agents such as the SALAs, modulate and shift the g-secretase enzyme to the shorter form. The first agents produced were the R flurbiprofen. The initial phase 2 trials encourages but the phase 3 RCTs failed to show benefits(Nyström et al., 1993).

e) a-*Secretase*-Shunting of the APP could be achieved by the stimulation of a secretase towards the Nano- myloid genesis. Through a chain of mechanisms, there were various treatment that could be used got the treatment of AD. Such type of candidates are present in phase 1 or 2 studies that has the tendency to increase the a-secretase activity to reduce aggregation(Santa-Maria et al., 2007).

Preventing Aβ Accumulation and Promoting Clearance.

In order to prevent from aggregation of the neurotoxicity Ab species have been proven to be the ideal regimen. I t was considered as an anti- aggregative inhibitor based on the recent studies because it showed phase 2 clinical trials positive. Results generated from phase 3 trials proved neglected because of high placebo response, high volumetric magnetic resonance as a result lead to hippocampal atrophy(Tariot and Aisen, 2009). AD was is promoted by the presence of certain pathological processes in the present of certain certain in organic metals such as, zinc, copper etc. Other agents such as quinolone also have the ability to interfere between the enzyme action of neuro degenerative that effects the murine models of the AD study. For these compounds phase 3 trials have not been known but phase 2

trials have been performed by the usage of polyphenol derived from green tea(Abou Youssef et al., 2018).

Promoting Clearance

The different advances towards the enhancement of promoting clearance were done by both active and passive immunization of anti- bodies. Passive immunisation involves candidates under phase 2 and 3 trials. The healthy subjects derives intravenous immune globulins that occurs as anti- bodies with the infected AD. It occurs naturally occurring anti Ab- reduces the effect of AD in the patients. However, polyclonal anti-bodies have shown favourable phase 2 of clinical trials in the AD patients(Pimplikar, 2009). Whereas, in the case of active immunisation, the phase1 trial that involves AN172 vaccine, first it was used in humans, had to be pre-maturely terminated due to the formation of aseptic meningitis. This aggressiveness to inhibit aggregation was done by sensitising the cyto-toxic cells. Based on other studies it was showed that some patients died during the study trials because the patient suffered from Ab plaques. Numerous new vaccines were introduced during the phase 1 trials which helped to reduce the Ab neuro generative disorder(Holmes et al., 2008).

Final Remarks: There are various pharmacological approaches towards the symptomatic treatment of AD. The outcomes for these desired experiments provided mild but sustained benefits.
Before the study of disease modifying studies, optimization of these desired events should be analysed for which it makes it crucial in order to understand the amyloid hypothesis. The drug discovery phase of the study involves the hypothesized pathophysiology would be generated. As a result of enthusiastic results from the phase 3 trials, there would be some scope to ensure the ability of the clinical trials for the modification of AD treatment in every patient that is necessary to show as negative.As a result, during the amyloid cascade hypothesis more attention is to be brought towards the study of disease mechanisms.

RESULTS

This approach was done to justify for the pharmacological AD approach on the basis of therapeutic, prevention and symptomatic with the study of cholinesterase inhibitor with the combination of memantine antagonist. The results generated are symptomatic, dose dependent and stability studies should be analysed at regular intervals which should not have the tendency to alter the drug course of action. According to the previous studies, it showed the only significant way in order to reduce the AD effect. Eventually, the following factors would be discussed, such as, realistic expectations, side effect management, switching agonist action, acceptance of discontinue treatments. The results got after the clinical studies also play a major role in the study of the formulation of the AD preventive drug will be reviewed. But according to this study, clinical trials did not generate accurate results for the pharmacological action.

CONCLUSION

Pharmacological surveys have been recently available for the symptomatic AD treatment which renders sustained effect.

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