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ALEGLITAZAR – AN UPCOMING DUAL PPAR ALPHA/GAMMA AGONIST IN REDUCING THE MACRO VASCULAR RISKS ASSOCIATED WITH TYPE 2 DIABETES MELLITUS

C.ANIRUDH JAGANNADH*[1], M.SRAVANI[2] AND DR M.D DHANARAJU[3]

[1]Pharm-D , GIET school of pharmacy , Rajahmundry , Andhra Pradesh.
[2]Department of pharmacy practice, GIET School of pharmacy, Rajahmundry.
[3]Department of pharmaceutics, GIET School of pharmacy, Rajahmundry.

ABSTRACT

Diabetes is a chronic disorder frequently associated with failure of vital organs like eyes, heart,kidneys, nerves, and blood vessels. Treatment of diabetic complications with drugs was classified as monotherapy, dual therapy and triple therapy. Many patients cannot obtain satisfactory glycemic control with current therapies, and eventually develope micro vascular and macro vascular complications. New and more effective agents targeted for therapy are required.This review focuses on the therapeutic potential of novel dual PPAR alpha/gamma agonist ,aleglitazar in comparision with PPARγ agonists.Aleglitazar exerts dual effects in lowering plasma triglycerides and increasing HDL cholesterol and is the first target for reducing cardiovascular risk among Glitazars. Further studies are needed to provide benefits of cardiovascular events and changes in long term lipid profiles.

KEYWORDS: **Aleglitazar, PPAR alpha/gamma agonist, Diabetes.**

C.ANIRUDH JAGANNADH
Pharm-D , GIET school of pharmacy , Rajahmundry , Andhra Pradesh.

**Corresponding author*

INTRODUCTION

Diabetes mellitus is a metabolic disease condition characterized by either reduced insulin synthesis (type 1) or reduced insulin sensitivity of body cells (type 2)[1]. Diabetes itself is a gateway for microvascular (nephropathy , neuropathy and retinopathy) and macro vascular (cardiovascular disease , stroke , peripheral vascular disease) complications leading to significant morbidity and mortality[2]. Intensive glycemic control and treatment for hyperglycemia has proven to efficiently reduce the risk of developing microvascular complications but has not proved to be beneficial in improving macrovascular complications[3]. This suggests the need to skip to a broader approach to prevent macrovascular complications along with adequate glycemic control[4]. GLITAZARS (dual PPAR agonists) are agonists of both PPAR-alpha and gamma receptors also referred as dual PPARs. They exert a dual effect i.e. as that of fibrates(PPAR alpha agonist) lower plasma triglycerides and increase plasma HDL-C and as thiazolidinedione(PPAR gamma agonists) increase insulin sensitivity and improve glycemic control[5]. Though there are many drugs in this class like naveglitazar , muraglitazar , tesaglitazar , ragaglitazar , aleglitazar the clinical development of the former four was halted due to their safety concern and clinical report of severe adverse effects , and hence the clinical trials of these four drugs was stopped in phase 2 and early phase 3 study. Whereas aleglitazar which is presently under phase 3 clinical study which has been showing promising results and a consistent safety profile up to date is the first agent expected to specifically target to reduce cardiovascular risk in diabetic patients[6][7]. This article focuses on the therapeutic role of aleglitazar in preventing diabetic macrovascular complication(cardiovascular in particular) and the reason for its selectivity then that of other drugs of its class[7].

ABOUT ALEGLITAZAR

Aleglitazar is a peroxisome proliferator-activated receptor agonist having affinity on both PPAR-alpha and PPAR-gamma subtypes being developed by Hoffmann-La Roche which is currently under phase 3 clinical trials[8]. This drug had undergone phase-II randomized , dose-finding , international clinical trial SYNCHRONY which involved the evaluation of increasing doses of aleglitazar among 332 patients with type-2DM . After 16 weeks treatment with aleglitazar at once daily dosing of 50 µg,150 µg ,300 µg and 600 µg as compared with placebo and open labeled pioglitazone 45mg the findings were as follows ,

- The effect of Aleglitazar on HbA1c levels was significantly decreased from base line after treatment.
- The maximum effect of decline on fasting blood glucose was observed after first 8 weeks.150 µg dose of aleglitazar was associated with a similar reduction versus placebo in both HbA1c (–0・85%,95% CI –0・50 to –1・20, p<0・0001) and concentrations of fasting plasma glucose (–2・16 mmol/L, –1・35 to –2・98,p<0・0001) to that detected with 45 mg pioglitazone(–0・71%, –0・36 to –1・06, p<0・0001; and –2・10 mmol/L,–1・29 to –2・90, p<0・0001, respectively.
- 10% reduction of LDL from base line was achieved with 150µg treatment dose of aleglitazar.An increase in LDL cholesterol by 2-16% with pioglitazone and 12-23% with rosiglitazone demonstrates cardiovascular risk.
- Dose dependent changes are seen with eGFR and serum creatinine and were less with 150µg of aleglitazar.
- An improvement in HDL was observed after 8 weeks of treatment, and reduction in apolipoprotein B concentrations, triglycerides were identified with all doses of aleglitazar. [7]

NEED FOR ALEGLITAZAR

Despite of currently available medications for diabetes , patients are secondarily suffering from an acute coronary syndrome or stable cardiovascular disease posing a high risk of life-threatening cardiovascular events. Reducing cardiovascular risk in diabetic patients might lead to significant reduction in mortality[10]. Accounting for 50 percent of deaths in patients with type 2 diabetes cardiovascular disease is the leading cause of morbidity and mortality among the patient population[11].Aleglitazar is a dual PPAR agonist investigated to treat major cardio vascular events in patients with type-2 diabetes/pre-diabetes along with ensuring glycemic control by efficiently improving insulin sensitivity.

MECHANISM OF ACTION

Peroxisome proliferator-activated receptors are ligand activated nuclear transcription factors that either induce or repress transcription of target genes which help to regulate lipid and carbohydrate metabolism by distinct mechanisms effecting both lipid metabolism and glycemic control. The three distinct subtypes of this family are PPAR alpha , gamma , and delta respectively each of which has distinct tissue distribution , gene targets , process of expressing their functions with only partial overlap in their activity[12]. The respective functions expressed by mimicking respective subtype is depicted in figure-1 .Aleglitazar is found to be balanced dual PPAR alpha and gamma agonist. As a ligand on PPAR alpha it promotes treatment of dyslipidemia by modulating the lipid metabolism by increasing HDL-cholesterol and reducing triglyceride levels hence slowing the progression of atherosclerosis and subsequent reduction of cardiovascular events. As a PPAR gamma agonist it shows improvement in glycemic control by increasing insulin sensitivity[12]. PPARs form heterodimeric complexes with retenoid-x receptor. This activated complex bind to PPRE a nucleotide sequence in the promoter region of the genes regulated by PPARs . These genes perform their respective function depending upon the subtype provoking this cascade[17] .

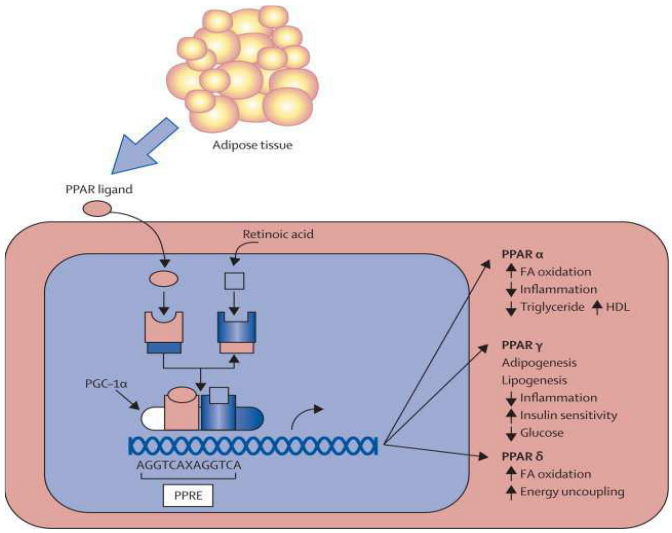

Figure-1
action of dual PPAR agonists

REASON FOR SELECTIVITY WITH NO CHOICE

Though other drugs of the same class were synthesized and accessed they were not successful to compete with Aleglitazar pertaining their clinical report of serious adverse effects. A meta-analysis of phase-2&3 clinical trials , conducted by Nissen and

coworkers on 2374 patients treated with muraglitazar revealed that it was associated with greater incidence of stroke , myocardial infarction , transient ischemic stroke and CHF when compared to placebo/pioglitazone[13][16]. Ragaglitazar and naveglitazar were found to be associated with increased incidence hyperplasia and bladder cancer in rodent studies due to which the phase 3 study of these drugs was not pursued[13]. Tesaglitazar was found to cause renal dysfunction and hence it was discontinued[14]. Fibrates (PPAR alpha agonists) , though improve the lipid profile were not as effective as aleglitazar in improving the lipid profile along with promising glycemic control[18].

SAFETY PROFILE OF ALEGLITAZAR

SYNCHRONY trial demonstrated significant beneficial effects on lipid profile with reduction in triglycerides and an increase in HDL cholesterol levels and reduction in cardiovascular risk markers. Futherly it was found to be safe and well tolerated over the course of therapy[7].AleNephro study in phase 2 clinical trial presented at the 2012 American Society of Nephrology(ASN) conference showed the average decrease in renal function during treatment with aleglitazar was reversible , mild and stabilized over time in patients with moderate renal impairement who have type 2 diabetes[9]. Following phase 2 trial data in cardiovascular safety of aleglitazar a phase 3 double blinded , parallel two-arm randomized clinical trial study referred as ALECARDIO was designed in collaboration with USFDA to study long term safety profile in patients with type 2 diabetes mellitus who have suffered from the recent acute coronary syndrome. It is estimated to be completed by May 2015[9][7].Incidence of anemia was expected with high doses of aleglitazar.Body weight gain and peripheral oedema was suggested as side effect with activation of PPARγ but less with aleglitazar 150µg dose.The most frequently reported adverse reactions with aleglitazar are nasopharyingitis,raised blood creatinine phosphokinase,upper respiratory tract infection in high doses(300µg-600µg).[7]

CONCLUSION

Considering the ideal pharmacological action , phase 2 clinical trial data and its relative safety profile then other drugs of the same class , Aleglitazar may become the first novel therapy demonstrated to reduce both macro vascular complications and improve glycemic levels in patients with type 2 diabetes mellitus. Further studies are needed to provide benefits of cardiovascular events and changes in long term lipid profiles

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