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Alternative Oral Drugs to Pioglitazone in Type 2 Diabetes Mellitus.

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ABSTRACT

Diabetes is a worldwide prevalent chronic disease with a significant disease burden and associated with many complications that significantly impact the quality of life. Pioglitazone has been a leading oral drug for the treatment of type 2 diabetes mellitus. However, recent studies reveal its association with increased bladder cancer risk with prolonged use. Due to this, alternative oral drug therapies have become the need of the hour. Currently available alternative drugs include α glucosidase inhibitors, incretins (GLP -1 agonists & DPP IV inhibitors), SGLT – 2 inhibitors, glitazars, meglitinides, dopamine agonists and bile acid sequestrants. Other agents currently in pipeline include GPR40 agonists, GPR119 agonists, Glucokinase activators, SPPARM's, 11β hydroxyl steroid dehydrogenase 1 inhibitors etc. This review aims to discuss alternative oral drugs to pioglitazone in type 2 diabetes mellitus.

Keywords: Type 2 diabetes, pioglitazone, bladder cancer, newer alternatives, oral drugs.

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INTRODUCTION

Type 2 diabetes mellitus is a chronic disease with a significant global presence and a marked influence on the quality of life. A vast proportion of diabetic patient pool exists in India and this number is pegged to reach 68 million by the year 2025 [1]. In this setting, it is necessary to continue research and development of newer anti-diabetic drugs to achieve good glycemic control and to monitor the existing drugs for their side effects. Metformin, even after several years of its launch, is considered as the “Gold standard” first line oral therapy in type 2 diabetes management. Other oral drugs introduced thereafter have failed to match metformin’s efficacy and potency and are used as combination or add – on therapy with metformin, thereby constituting the second line oral therapy in type 2 diabetes. However, despite the availability of these drugs, many patients ultimately show a progressive worsening of glycemic control and end up requiring daily insulin.

Pioglitazone is an anti-diabetic drug which is widely used as a combination therapy with metformin and other anti-diabetic drugs or even alone as a monotherapy in the management of type 2 diabetes mellitus. It is well tolerated by majority of the patients and is relatively cheap and cost effective. However, recently conducted studies reveal an increased incidence of bladder cancer among long term pioglitazone users and it was even withdrawn / suspended from the market in some countries like France and Germany [2]. In US and India, it is still available in the market but with a label warning. Following the controversy surrounding its prescription and use, there has been a narrowing of the gap between oral metformin use and daily insulin requirement in the treatment of type 2 diabetes mellitus. This gap, therefore, needs to be addressed with newer and safer, potent oral anti-diabetic drugs that can act as an alternative to pioglitazone and one day, can even rival metformin as the first line therapy in the management of type 2 diabetes.

PIOGLITAZONE: THE CONTROVERSY

Pioglitazone is an anti-diabetic drug belonging to a class of drugs known as thiazolidinediones. It was approved in 1999 for the treatment of type 2 diabetes mellitus. It has a selective agonist action on peroxisome proliferator activated receptor gamma (PPAR γ) and to a lesser extent, on PPAR α . Other compounds of this class of drugs, like troglitazone and rosiglitazone, were associated with adverse hepatic and cardiovascular profile respectively. Pioglitazone is the only member of this drug class that is widely used at present and has a comparative favorable cardiovascular profile as compared to the other members of this class. However, a series of studies published recently have linked long term pioglitazone use with an increased risk of bladder cancer [3,4].

In 2010, a 10-year epidemiological study indicated a possible link between long term pioglitazone use and bladder cancer, which prompted US FDA to order drug safety reviews. In a retrospective, case control study on 115,727 new users of oral hypoglycemic drugs in the UK, which included over 600 general practices between January 1988 and December 2009, Laurent Azolay and Hui Yin et al. found a definitive evidence of long-term pioglitazone use with increased risk of bladder cancer [3]. The risk was highest in patients exposed for more than 24 months and in those with a cumulative dosage greater than 28,000 mg [3]. Another meta-analysis study done by Zhaowei Zhu, Xiaohua Zhang et al. revealed that pioglitazone

use was associated with a significantly higher risk of bladder cancer and this effect was even stronger for cumulative treatment duration of more than 24 months [4].

On June 9, 2011, the French agency for the safety of health products decided to withdraw pioglitazone from the market due to high risk of bladder cancer based on an epidemiological study done by the French National Health Insurance [5]. This study revealed a significant increased risk of bladder cancer in patients taking pioglitazone as compared to patients who were taking other anti-diabetic medicines. On June 10, 2011, Germany's Federal institute for Drugs & Medical devices also decided to withdraw the drug from the market over similar concerns. On June 15, 2011, US FDA announced that pioglitazone use for more than 1 year may be associated with an increased risk of bladder cancer and stipulated that this information should be added to the warnings section on the label of medicines containing pioglitazone [6]. In June 2013, Drug controller general of India (DCGI) decided to withdraw pioglitazone from the market owing to its increased bladder cancer risk [7,8]. However, several eminent endocrinologists and diabetologists in India voiced their opinions in favour of the use of pioglitazone, owing to its good glycemic control, favorable lipid profile, potency and affordable pricing. Hence DCGI decided to re-introduce it a couple of months later with a warning label [9,10].

Due to above such negative publicity in media and research papers, there has been a stigma associated with pioglitazone prescription and use. So, physicians and researchers have alternatively now started looking for newer oral drugs for the management of type 2 diabetes mellitus. In this review, alternative oral drug therapies as well as emerging drug targets as an alternative to pioglitazone in the management of type 2 diabetes mellitus are discussed.

DRUGS

Alpha Glucosidase Inhibitors

These drugs act by preventing the absorption of carbohydrates by reversibly inhibiting the enterocyte membrane-bound α glucosidase enzyme and pancreatic amylase enzyme. As a result, in a diabetic patient this will lead to delayed absorption of the ingested carbohydrates and thus prevent postprandial hyperglycemia. α glucosidase inhibitors lower HbA1c levels by upto 0.5 – 0.75% on long term use and confer the additional advantage of being weight neutral. Agents in this class include acarbose, miglitol and voglibose. Their main side effects are gastrointestinal symptoms like bloating, flatulence, and diarrhea and are dose related. These drugs are taken at the start of the meal and their effect on postprandial glucose levels depend upon the amount of complex carbohydrates in the meal. A recent study concluded that acarbose was effective and well tolerated in a large cohort of Asian patients with type 2 diabetes mellitus [11]. This can be attributed to relatively high carbohydrate content present in the eastern diet as compared to the western diet.

Incretin mimetics

Incretins are endogenous substances secreted from the gut and they increase insulin response to orally administered glucose. Nauck et al. calculated that approximately 20 – 80

% of insulin response following an oral dose of glucose was due to incretins [12]. This response, however, was missing with glucose given intravenously [12].

Two incretin peptide hormones have been identified in humans, namely glucose dependent insulin releasing polypeptide (GIP) produced by K cells and glucagon like peptide – 1 (GLP-1) produced by L cells. Incretins are rapidly degraded by a protease enzyme dipeptidyl peptidase IV (DPP IV), which decreases the “*Incretin effect*”. Based on these, two promising therapies for management of type 2 diabetes have come up:

GLP -1 Agonists

GLP-1 agonists bind to GLP-1 receptor and produce glucose-dependent insulin secretion and other anti-hyperglycemic actions like inhibition of glucagon secretion and suppression of appetite. Other potential benefits shown by preclinical studies include β cell proliferation [13] and decreased β cell apoptosis [14]. Endogenous GLP-1 has a very short half life (2-5 min.) and is rapidly inactivated by the enzyme DPP IV. To overcome this effect, longer acting derivatives that are resistant to degradation by DPP IV are being developed. Currently, drugs available in this class are Exenatide, Liraglutide and Lixisenatide. But, these are given via subcutaneous injection just like insulin by a pen like device which is a major disadvantage. However, development of small molecule peptidic GLP -1 agonists that can be used for oral administration has raised hopes to overcome this hurdle [15]. An example of such novel GLP-1 agonists is TTP054 which is currently in phase 2 clinical trials [15,16].

Their chief advantages are lesser incidence of hypoglycemia and appetite suppression, leading to weight loss. In addition, they offer added benefit of reducing systolic blood pressure which offers additional cardiovascular protection. Side effects are minor and mainly include nausea, which is transient in nature, vomiting, headache, dizziness, diaphoresis etc. Rare side effects like pancreatitis [17,18] and thyroid cancer (in rodents) [19] have emerged and are currently under investigation.

DPP IV Inhibitors

Dipeptidyl peptidase IV (DPP IV) is a serine protease enzyme which degrades GIP and GLP-1. Thus, DPP IV inhibitors offer a suitable treatment option in type 2 diabetes. They act by increasing the incretin levels, mainly GLP-1 which is the major incretin hormone responsible for postprandial insulin secretion. Various DPP IV inhibitors like Sitagliptin, Saxagliptin, Vildagliptin, Alogliptin and Linagliptin are currently available while few others, like Gemigliptin and Dutogliptin, are currently in clinical trial phase. In clinical trials, they have shown to reduce HbA1c levels by 0.6-0.75%.

As compared to injectable GLP-1 agonists, these can be given orally and have shown good tolerability. Also, in moderate doses, they can be safely given to diabetic patients with renal dysfunction/renal failure whereas GLP-1 analogues are contraindicated in this condition [20]. Other advantages include lesser risk of hypoglycemia, weight neutrality and cardio protective effects [21]. Side effects are minor and include dizziness, diarrhea and pruritus. Another advantage is that unlike GLP-1 agonists, they do not cause nausea [22].

SGLT-2 Inhibitors

SGLT-2, a member of the sodium glucose co-transporter family, is present in proximal renal tubules and is responsible for glucose reabsorption from the kidney. It accounts for roughly 90% of glucose reabsorption from the kidney. Inhibition of this co-transporter thus lowers glycemia by decreasing renal glucose reabsorption and by promoting glycosuria. These drugs do not cause hypoglycemia and promote mild to moderate weight loss due to their glycosuric action. They have also been shown to decrease blood pressure in type 2 diabetes mellitus patients [23], possibly due to sodium loss [24]. Approved drugs in this class include Canagliflozin (approved by US FDA in March, 2013) and Dapagliflozin (approved only in Europe in Nov. 2012). Other drugs under development include Ipragliflozin, Empagliflozin, Luseogliflozin etc.

Their main side effects are vaginal yeast infections and urinary tract infections, due to the presence of increased amount of glucose in urine. These drugs are contra-indicated in patients with end stage renal disease and also in patients with ketones in their blood and urine. Long term effects on lipid profile and cardiovascular safety data are currently being investigated through Canagliflozin Cardiovascular Assessment Study (CANVAS) [25].

Combined α and γ PPAR Agonists (Glitazars)

Peroxisome Proliferator – activator receptors (PPAR's) are a group of nuclear receptors that are involved in a variety of gene expressions. Two of these, namely PPAR α and PPAR γ are involved in the modulation of lipid metabolism and peripheral insulin resistance respectively and act as molecular targets for a variety of drugs. Therefore, compounds with dual α and γ PPAR agonist activity (glitazars) provide the combined benefit of increasing insulin sensitivity, improving glycemic control, lowering of plasma triglycerides and increasing HDL cholesterol. Thus, this class of drugs improves both dyslipidemia and hyperglycemia and reduces cardiovascular risk in type 2 diabetes patients [26]. It can thus help to reduce multiple oral drug use for diabetes-associated co-morbid conditions, thereby increasing the patient compliance. They also have the additional advantage of not causing hypoglycemia.

The first agent to be approved in this class is Saroglitazar, which was approved by the Indian regulatory authority DCGI in June, 2013 [27]. Other drugs in this class include Tesaglitazar, Muraglitazar and Aleglitazar etc. all of which were discontinued during various phases of clinical trials citing a variety of adverse events, especially cardiovascular and renal. Due to this, long term safety data and cardiovascular risk profile of these drugs has to be monitored to establish them as an effective tool in management of type 2 diabetes mellitus.

Meglitinides

Meglitinides bind to ATP dependent potassium channel on β cells of the pancreas in a same manner as sulfonylureas, but with a weaker binding affinity, leading to their relatively shorter duration of action. They are taken before a meal and reduce postprandial hyperglycemia by promoting insulin secretion from the pancreas. Because these drugs depend on functioning β cell mass for insulin secretion, they are less efficacious in advanced

stage of the disease. They reduce HbA1c level by up to 1%. Available drugs in this class include Repaglinide, Nateglinide and Mitiglinide (Mitiglinide is approved only in Japan). Hypoglycemia and weight gain are their most important side effects. Repaglinide also caused an increased incidence of benign adenomas of thyroid and liver in male rats, however no such effects were noted with Nateglinide [28,29]. Due to their prominent hepatic metabolism, they should be used with caution in patients with hepatic dysfunction. However in case of renal dysfunction, these drugs can be suitably used with dose-adjustments.

Dopamine Agonists (Bromocriptine)

Bromocriptine mesylate is a dopamine agonist used in a variety of conditions like Parkinsonism, hyperprolactinemia, pituitary tumors etc. It was approved by US FDA in the year 2009 for use in type 2 diabetes mellitus. Based on animal and human studies, an early morning administration of bromocriptine (preferably within 2 hours after waking up) is supposed to increase dopamine levels in the hypothalamus and reduce central adrenergic tone, which results in decreased postprandial glucose levels, triglycerides and free fatty acids without affecting the plasma insulin levels [30]. A 16-week randomized, double blind, placebo-controlled study of bromocriptine in obese type 2 diabetes patients showed a significant decrease in fasting glucose levels and improvement in HbA1c, without affecting the insulin level [31]. Bromocriptine produces a 0.4-0.8 decline in HbA1c value, either as a monotherapy alone or as a combination therapy with other drugs. There is also evidence to suggest that it improves insulin sensitivity in the peripheral tissues via a centrally mediated action [32].

In safety studies, bromocriptine has shown minor side effects like nausea, dizziness and headache. It also possesses some cardio protective benefits [30], but the exact mechanism for this is unknown. It has the advantage of being weight neutral and negligible tendency to produce hypoglycemia. It can be given safely without dose adjustments to type 2 diabetes mellitus patients with mild to moderate renal failure. Also, due to its dopaminergic action, bromocriptine can be a useful tool for the management of an urban diabetic patient, who has high levels of stress in life [33]. Further studies are currently underway to elucidate the exact mechanism and the additional benefits associated with its use.

Bile Acid Sequestrants

These are a group of non-soluble resin polymers that decrease the enterohepatic circulation of bile acids by binding to certain bile elements. Though primarily used as hypolipidemic agents, they have also shown to improve glycemic control in patients with type 2 diabetes in various studies [34,35]. However, the exact mechanism by which they lower blood glucose is unknown. Currently approved drugs in this class include Colesevelam and Colestimide (Colestimide is approved only in Japan). It is hypothesized that these drugs produce their glucose lowering effects by binding to the bile acid receptor FXR (Farnesoid X receptor) in the liver, which decreases endogenous glucose production [36,37]. Another possible mechanism is by increasing incretin hormones secretion, especially GLP-1 levels [38]. Several studies have indicated a reduction in cardiovascular risk factors and

improvement in lipid profile apart from significant HbA1c reduction [38]. They are weight neutral and can be used safely in high-risk pre-diabetes population to reduce the risk of progressing to type 2 diabetes mellitus [39]. However, this warrants additional research. These compounds can also be safely added to other anti-diabetic drugs as an effective combination therapy for the treatment of both early as well as advanced stage diabetes and have a low risk of hypoglycemia.

Main side effects are gastrointestinal, including constipation, bloating, nausea and are mostly mild in nature. Due to their dual effect on lowering both cholesterol and blood glucose, they can be an effective tool for the treatment and management of type 2 diabetes mellitus and multiple studies to understand their exact mechanism of action and additional benefits are currently ongoing.

Other Oral Drugs Currently Undergoing Clinical Trials

GPR40 Agonists

GPR40 is a G-protein coupled receptor that is prominently expressed on pancreatic β cells and is activated by fatty acids [40] to promote a glucose dependent insulin secretion. Thus, it is an attractive drug target to improve insulin secretion and glucose tolerance in type 2 diabetes patients [41]. Fasiglifam (TAK-875) is a novel orally active compound belonging to this class and is currently undergoing phase III clinical trials [42]. It has shown significant improvement in glycemic profile with minimal risk of hypoglycemia and good tolerability in clinical studies [43]. Adverse effects reported are mild and include mild weight gain, nasopharyngitis etc.

GPR119 Agonists

GPR119 is a G-protein coupled receptor which is expressed by L cells and K cells in the small intestine and also by β cells of the pancreas. Its activation causes an increased intracellular concentration of cAMP which leads to enhanced insulin secretion and also increased incretin production in a direct and indirect manner respectively [44]. Thus, it is an attractive target for the development of newer oral anti-diabetic drugs. These drugs decrease appetite, thereby promoting weight loss and rarely cause hypoglycemia. Compounds in this class include MBX-2982, GSK-1292263 and PSN-821 (all in phase II trials) [45]. Their co-administration with DPP IV inhibitors theoretically could provide the dual benefit of good glycemic control coupled with weight loss and extensive studies are being carried out to evaluate this hypothesis.

Glucokinase Activators

Glucokinase is a hexokinase isoenzyme present in humans in liver, pancreas, gut and brain. It is involved in phosphorylation of glucose to glucose-6-phosphate. Glucokinase activators therefore, promote insulin release by causing depolarization due to calcium ion influx and also cause increased glucose uptake by the liver, thereby decreasing blood glucose in a dose dependent manner. Clinical trials for various compounds in this class like MK0941 and R1440 were terminated prematurely by their manufacturers due to

undisclosed reasons. The main side effects included hypoglycemia (in higher doses), hepatosteatorosis and dyslipidemia. Recently, a hepatoselective glucokinase activator compound called TTP-399 has been discovered that has shown HbA1c value reduction with no hypoglycemia in clinical trials [46]. Another novel compound, ZYGK 1, has recently got the US FDA nod to start phase I clinical trials after preclinical data revealed encouraging results.

SPPARM (Selective PPAR γ Modulators)

These agents represent a new class of selective PPAR γ ligands and have partial agonist activity as compared to thiozolidinediones. They aim to retain the therapeutic benefits of PPAR γ full agonists but without their undesirable side effects like fluid retention, weight gain, increased cardiovascular risk etc. Compounds in this class currently undergoing clinical trials are Mitoglitazone, INT 131 [47] and PN 2034. A new subset of drugs called SPPARM α are also being developed that are beneficial in diabetic dyslipidemia. K 877 is one such selective SPPARM α agonist that is currently undergoing phase I trials in Europe and US [48].

11- β Hydroxy Steroid Dehydrogenase 1 Inhibitors

11 – β hydroxy steroid dehydrogenase 1 (11- β HSD 1) is an enzyme involved in active regeneration of cortisol from the inactive cortisone in liver and adipose tissue, which causes gluconeogenesis and decreases glycogenesis. Inhibition of 11 – β HSD 1 thus offers a potential novel therapy for treatment of type 2 diabetes mellitus. Compounds under this class are undergoing early phase clinical trials and include DIO-902, INCB-13739 [49], AZD 4017 etc. Preliminary results have been promising with good tolerability and beneficial effects on HbA1c levels as well as on dyslipidemia. They have also shown to improve hepatic sensitivity to insulin [50].

Glycogen Phosphorylase Inhibitors

Glycogen phosphorylase enzyme is responsible for catalytic conversion of glycogen to glucose-1-phosphate in liver. Inhibition of this enzyme therefore can be a useful target in development of anti-diabetic drugs. In vivo testing on animal models revealed a decrease in hyperglycemia without causing hypoglycemia[51]. GSK 1362885 is a novel oral compound under this category and has recently completed phase I trials in the US [52].

Diacylglycerol Acetyltransferase 1(DGAT-1) Inhibitors

Diacylglycerol Acetyltransferase 1 (DGAT-1) is the enzyme responsible for the final step in triglyceride synthesis. Inhibition of DGAT-1 in animal studies has shown beneficial effects like weight loss and improvement in lipid profile with improved insulin sensitivity [53]. Compounds in this class undergoing clinical trials include LCQ-908 (Phase III). Side effects reported so far are minor and mainly constitute gastrointestinal symptoms like nausea, diarrhea etc.

CONCLUSION

Type 2 diabetes mellitus is a widely prevalent disease with significant impact on society and public health due to its chronic nature and associated complications. Pioglitazone has played a vital role in the management of diabetes due to its high efficacy. Due to the recent controversy surrounding Pioglitazone use and its association with bladder cancer, it is thus necessary to seek for newer oral treatment modalities for the treatment and management of type 2 diabetes mellitus that can serve as an effective alternative to Pioglitazone and that can provide good glycemic control, thus reducing the eventual dependence on insulin use. Some of these new drugs mentioned above look promising, but cost is a prohibitory factor for majority of them. Continuous research, coupled with affordability and wider availability, is thus required for the development of more safe, potent and economical drugs to combat this disease.

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