A DISCUSSION ON THE EFFECTIVENESS AND THE SAFETY OF ORAL DIABETES MEDICATION

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Abstract

Oral type 2 diabetic medicines have been approved recently. To maximize oral diabetic medicine therapy, you must understand the efficacy and safety of new and older treatments. DPP-4 inhibitors are one of the newest oral hypoglycemic/antihyperglycemic drugs. Compared to metformin, the conventional treatment, they have less adverse effects and are moderately successful. They work well with other oral drugs including insulin. They are recommended when metformin is limited by GI side effects if SU treatment produces significant hypoglycemia or weight gain. AGIs and meglitinide analogs are limited by frequency, cost, and hypoglycemia (repaglinide > nateglinide). BAS and bromocriptine, which have GI side effects but low hypoglycemic risk, cut HbA1c the least.

Keywords: *α-glucosidase inhibitor; bile-acid sequestrant; bromocriptine; DPP-4 inhibitor; meglitinide; metformin; sulfonylurea; thiazolidinedione; type 2 diabetes*

Introduction

Patient factors, hyperglycemia intensity, and treatment alternatives determine type 2 diabetes treatment. Metformin, SU, and TZD are the most researched oral medicines globally. The ADA and EASD type 2 diabetes treatment protocol starts with them. Metformin is first-line treatment if tolerated.

Declaration of interest

The authors declare no conflicts of interest and were not paid for this publication. contraindicated. Second-line treatments include SUs, TZDs, DPP-4 inhibitors, GLP-1 agonists, and insulin. DPP-4 inhibitors, the only oral incretin family medicinal target, are novel. Several less popular oral type 2 diabetes medications have been approved. Meglitinides are advised for irregular mealtimes or late post-prandial hypoglycemia with usual SU therapy. Although briefly discussed as potential therapies for some people, bromocriptine, bile-acid sequestrants, and -glucosidase inhibitors (AGIs) are not presently on the therapy plan. DPP-4 inhibitors, meglitinide analogs, AGIs, BAS, and bromocriptine will be reviewed for efficacy and safety. However, long-term clinical usage of metformin, SUs, and TZDs will be discussed.

Metformin, SUs, and TZDs may lower HbA1c by 1–1.5%. Metformin reduces weight, LDL cholesterol, and hypoglycemia more than SUs and TZDs. The SU class is efficacious, although a retrospective cohort examination of Veterans who began metformin or SU monotherapy showed a greater risk of major cardiovascular events with SU. TZDs perform similarly to metformin and SU. Pioglitazone reduces TG, dense, atherogenic LDL particles, and HDL cholesterol [4,5]. The Prospective

Pioglitazone Clinical trial in Macrovascular Events (PROACTIVE) study confirmed that type 2 diabetics treated with pioglitazone had vascular improvements. Rosiglitazone elevates TG, LDL, and HDL less than pioglitazone. Rosiglitazone raises LDL cholesterol faster than pioglitazone. The TZD receptor, peroxisome proliferator-activated receptor-gamma (PPAR-), inhibits CD36, a protein on macrophage cells that binds oxidized LDL and helps atherosclerotic foam cells form. Targeted CD36 gene disruption can prevent atherosclerotic plaques. TZDs are unsafe. Rosiglitazone was stopped because to myocardial infarction concerns, while pioglitazone was connected to bladder cancer in 2011. TZDs can cause edema and bone fracture.

DPP-4 inhibitors

DPP-4 inhibitors increase GLP-1 and GIP levels by blocking DPP-4 enzyme degradation. In the 1960s, an intrajejunal glucose infusion produced a greater insulin response than an intravenous one, demonstrating the incretin effect. GLP-1 and GIP produce most nutrient-stimulated insulin. GLP-1 slows stomach emptying, reduces glucagon secretion, increases -cell bulk in mice and rats, and preserves -cell function. Since diabetes causes incretin loss, treatments that reproduce and enhance the axis were studied. DPP-4 inhibitors increase GLP-1, GIP, insulin, and decrease glucagon.

In 2006, saxagliptin and linagliptin joined sitagliptin as US-licensed DPP-4 inhibitors. Sitagliptin, saxagliptin, and linagliptin are taken once day at their maximum dosages. Vildagliptin is approved for clinical use in Europe and many other countries, whereas alogliptin is only licensed in Japan. Vildagliptin has a 100-mg daily limit, whereas alogliptin has 25 mg.

With a few exceptions, DPP-4 oral diabetic medications have similar pharmacokinetics. This class's oral bioavailability is good and unaffected by diet. Sitagliptin, linagliptin, and alogliptin have long half-lives, allowing once-daily administration. Unlike vildagliptin, saxagliptin is dosed once day due to its active metabolite. Despite shorter half-lives. Most DPP-4 inhibitors are cleared via the kidney, except linagliptin and vildagliptin. Renal impairment affects renal excretion, thus all drugs except linagliptin should be modified. There are no dose modifications for hepatic impairment other than avoiding using vildagliptin, perhaps due to a lack of evidence on severe liver dysfunction. Saxagliptin's drug-drug interactions with CYP3A4 inhibitors such ketoconazole, clarithromycin, and atazanavir need a dose reduction. Pharmacodynamic testing shows DPP-4 suppression and GLP-1 increase after a meal challenge. DPP-4 inhibitors have been extensively studied against placebo, oral medicines, and combination therapy.

DPP-4 inhibitor monotherapy

Each DPP-4 inhibitor has multiple randomized, placebo-controlled studies proving its effectiveness. In a 24-week sitagliptin experiment, individuals on baseline diet or OHA received placebo, 100, or 200 mg after a washout period. HbA1c changed +0.2, −0.6, and −0.8% from baseline (8.0%) ($p < 0.001$). Sitagliptin 100 and 200 mg decreased fasting plasma glucose (FPG) by 13 and 16 mg/dl, respectively, whereas the placebo group increased by 5 mg/dl ($p < 0.001$). Post-prandial glucose (PPG) reduced by 2, 49, and 56 mg/dl in the placebo, sitagliptin 100, and 200 mg groups ($p < 0.001$). In

another 18-week research, sitagliptin reduced HbA1c, FPG, and PPG more than placebo. Sitagliptin 100 and 200 mg groups decreased 0.5 and 0.4% from a mean baseline HbA1c of 8.1%, whereas the placebo group increased 0.2% ($p < 0.001$). Treatment reduced HbA1c more in higher-baseline patients. These findings revealed sitagliptin 100- and 200-mg dosages were equally effective, leading to the recommended level of 100 mg.

Saxagliptin monotherapy was tested in a 24-week study of diet and exercise-resistant diabetics. Saxagliptin 2.5, 5, or 10 mg/day decreased HbA1c by 0.4, 0.5, or 0.5% from a mean baseline of 7.9%, whereas the placebo group increased by 0.2% ($p < 0.0001$). Saxagliptin reduced baseline HbA1c by 0.8 to 1.3%, whereas placebo increased by 0.1%. FPG decreases from baseline were −15, −9, and −17 mg/dl for saxagliptin 2.5, 5, and 10 mg groups, respectively, and +6 mg/dl for placebo.

PPG decreases from baseline for saxagliptin 2.5, 5, and 10 mg were −45, −43, and −54 mg/dl, respectively, compared to placebo's −6 mg/dl. Saxagliptin studies showed peak HbA1c, FPG, and PPG responses at 5 mg without a dose-response association at higher doses.

Accordingly, saxagliptin 5 mg is the recommended dose.

Linagliptin 5 mg/day or a placebo was randomly given to participants in a 24-week study. Linagliptin decreased HbA1c by 0.4% from 8.0%, whereas a placebo increased it by 0.3% (p 0.0001). Linagliptin-treated patients with baseline HbA1c 9% saw even greater reductions of 0.9%. Linagliptin reduced FPG by 9 mg/dl, whereas placebo increased it by 14 mg/dl (p 0.0001).

Linagliptin reduced 2-h PPG by 34 mg/dl, whereas placebo increased by 25 mg/dl (p 0.0001).

Vildagliptin outperformed placebo in uncontrolled diabetics assigned to 50 mg, 50 mg twice a day, or 100 mg. From a mean baseline HbA1c of 8.4%, vildagliptin 50 mg, 50 mg b.i.d., 100 mg/day, and placebo groups exhibited decreases of 0.4, 0.7, and 0.8%, respectively, compared to a 0.1% increase. HbA1c decreased more in those with baseline values over 8.0%. The 100 mg/day vildagliptin group reduced FPG significantly, however the 50 mg/day group did not. Vildagliptin's efficacy was dose-related, hence the recommended daily dose is 100 mg, unless used with an SU, in which case 50 mg/day is indicated.

The 12.5 mg and 25 mg alogliptin monotherapy groups in treatment-nave individuals had 0.6% lower HbA1c than the placebo group after 26 weeks (p 0.001). The placebo group increased FPG by 11 mg/dl, whereas the alogliptin 12.5 and 25 mg groups decreased FPG by 10 and 14 mg/dl, respectively (p 0.001).

DPP-4 inhibitors versus metformin

Since metformin is first-line therapy, DPP-4 inhibitors have been compared to it. Participants randomly randomized to 100 mg sitagliptin or 2000 mg metformin/day had HbA1c decreases of 0.4 and 0.6%, respectively, from baseline (7.2%). Metformin had a greater impact on FPG than sitagliptin (19 vs. -12 mg/dl). More metformin patients (76 vs. 69%) attained their 7% HbA1c goal. This study's low baseline HbA1c levels limited HbA1c reductions. Non-inferiority was another negative.

In another experiment, diet-unmanaged patients were randomized to receive 100 mg of vildagliptin or 2000 mg of metformin per day for 52 weeks.

Vildagliptin and metformin both decreased HbA1c from 8.4% to 1.0% and 1.4%, respectively (p 0.001). Vildagliptin's superiority to metformin remained unproven. 35% of vildagliptin and 45% of metformin recipients had HbA1c < 7.0%. Vildagliptin increased FPG by 16 mg/dl (p 0.001 vs baseline), whereas metformin increased it by 34 mg/dl (p 0.001 vs baseline and vildagliptin).

A meta-analysis of metformin monotherapy and DPP-4 inhibitor studies was conducted recently. DPP-4 inhibitors reduced body weight and HbA1c less than metformin (weighted mean difference 1.50, 95% CI 0.90-2.11) and 0.20 and 0.08, respectively. Metformin was also more likely than DPP-4 inhibitors to reach a 7.0% HbA1c (risk ratio 1.18, 95% CI 1.07 - 1.29).

DPP-4 inhibitors versus SU

SU's effectiveness makes a comparison with DPP-4 inhibitors interesting. In subjects with uncontrolled blood sugar on metformin alone, sitagliptin 100 mg/day was compared to glipizide 5 mg/day (titrated to 20 mg/day) over 52 weeks. Sitagliptin was non-inferior to glipizide based on the 0.7% decrease in HbA1c from a mean baseline of 7.7%. Sitagliptin (63%) and glipizide (59%) showed similar numbers of patients with HbA1c levels 7% at week 52 and similar increases in FPG from baseline (10 mg/dl, sitagliptin; 8 mg/dl, glipizide).

In a study comparing DDP-4 with SU therapy, subjects with inadequate glycemic control on metformin alone or with one additional antidiabetic medicine (washed out during screening) were randomized to receive either linagliptin 5 mg/day or glimepiride 1 mg/day (possible escalation to 4 mg/day). Linagliptin and glimepiride had equivalent 2-year HbA1c reductions from a mean baseline of 7.7% (0.2% and 0.4%, respectively). 30% of linagliptin and 35% of glimepiride patients had HbA1c ≤ 7.0% at week 104. Other study suggests DPP-4 inhibitors are comparable to SUs.

DPP-4 inhibitors in combination

The efficacy and safety of DPP-4 inhibitors in combination treatment with metformin, SUs, TZDs, and insulin have also been shown. In a 24-week trial, participants were randomly assigned to receive placebo, 100 mg/day of sitagliptin (S100), 500 mg or 1000 mg/day of metformin (M1000, M2000), or 50 mg/day of sitagliptin combined with 500 mg or 1000 mg/day of metformin (S100/M1000, S100/M2000). HbA1c changes from baseline (mean 8.8%) were +0.2% for the placebo, -0.7% for the S100, -0.8% for the M1000, -1.1% for the M2000, -1.4% for the S100/M1000, and -1.9% for the S100/M2000. Each group saw a statistically significant change in comparison to the placebo (p 0.001). In comparison to placebo, metformin alone, and sitagliptin alone, the combination treatment significantly reduced HbA1c, FPG, and PPG (p 0.001). Due to their complimentary modes of action, this research showed that the DPP-4 family of drugs and metformin had an additive impact in patients who are not effectively managed by diet and exercise. It shown that this combination is a viable first line of treatment for individuals with increased HbA1c levels who are unlikely to respond to monotherapy.

Subjects with insufficient glycemic control on metformin alone were randomized to the addition of placebo or saxagliptin 2.5, 5 or 10 mg/day in another research of DPP-4/metformin combination treatment. Saxagliptin 2.5, 5 and 10 mg groups had reductions of 0.6, 0.7, and 0.6% from a

mean baseline HbA1c of 8.0%, compared to a rise of 0.1% in the placebo/metformin group (p 0.0001). Statistically significant decreases in FPG and PPG were also seen in the saxagliptin vs placebo add-on groups. Each DPP-4 inhibitor is available as a single pill combination tablet with metformin for simplicity of administration due to the shown effectiveness of DPP-4 and metformin combination treatment.

The addition of a DPP-4 inhibitor to SU treatment has also received substantial research. When sitagliptin was added to glimepiride and metformin-treated patients, the change in HbA1c from baseline (8.3%) was reduced by 0.5%, compared to a 0.3% rise with placebo (p 0.001). In the sitagliptin add-on group, FPG and PPG levels decreased by 4 and 23 mg/dl, respectively, whereas they increased by 16 and 14 mg/dl in the placebo group. Sitagliptin added to glimepiride and metformin improved glycemic control, but at the price of a greater incidence of overall (60 vs 47%) and drug-related unpleasant events (15 vs 7%) in the sitagliptin group compared to the placebo group. The greater incidence of hypoglycemia with sitagliptin added to SU metformin treatment was primarily responsible for the increased incidence of side events.

When sitagliptin was introduced to patients receiving pioglitazone medication but with poor glycemic control, DPP-4 inhibitor therapy also shown effectiveness in conjunction with TZDs. After 24 weeks, the inclusion of sitagliptin caused a reduction in HbA1c of 0.9% as opposed to 0.2% for the placebo (p 0.001). In the sitagliptin group, FPG fell by 17 mg/dl, but in the placebo group, it rose by 1 mg/dl (p 0.001). The addition of sitagliptin to pioglitazone was generally well tolerated, and both the sitagliptin and placebo add-on groups saw comparable rates of total adverse events and hypoglycemia.

DPP-4 inhibitor and insulin combo treatment has also proved effective. The addition of sitagliptin reduced HbA1c by 0.6% in patients with suboptimal glycemic control who were receiving insulin monotherapy or metformin in combination (baseline HbA1c 8.7%); this was in contrast to the placebo group, which had no change from baseline (p 0.001). When sitagliptin was introduced to insulin treatment in comparison to placebo, both FPG and PPG dropped dramatically (p 0.001). Despite better glycemic control, sitagliptin had a greater incidence of adverse events (52%) than a placebo (43%), mostly because it caused more hypoglycemia (16% vs. 8% with sitagliptin). Unless hypoglycemia developed, the dosages of metformin and insulin were constant throughout the research. From a mean baseline of 8.4%, patients in the vildagliptin/insulin group saw reductions in HbA1c of 0.5%, compared to reductions of 0.2% in the insulin-only group (p = 0.01). In a subgroup analysis of individuals under 65 years old, the vildagliptin add-on group saw larger reductions in HbA1c of 0.7% compared to declines of just 0.1% in the placebo/insulin group (p 0.001). In this trial, insulin changes were permitted. It's interesting to note that individuals using vildagliptin had substantially reduced incidence of hypoglycemia than those taking a placebo (p 0.001).

Comparison between DPP-4 inhibitors

The absence of randomized controlled trials comparing DPP-4 inhibitors has hindered head-to-head comparisons. Indirect comparisons suggest similar efficacy and safety. An 18-week non-

inferiority trial compared sitagliptin 100 mg/day to saxagliptin 5 mg/day in metformin-resistant patients. Saxagliptin and sitagliptin had 0.6% and 0.5% adjusted mean HbA1c changes, respectively. Each group had similar adverse events. A meta-analysis of studies comparing the two medicines to placebo found that sitagliptin lowered HbA1c by 0.6% and vildagliptin by 0.7% (p 0.00001). Sitagliptin and vildagliptin were tested on daily blood glucose fluctuations. After 3 months, both groups had lower HbA1c, FPG, and PPG levels, but vildagliptin reduced glycemic excursions more.

Safety and tolerability

DPP-4- and placebo-treated individuals had similar rates of total, severe, drug-related, and GI side events, including hypoglycemia. Constipation, nasopharyngitis, urinary tract infection, myalgias, arthralgias, headache, and dizziness are more common in DPP-4-treated groups, although not statistically significant. Drug-related adverse events are fewer than metformin, mainly due to GI side effects. DPP-4 inhibitor with metformin do not increase GI adverse events statistically. DPP-4, which is similar to CD26, is present in immune-related tissues. DPP-4 inhibitors were suspected of immune-modulating. DPP-8 and DPP-9, not DPP-4, appear to impact immunological activation. DPP-4 inhibitor medication has increased white blood cell count, uric acid, and alkaline phosphatase somewhat from baseline, but these variations have not been statistically or clinically significant. The FDA mandated warning labeling on all products after 88 post-marketing pancreatitis incidences between 2006 and 2009. Preclinical pancreatic histology data from numerous animal species showed no treatment-related pancreatitis. A pooled review of controlled clinical trials found no increase in pancreatitis in DPP-4 inhibitor patients compared to placebo or other diabetic medications. Before and throughout therapy, vildagliptin 100 mg once day should be monitored for hepatic impairment due to rare instances. DPP-4 inhibitors seldom cause hypoglycemia. SU causes greater hypoglycemia than DPP-4 inhibitors. A DPP-4 inhibitor administered to an SU, but not metformin, increases drug-related side effects, primarily hypoglycemia. If not monitored for insulin dosage modification, adding a DPP-4 inhibitor to insulin might exacerbate hypoglycemia. DPP-4 inhibitors have no weight impact. Metformin loses more weight than gliptins and SU treatment gains weight. DPP-4 inhibitors do not enhance cardiovascular or cerebrovascular risk. These retrospective studies used Phase II and III data. Data reveal a cardioprotective effect that warrants further study. Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 Trial (SAVOR-TIMI 53), Sitagliptin Cardiovascular Outcomes Study (TECOS), and Cardiovascular Outcomes DPP-4 inhibitors are being tested for long-term safety and cardiovascular outcomes in EXAMINE and CAROLINA. DPP-4 inhibitors are safe and effective for seniors. Due to decreased hypoglycemia risk, they are ideal for this demographic. Due to absence of CYP isoform interaction, drug–drug interactions are rare, except for saxagliptin, which is metabolized by CYP3A4/5. Renal impairment is safe and effective with DPP-4 medicines. Except for vildagliptin, their

pharmacokinetics do not vary with hepatic impairment, making them safe to use.

Meglitinide monotherapy

In randomized, double-blind multicenter studies, repaglinide improved glycemic control over placebo. After a washout period, background diet or OHA individuals received repaglinide 1 or 4 mg with meals for 24 weeks. HbA1c rose 1.4% in the placebo group and reduced 0.7 and 0.5% in the repaglinide 1 and 4 mg groups, respectively, from a mean baseline of 8.7% ($p < 0.001$). The placebo, repaglinide 1, and 4 mg groups had mean FPG changes of +19, −47, and −49 mg/dl ($p < 0.001$). In another 16-week trial in individuals poorly managed by diet alone, repaglinide and placebo reduced HbA1c by 1.1 and 0.2% (from 7.7%), respectively ($p < 0.001$). Repaglinide therapy lowered FPG by 32 mg/dl ($p < 0.001$).

Meglitinide versus metformin

Repaglinide monotherapy improves glucose control equivalent to metformin. Pharmacotherapy-naïve patients assigned to repaglinide or metformin had substantial HbA1c, FPG, and PPG reductions at 12 months ($p < 0.05$). Repaglinide and metformin reduced HbA1c by 0.8 and 0.9% from a mean baseline of 7.5%. HbA1c, FPG, and PPG did not change across groups, however repaglinide substantially reduced PPG ($p < 0.05$).

Meglitinides versus SU

Patients received repaglinide or glipizide (up to 15 mg/day) after a washout period for one year. HbA1c increased from 7.3% to 7.8% when treated with repaglinide and glipizide, respectively ($p < 0.05$ across groups). FPG fell initially but rose in both treatment groups. Glipizide increased FPG more than repaglinide (23 vs 9 mg/dl, $p < 0.05$). Repaglinide with glyburide monotherapy raised HbA1c by 0.1% from a mean baseline of 8.8% in a 1-year trial. Repaglinide and glyburide reduced HbA1c by 1.3 and 1.1% in OHA-naïve patients. Groups had comparable FPG alterations.

Meglitinides in combination

Repaglinide combined to metformin decreased HbA1c by 1.4% (from 8.3%) in poorly managed patients ($p < 0.05$). Repaglinide and metformin monotherapy reduced HbA1c by 0.4 and 0.3%, respectively ($p < 0.05$ compared to combination treatment). The combination group's mean FPG dropped 40 mg/dl ($p < 0.05$) but neither mono-therapy group did. In this trial, combined treatment with repaglinide as a metformin substitute showed no glycemic control loss. A 6-month experiment compared repaglinide and pioglitazone [80]. Patients with insufficient metformin or SU control were randomized to combination repaglinide/pioglitazone, monotherapy, or monotherapy. HbA1c changes from a mean baseline of 9.1% were −1.8, −0.2, and +0.3% for combination treatment, repaglinide monotherapy, and pioglitazone monotherapy, respectively ($p < 0.001$). Monotherapy groups were similar. Combination treatment reduced FPG by 82 mg/dl, compared to 34 and 19 mg/dl for repaglinide and pioglitazone monotherapy ($p < 0.001$).

Repaglinide versus nateglinide

Repaglinide and nateglinide monotherapies were examined over 16 weeks in uncontrolled dieters and exercisers. Repaglinide reduced HbA1c and FPG from baseline (8.0%) more than nateglinide monotherapy (−1.6 vs −1.0%; $p = 0.002$). Groups had similar post-prandial glycemic effects.

Safety and tolerability

Glinides, notably repaglinide, cause hypoglycemia most often. 11, 27, and 35%

of placebo-, repaglinide 1-, and 4-mg-treated participants had hypoglycemic symptoms. Only two repaglinide 4 mg patients reported hypoglycemia symptoms with a blood glucose reading < 45 mg/dl. No serious occurrences required third-party help or hospitalization. Hypoglycemic episodes are more common in OHA-naïve or HbA1c < 8% patients and less common with lower doses of repaglinide, with 3, 11, and 18% of subjects reporting symptoms with placebo, 0.5, and 1 mg, respectively. 15% of repaglinide patients and 19% of glipizide or glyburide patients have hypoglycemia symptoms. With SU therapy, hypoglycemic blood glucose levels were lower and more commonly below 45 mg/dl. Repaglinide has a greater risk of hypoglycemia than nateglinide due to KATP channel interaction. Minor hypoglycemia events, defined as blood glucose levels < 50 mg/dl, occurred in 7% of the repaglinide group but 0% of the nateglinide group. No serious hypoglycemia incidents required third-party help.

Weightless glinides. Repaglinide-treated individuals gained 0.4 kg, similar to placebo-treated patients. SU treatment did not affect weight change. Repaglinide gained more than metformin but less than pioglitazone.

In a major research (n = 9306), individuals with poor glucose tolerance were randomized to nateglinide or placebo and monitored for a median of 5 years to assess diabetes and cardiovascular risk. Nateglinide did not reduce new diabetes, cardiovascular outcomes, or mortality from any cause.

Nateglinide was well-tolerated and safe in treatment-naïve elderly adults. Meglitinides are substantially metabolized by cytochrome P450 enzymes, therefore patients using ketoconazole, gemfibrizol, trimethoprim, cyclosoporin, or rifampin should take them with care. Over three months, renally impaired patients switched to repaglinide were evaluated. Except during the runin phase, renal impairment did not exacerbate hypoglycemia. The final medication dosage decreased significantly with renal impairment (p = 0.03). In pharmacokinetic investigations of nateglinide, renal clearance decreased with renal failure, while plasma area under the curve and half-life did not. Renal impairment and hemodialysis patients tolerated nateglinide. Despite uncommon hepatotoxicity, glinides are safe in liver impairment.

α-Glucosidase inhibitors

1990s AGIs were authorized for type 2 diabetic therapy. AGIs compete with enterocyte brush boundary α-glucosidase enzymes. Delaying carbohydrate absorption lowers plasma glucose. GLP-1 secretion is increased but not insulin secretion. The US approves just acarbose and miglitol. Both are taken with meals at 100 mg t.i.d. Table 3 covers studies with acarbose, the most studied AGI, either monotherapy or in combination with major diabetic medications.

Acarbose monotherapy versus metformin versus SU

Acarbose reduced HbA1c, FPG, and PPG better than diet (p 0.01, 0.05, and 0.05). HbA1c dropped from 6.8% to 0.7% against placebo. The Essen and Essen II studies compared acarbose to placebo, SU, and metformin as first-line treatment for type 2 diabetes in unmedicated adults. Over 24 weeks, acarbose plus metformin or glibenclamide therapy decreased HbA1c, FPG, and PPG by the same amount. All treatment groups lowered

HbA1c by 1%.

Acarbose in combination

When combined with metformin or SU, acarbose reduced HbA1c by 0.6–0.9% and FPG and PPG by 30 mg/dl. Chiasson et al. added acarbose to baseline diet, metformin, SU, and insulin therapy for a year. Acarbose reduced HbA1c by 0.9% (diet, p=0.005) to 0.4% (insulin, p=0.07) in all groups. Only diet and SU treatment decreased FPG (p 0.001 and p = 0.013, respectively), whereas add-on acarbose therapy decreased PPG (p 0.01). A similar 3-year experiment showed that acarbose, when added to pre-existing medicine, reduced HbA1c from placebo by 0.7% (multiple insulin, p = 0.025) to 0.1% (SU plus insulin, p = 0.9). After three years of treatment, FPG did not improve, although HbA1c improved by 0.5% across all groups (p 0.001).

In a pooled analysis of 41 AGI trials (n = 8130), 30 of which evaluated acarbose, HbA1c decreased by 0.8%, FPG by 20 mg/dl, and PPG by 41 mg/dl.

Safety and tolerability

Acarbose has a greater risk of flatulence (30 vs 12%, p 0.00001) and diarrhea (16 vs 8%, p 0.0001) than placebo, which adds to its high non-compliance rate (49% after 1 year of medication). At 3 years, urine albumin, -cell function, and insulin sensitivity were unchanged from placebo. Acarbose with SU or insulin frequently cause hypoglycemia.

Acarbose is weight-neutral in placebo-controlled studies but weight-beneficial in SU-controlled study. Acarbose outperformed SU by 1.9 kg in the pooled analysis.

1429 people with impaired glucose tolerance received acarbose for three years in the STOP-NIDDM study.

New-onset diabetes and hypertension were reduced by 25% and 34%, respectively. Myocardial infarction and any cardiovascular episode had significantly decreased risks (HR 0.09, p = 0.02, and HR 0.51, p 0.03, respectively). The scientists think targeting PPG may have produced these cardiovascular benefits.

Acarbose monotherapy helps older patients. Acarbose improved glucose clamp and homeostasis model assessment (HOMA) insulin sensitivity in older people (average age 68) over 12 months. Acarbose may affect digoxin bioavailability. Acarbose plasma concentrations grow proportionally with renal impairment in patients with serum creatinine levels > 2.0 mg/dl, although long-term data are lacking.

Rare liver transaminase increases in patients taking 100 mg t.i.d. (62 post-marketing incidences in over 3 million patient years).

Bile-acid sequestrants

Despite originally intended to treat hyperlipidemia, BAS were accidentally found to reduce plasma glucose in lipid-lowering studies. Process is unknown. The liver and stomach farsenoid X receptor may reduce endogenous glucose production. BAS may boost incretin hormone secretion. Only colestivelam is approved for type 2 diabetes in the US and Europe. Take Colesevelam 3.8 g with meals once or twice a day.

BAS in combination

Colesevelam has only been examined in combination therapy. Colesevelam reduced average FPG by 14 mg/dl and HbA1c by 0.5% compared to metformin, SU, or insulin. Patients with baseline HbA1c > 8% exhibited a somewhat higher drop than those with 8%. In all background groups, more than 47% of colesevelam-treated patients reduced their

HbA1c by 0.7% and their FPG by 30 mg/dl. After the investigations, colesevelam patients with > 80% compliance (n = 509) were eligible for a 52-week open-label extension trial. In the open-label extension experiment, patients who maintained colesevelam had a 0.1% HbA1c decrease and a 4 mg/dl FPG drop from baseline, compared to 0.3% and 9.5 mg/dl for placebo-treated patients. When administered with metformin, colesevelam 3.75 mg/day lowered HbA1c by 0.3% (p = 0.031) compared to rosiglitazone 4 mg/day (0.6%, p 0.001) and sitagliptin 100 mg/day (0.4%, p 0.009).

Colesevelam enhanced lipid indicators and glycemic control. LDL cholesterol dropped 15% from placebo in colestipol-treated patients. Colesevelam raised TG levels by 16% in those with baseline average TG levels below 180 mg/dl. TG and LDL cholesterol decreased similarly in the open-label extension trial. Colesevelam reduced LDL cholesterol by 11% from baseline (p = 0.001), compared to Rosiglitazone (8%, p = 0.04) and Sitagliptin (8%, p = 0.029). The colesevelam- and rosiglitazone-treated groups had significantly increased TG levels (15 and 24%, respectively, p 0.001).

Safety and tolerability

The 52-week open-label extension experiment assessed colesevelam safety and effectiveness. 361 of 509 patients completed the extended study. Colesevelam caused 11% of adverse events in 71% of individuals. Constipation and flatulence were the most prevalent adverse effects. 1 metformin, 5 SU, and 11 insulin patients had hypoglycemia (16/17 mild-moderate). Those who finished the extension lost 0.2 kg.

Colesevelam's long-term effects on TG levels and pancreatitis or cardiovascular consequences in diabetic patients are unknown. No long-term evidence exists on cardiovascular outcomes associated to LDL cholesterol improvement, which authors think may be mitigated by TG rise. In the big efficacy studies of colesevelam (n = 1128), 22% of individuals were over 65, although effectiveness was not different. Colesevelam should be given 4 hours before cyclosporine, levothyroxine, glyburide, ethinyl estradiol, and norethindrone. No renal or hepatic dosage modification is advised.

Colesevelam is contraindicated in people with TG levels above 500 and should be taken cautiously in those over 300. Gastroparesis and GI motility abnormalities should not use colesevelam.

Bromocriptine mesylate

Bromocriptine mesylate is a central dopamine receptor agonist. Bromocriptine may alter the hypothalamic circadian rhythm, resulting in enhanced glucose tolerance and insulin sensitivity. In 2009, the FDA authorized the fast-release form of bromocriptine to treat type 2 diabetes. It should be taken within two hours of waking up at 1.6 mg/day and titrated to 4.8 mg/day. Bromocriptine has been tested alone or with SU, metformin, and insulin.

Bromocriptine as monotherapy

Two 6-month studies assigned overweight or obese type 2 diabetics to bromocriptine monotherapy or diet. In a cohort with an average baseline HbA1c of 8–9%, placebo reduced HbA1c by 0.4% and FPG by 27 mg/dl compared to diet alone. Bromocriptine-treated individuals were more likely to reduce PPG (p < 0.002) and HbA1c (28%) from baseline than diet alone (8%).

Bromocriptine in combination

Adding bromocriptine to SU treatment improves glycemic parameters.

Overweight adults receiving bromocriptine for six months (n = 730) had mean HbA1c and FPG reductions of 0.6% and 20 mg/dl, respectively, compared to placebo. The third and largest trial (n = 485) showed decreased PPG (p 0.0002). Smaller studies with 40–60 people over 12–16 weeks showed greater HbA1c reductions from placebo (1–1.8%).

Over 12 weeks, 105 type 2 diabetics (mean HbA1c 7.8%) received bromocriptine monotherapy, dual bromocriptine and metformin treatment, or metformin monotherapy. Metformin outperformed bromocriptine in decreasing HbA1c and FPG. Bromocriptine + metformin improved HbA1c and FPG somewhat (p-value not reported) compared to monotherapy.

In the largest bromocriptine safety and efficacy study, 3070 type 2 diabetics were randomly assigned to receive a placebo or their usual diabetic therapy plus once-daily bromocriptine for 52 weeks. Insulin alone, two OHAs, or one OHA is typical diabetes therapy. After week 12, pre-trial diabetes medication may be increased or titrated to maintain glycemic control or avoid hypoglycemia. At week 24, the placebo group's mean HbA1c decrease was 0.2%, whereas the bromocriptine group's was 0% (no p-value). 60% of patients had HbA1c sub 7% at enrollment. Bromocriptine-treated individuals with HbA1c 7.5% had a larger drop (0.5% from baseline, p 0.001). Bromocriptine reduced HbA1c by 0.8% compared to placebo in intention-to-treat analysis. Bromocriptine added to HbA1c 7% patients did not improve outcomes.

Safety and tolerability

In the largest 52-week safety and efficacy trial (n = 3070), 47% of bromocriptine patients quit compared to 32% of placebo patients. Bromocriptine caused nausea (8% vs. 1% with placebo). This and other studies reveal that bromocriptine-induced nausea was more common during initial titration and lasted around 2 weeks. Hypotension and orthostatic hypotension were reported (2.2, 0.3%, respectively) in bromocriptine-treated groups, and 98% of symptomatic patients were taking at least one antihypertensive treatment. Bromocriptine and TZDs did not increase peripheral edema, weight gain, or cardiac events. Post-marketing investigations of bromocriptine-treated patients (n = 2500) reported no hallucinations, psychosis or mental difficulties, severe fibrotic sequelae, stroke, or neuroleptic-like malignant syndromes.

Hypoglycemia was more prevalent in the bromocriptine-treated group (6.9% vs. 5.3%), defined as symptoms that quickly resolved with sufficient treatment, symptoms with a measured glucose 60 mg/dl, or symptoms with 49 mg/dl.

Over six months, bromocriptine monotherapy increased weight by 0.25 kg compared to placebo. Bromocriptine-treated SU patients gained 1.2 kg vs to 0.3 kg for placebo (p 0.0002).

Bromocriptine had a 0.58 hazard ratio and a 42% relative risk reduction for the time to first secondary cardiovascular end point compared to placebo, suggesting cardioprotection. Kaplan-Meier calculations suggest treating 79 persons to avoid one first major cardiovascular event.

The 52-week safety trial included 29% under 65. All age groups were safe and effective. Bromocriptine QR has not been tested in people using other dopamine receptor agonists or antagonists. Although cytochrome P4503A metabolism is significant, no renal or liver dose is recommended.

Conclusion

Metformin is an effective first-line therapy with good lipid and weight profiles. DPP-4 inhibitors, however less efficacious than metformin, are non-inferior to SU treatment because to their benign side effects and decreased risk of hypoglycemia. The meglitinides are equivalent to longer-acting SUs, however they have a more frequent daily dosing schedule, unknown effects on cardiovascular preconditioning, and similar hypoglycemia with repaglinide (less so with nateglinide). AGIs work, but their t.i.d. dose schedule and GI side effects restrict its use. BAS and bromocriptine have poor GI side effects and are less efficacious than metformin, SU, and TZD. These drugs seldom cause hypoglycemia without SU or insulin.

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