

Pharmacotherapy of Type 2 Diabetes – The Future

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In the last decade, explosion in therapeutic options for management of type 2 diabetes mellitus (DM) have increased significantly with advances in recombinant DNA technology, molecular biology, clinical chemistry; analogs of insulin have replaced animal insulin, and may displace NPH, regular lente, ultra lente, insulin's. Analogs such as insulin glargine, insulin lispro, insulin aspart, and insulin glulisine are becoming mainstream therapy for even type 2 DM Besides oral hypoglycemic agents i.e., sulphonyl ureas, biguanides and thiazolidinediones, newer insulin analogs and non-insulin antidiabetics are in various stages of development. Incretin analogs, amylin analogs, combined P PAR- γ and α agonists, islet-neogenesis gene-associated protein (INGAP) are most prominent amongst these. This review focuses on pramlintide, an amylin analog, GLP-1 agonists and exenatide, an exendin 4 analog recently approved for use in type 2 diabetes by US FDA. Newer insulin delivery methods and drugs have also been reviewed.

Key Words: Pharmacotherapy, Diabetes, Insulin

Received: 09/03/2006- Accepted: 09/07/2006

Introduction

Madhu meha (diabetes mellitus) has been known since ages, mentioned in Ayurveda by Sushruta, as sweetness of urine in a diabetic patient. Even though many scientists tried to

extract insulin from islets in pancreas (Paul Langerhans in 1869 and Zeulzer in early 1900's)¹ banting and best tested the active extract of insulin on a diabetic patient with success, and were awarded the Nobel Prize in 1923. Since then the clinical management of DM has undergone significant changes.

There is a continuing need for new and better drugs to treat diabetes as available treatments do not normalize glucose homeostasis or eliminate the threat of chronic diabetic complications; current methods of insulin therapy, also, do not accurately mimic the physiological behavior of normal β -Cell.² Although oral blood glucose-lowering agents and dietary measures only partially correct the insulin resistance and β -cell failure,³⁻⁵ epidemiological data confirm an insight that diabetic patients are still at risk of chronic tissue damage and premature death, even with assiduous use of the available therapies and the certainty that strict glycaemic control can diminish the threat of micro-vascular complications.⁶⁻⁸ This review discusses these novel therapeutic options in type 2 DM, including those whose potential for clinical use is still unclear, but does hold particular theoretical promise.

Based on the model(s) and site(s) of action of drugs, we can classify antidiabetic drugs as:

The *intestinal agents* inhibiting carbohydrate digestion, glucose absorption like miglitol, voglibose, plant polysaccharides,

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acarbose, Guar gum and modulators of Incretin hormones.

Insulin and insulin-modulating strategies using insulin analogs with designer pharmacokinetics like thyroxyl insulin, alternative insulin delivery methods and routes like oral and inhaled insulins, endogenous insulin secretagogues, initiators – like sulphonylurea, meglitinides, esters of succinic acid, potentiators –like GLP-I, exendin – 4, DPP-IV, Inhibitors, $\alpha 2$ blockers, phospholipase C activators.

Pancreatic β -cells regeneration agents like GLP-1 analogs, transcription factor PDX-1.

Insulin mimetics act on the insulin receptor inhibiting the dephosphorylation and inactivating the receptors. For example deoxyfrenolicin, vitamin K5, spermine, diamide, Peroxides, okadaic acid, phorbol esters, vanadium and trace elements like zinc, magnesium, manganese, selenium, molybdenum, tungsten, mercury and cadmium salts.

Insulin sensitizers like systemic insulin sensitizers, hepatic insulin sensitizers and global insulin sensitizers (which have both systemic / hepatic insulin sensitizing properties)

Incretins like amylin and analogs like pramlintide, glucagon like peptide-1 (GLP-1) agonists and related analogues, dipeptidyl peptidase IV inhibitors [DPP-IV inhibitors]

Other agents include inhibitors of counter regulatory hormones like glucagon receptor antagonists-Bay 27-9955, skymin, MB39890A, somatostatin analogues octreotide, Antilipolytic agents like nicotinic acid and its analogue acipimox. Fatty acid oxidation inhibitors like etomoxir, methyl palmoxirate, inhibitors of gluconeogenesis – like AICAR, aetiocholanolone and related analogues of dehydroepiandrosterone, glycogenolysis inhibitors – like BAY R3401, VLDL lipoprotein synthesis inhibitors-bezafibrate, gemfibrozil, antiobesity agents like ben flourex, medical16, orlistat, sibutramine, $\beta 3$ - adrenergic agonists, genetherapy and stem cell therapy.^{9,10}

Amylin is a naturally occurring 37-amino acid peptide, normally co-secreted from β -cell with insulin and c-peptide.¹¹ Amylin secretion is delayed and diminished in advanced type 2 DM and markedly reduced to absent in people with type 1 DM.¹² Amylin secretion is impaired in gestational diabetes, characterized by exaggerated secretion during pregnancy followed by impaired post stimulatory secretion.¹³ The metabolic effects of amylin and pramlintide include suppression of endogenous glucagon production especially in the postprandial state, consequent reduction of post prandial hepatic glucose production, reduction in gastric emptying time, and centrally-mediated induction of satiety and reduction in postprandial glucose levels.¹⁴⁻²²

Pramlintide is a synthetic stable and soluble analogue of amylin that does not aggregate and accumulate in islet tissue showing moderate improvement on glycaemic control in type 1 and 2 DM patients, in a dose range of 30-120 mg three times daily given subcutaneously (SC), at or just before meals,⁹ its structure is as follows:

K-C-N-T-A-T-C-A-T-O-R-L
-A-N-F-L-V-H-S-S-N-N-F
-G-P-I-L-P-P-T-N-V-G-S-N
-T-Y-NH₂

(American Association of Pharmaceutical Sciences).

It consists of a disulfide bridge between C2 & C7, with alanine, serine, serine in human amylin being replaced by 3 prolines. Potential sites of deamidation are at asparagine, glutamine and C terminal Tyrosine. All carboxyl groups in pramlintide are amidated rendering the molecule cationic at acidic pH. Isolation is done as a lyophilized salt with acetate as the counter ion. Amylin and presumably pramlintide potently inhibit the orexigenic (appetite-stimulating) stomach hormone ghrelin causing appetite suppression.²³

Long-term efficacy of pramlintide as an adjunct to insulin in type 1 & type 2 DM patients has been established.²⁴⁻²⁹ It has shown

significant reductions in HBA1c (0.6% - 0.9%) with mean weight loss of ~ 2kg without increase in insulin doses or frequency of hypoglycemic episodes.²⁴⁻²⁹ It is an adjunct for reducing postprandial glycaemic surges even in subjects treated with regular insulin or insulin lispro; it shows similar pharmacokinetics and pharmacodynamics even in adolescents.

It also shows reduction of postprandial glucagons and triglyceride excursions and reductions in overall daily glycaemic flux in Type I DM patients on insulin pumps.³⁰ In spite of 3 additional SC injections, as the drug cannot be mixed with insulin and given preprandially, patients have reported significant improvements in quality of life measures like perception of better glucose control, better functional ability at work, home and school and better self confidence in DM self-management.³¹ Safety of pramlintide has been established in extensive phase 2 and 3 trials. U.S.F.D.A. has officially approved pramlintide as an adjunct for diabetic pharmacotherapy.³² Major side effects are gastrointestinal, mild to moderate nausea, anorexia, early satiety and vomiting. Nausea is common during the first few weeks of therapy and tends to resolve after continuous use.²⁴⁻³⁰ All side effects are dose dependent and tolerance occurs after continued use. Hypoglycaemia, which resolves on reducing insulin dose, is mild to moderate. It is used in the management of individuals who have wide glycaemic swings, insulin resistance in obese people requiring large amounts of insulin and management of post prandial hyperglycemia in type 1 and type 2 DM patients who are already on insulin and are not needle phobic.

Incretins: Incretins are hormones released by nutrients from the gastrointestinal tract. Rising levels of incretin hormones amplify the glucose induced insulin release. This incretin effect is responsible for 50-70% of insulin response to oral glucose in healthy individuals. In patients with type 2 DM, the incretin effect is decreased because of loss of

second phase of insulin secretion mainly regulated by GIP and GLP-1.

Glucagon like peptide-1 agonists (GLP-1 agonists): Several hormones of enteroinsular axis, especially gastric inhibitory peptide (GIP) and glucagon like peptide amides stimulate insulin secretion.³³ GLP-1 is a major mediator of the 'Incretin effect', which results in enhanced insulin secretion associated with caloric intake.^{34,35} These hormones function in the ileal break system, which inhibits upper G.I. motility, and bowel associated secretions when food reaches the small intestines.³⁵ These 'Incretin' hormones potentiate nutrient – induced insulin secretion, at least partly through an increase in cyclic adenosine monophosphate (AMP) and protein kinase A (PKA) production within β -cell. This causes altered Ca²⁺ sensitivity through phosphorylation of intracellular proteins.³⁶

GLP-I receptors are widely distributed in the pancreatic islets, brain, heart, kidney and GIT. G.L.P-1 is a 30/31 amino acid peptide hormone (mol. W ~ 3000 KD) produced by endoprotease cleavage of proglucagon precursor. It is secreted by intestinal L-cells present predominantly in the ileum and colon. Biologically active GLP-1 is of two major types, GLP-1 (7-37) and GLP-1 (7-36) amide differing by a single amino acid. Neural and endocrine cells control secretion of GLP-1. It is caused by entry of nutrients into proximal GIT and subsequent contact of open type L cells with nutrients that have been digested. GLP-1 (7-36) amide is the major circulating amide even though both GLPs are equipotent. GLP-1 is an insulintropic hormone that also inhibits secretion of glucagon in a glucose dependent manner requiring at least euglycemia or hyperglycemia. Dipeptidyl peptidase IV (DPP-IV) enzyme rapidly cleaves GLP-1 into truncated inactive metabolite leading to a short half-life in both non-diabetics and diabetics.

Other effects of GLP-1 are induction of satiety and promotion of insulin mediated tis-

sue glucose uptake partly by enhancing endogenous insulin release in response to caloric intake.^{35,36} Inhibition of endogenous glucagon secretion; appetite suppression and satiety induction, reduction in speed of gastric emptying, Stimulation of islet growth, differentiation, and regeneration apparently mediated by transcription factor PDX-1^{35,41-43} possible role in protection and preservation of β -cells from cytokine and free fatty acid – mediated injury and apoptosis.⁹

Pharmacokinetics of GLP-1: Plasma half-life for IV infusion is 4-11 min with a clearance of ~13 ml/kg / min^{37,38} Time for reaching maximum concentration in plasma following SC injection is ~30 minutes. Basal levels are restored in 90-120 minutes. Nausea and vomiting develop over 500 pmol/L (major side effects).⁹ Unfavorable pharmacokinetics of endogenous GLP-1 (Plasma half life for I.V. administration in humans is 4-11 minutes, clearance is ~ 13mL/kg /min)^{37,38} has led to development of analogues, now in various stages of development.

Analogs of GLP-1 (agonists) include Liraglutide (an acylated GLP-1 analog bound to albumin), exendin 4 and its synthetic analog exenatide (AC-2993), which is a 39 amino acid – GLP-1 receptor antagonist.³⁶

Circulating enzyme, DPP-IV that cleaves off an N-terminal dipeptide, mainly inactivates GLP-1. Oral DPP-IV inhibitors are being evaluated as a means to enhance the activity of endogenous and exogenously administered GLP-1.³⁹

Other methods of increasing GLP-1 activity are resistance to DPP – IV; linking GLP-1 to a fatty acid (NN2211), albumin-binding also increases the time in circulation, and depot implants, buccal and oral formulation.⁴⁰

Liraglutide: it is a GLP-1 agonist analog with 97% homology with GLP-1, and has a fatty acid binding moiety leading to slow release from injection site and noncovalent dis-

sociable albumin binding. The half-life after single injection is 11-15 hours causing a decrease in glucagon and an increase in insulin levels. Single daily dose improves glucose profile within 24h in Type 2 diabetics. It is able to reduce fasting morning glucose and breakfast related glycaemic excursions.⁴⁴⁻⁴⁶

No side effects are seen except headache, nausea and vomiting.⁹ Dose of 0.45 mg/day – 0.75 mg/d were associated with glycaemic control comparable to glimepiride monotherapy with minimal side effects, weight loss and low risk of tight hypoglycaemia.⁴⁷

Exendin-4: It is a more stable peptide (39 amino acid) analog of GLP-1 that activates the GLP-1 receptor and produces the same profile of biological effects as GLP-1. It is a now a prototype drug.¹⁰ Dose range is from 5mcg/day – 10 mcg/day with a side effect profile of nausea and vomiting similar to GLP-1. Its immunological profile is under investigation.⁹ It is associated with endogenous autoantibody production in humans (in injections), its clinical significance often being seen in terms of any allergic reactions, serum sickness; it does not influence glycaemic response (Amigo Trials).⁴⁸ It is capable of increasing β -cell mass by inducing β -cell neogenesis, raising concerns of potential association with nesidioblastosis, insulinomas, and other pancreatic islet proliferative disorders.⁹

CJC-1131 a long acting analog of GLP-1 based on binding the GLP-1 analog to a reactive moiety at the carboxyl terminus and a D-Ala8-substitution with a linker. It binds to Lys34 of albumin on in vivo SQ/IV injection giving half – life similar to that of albumin (~ 2 weeks). It is not associated with significant cell or humoral – based immunogenicity.⁴⁹ The exact dosing schedule, interval and amount to use in humans are the subject of ongoing clinical trials.⁹

Ly-307161 a DPP-IV resistant GLP-1 agonist which has been shown to normalize

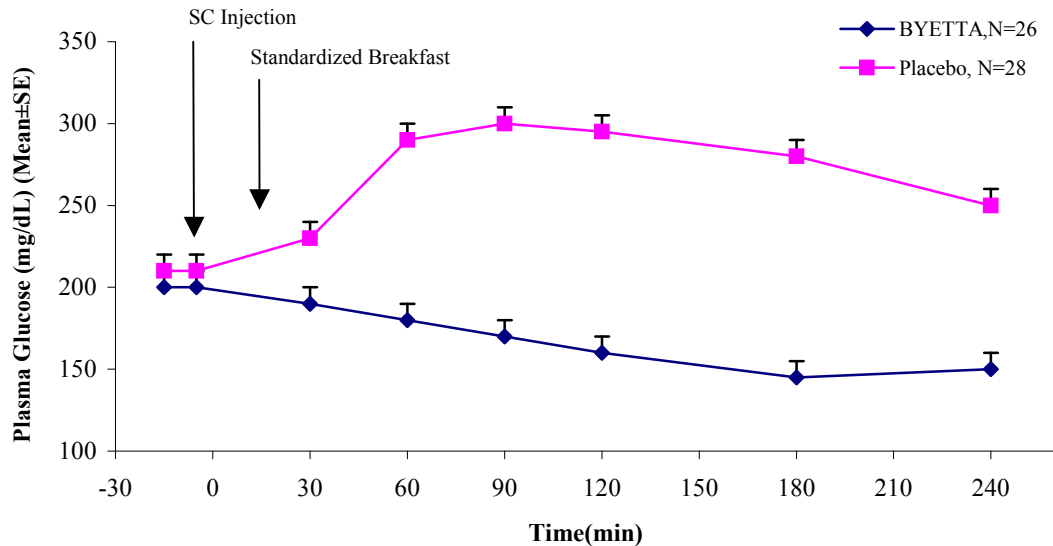


Fig.1. Postprandial plasma glucose concentrations on day 1 of treatment in patients with type 2 diabetes treated with a sulfonylurea, or both (N=54). * Mean dose (7.8 mcg based on body weight) of ByETTA was administered by subcutaneous injection.

glycaemic profiles and cause weight loss in type 2 DM patients on single daily doses of 4.5 mg / day. Nausea and injection site discomfort has caused it to be withdrawn from studies.⁵⁰⁻⁵⁵

Exendin-4's main potency and utility is in managing post prandial hyperglycemia as an adjunct to oral agents.⁹ CJC-1131 can be used as an adjunct for improving glycaemic control with efficacy lasting for 1 week post administration. GLP-1 agonists in various stages of progress will become a part of the therapeutic arsenal against DM in next 1-5 years.

Exenatide has completed fairly extensive phase 3 trials (Amigo trials) and has been recently approved by the US FDA for use in patients with Type 2 diabetes who have sub optimal glycaemic control, even those on treatment with metformin and /or other sulfonylureas. It improves glycaemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes. It is available in 300µg and 600 µg pre-filled pens delivering 5 and 10 µg per unit

dose as SC injections. It restores the first phase insulin response to iv glucose administration along with the second phase response. Loss of first phase of response is an early beta cell defect in type 2 diabetes (fig.1.). SQ injection in type 2 DM patients has a Tmax of 2.1 hours, and a Cmax of 211 pg/ml; AUC (0-inf) is 1036 pg.hr/mL increasing over the range of 5-10 mcg. The mean apparent volume of distribution is 28.3 L. It is excreted by predominantly glomerular filtration and proteolytic degradation with mean clearance of 9.1L/h and a mean terminal half-life of 2.4 h.¹²¹

Albugon is a fusion protein containing the DPP-IV resistant analog of GLP-1 covalently binding to human albumin with no "free" albugon available after in vivo administration.¹²⁰

Extended release formulations permitting once weekly intra muscular [IM] injection dosing schedule are in development, with dose titration being the only problem.⁹ Oral (buccal) delivery systems for GLP-1 are also

being investigated.^{56,57} These are very useful in controlling postprandial hyperglycemia in advanced type 2 diabetes, obese patients inadequately controlled with multiple oral agents.⁹ They have a favorable side effect profile except for nausea, fullness, bloating and vomiting which are generally dose dependent and can be ameliorated by reducing doses and or doing slow dose escalations. They do not cause clinically – significant hypoglycaemia except when associated with sulfonylureas.⁹

Dipeptidyl peptidase – IV inhibitors (DPP-IV inhibitors). The duration of action of GLP-1 is limited by rapid enzymatic breakdown by endopeptidase DPP-IV.^{58,59} DPP-IV inhibitors enhance the incretin system activity by blocking the GLP-1 degradation.

Various DPP-IV antagonists are being investigated in animal models and human subjects, the most promising being Vidagliptin (LAF-237) (Phase 3 trial),⁶⁰⁻⁶³ MK-0431 (Phase 2 & 3)⁶⁴ NVP-DPP-728⁶² (Phase 2). These will have a utility as oral agents, adjuncts or monotherapy in subjects with early onset type 2 diabetes, especially obese people. Oral metformin also inhibits DPP-IV in type 2 diabetes suggesting its potential role in combination therapy. They may be associated with mild weight loss and demonstrated efficacy in controlling fasting and postprandial hyperglycemia in twice daily and thrice daily dosing schedules so far tested. Adverse effects are pruritis, diarrhea, dizziness, and diaphoresis. The long term consequences of chronic inhibition of DPP-IV in humans are still unclear given the ubiquitous nature of the enzyme and degradation of over 20 different peptides like substance P, insulin like growth factor, neuropeptide Y, GLP-2 and G.I.P.⁹

Dual PPAR γ - PPAR α agonists (Glitazars) PPAR- α is strongly expressed in muscle and liver, mediates increased oxidation of fatty acids through increased transcription of acyl-CoA synthase, acyl-CoA oxidase and thiolase⁶⁶ stimulation of PPAR α by fibrates like,

Gemfibrozil, Clofibrate and Fenofibrate, accounts for much of the lipid lowering, especially triglycerides. Thus glitazars might lower both glucose and lipids, being dual agonists (PPAR- γ & PPAR- α). Several thiazolidinediones and non-thiazolidinedione binding to both PPAR- α & γ have been reported like TTT-501.⁶⁷⁻⁶⁹ The glitazars can be broadly classified into thiazolidinedione variants (DRF-2189, KRP-297) and non- Thiazolidinediones (ITT-501, BMS-298585 (Muraglitazar) AZ-242 (Tesaglitazar), NN-622 (Ragaglitazar).⁹ Published data of human trials is scant. Aryloxazolidinediones, a group of glitazars have shown efficacy in management of type 2 DM in the db/db mice.^{70,71} Their efficiency in amelioration of hypertriglyceridemia in db/db mouse is suggested to be superior to rosiglitazone.^{72,73} These show a favorable side effects profile with no cardiac hypertrophy as seen in rats using selective PPAR- γ agonists, which show antiproliferative properties, angiotensin 2 antagonism antioxidant effects.⁷⁴ Many beneficial vascular effects are seen like blood pressure reduction, correction of endothelial dysfunction, amelioration of cardiac fibrosis associated with hypertension and myocardial infarction.⁷⁴⁻⁷⁷

KRP-297: Studies in db/db and C57BL/65 mice show better effect of KRP-291 on glucose stimulated pancreatic insulin secretion and less weight gain in comparison with Pioglitazone or on combination of Pioglitazone with Bezafibrate (PPAR- α agonist).⁷⁸ Tesaglitazar showed similar findings in ob/ob diabetic mice and obese zucker rats.⁷⁹ Ragaglitazar, showed potent improvement in insulin sensitivity, reduction in hepatic glucose output, reduced serum triglyceride levels and reduced intramyocellular lipid accumulation, which was superior to rosiglitazone / PPAR α agonist WY-14643 in fat-fed rats. Resolution of visceral adiposity and hepatic fatty infiltration without associated hepatomegaly was seen.⁸⁰ Pan-PPAR agonists like propyl benzisoxales show efficacy superior to

rosaglitazone in db/db mouse. Glitazars up regulate human macrophage lipoprotein lipase activity,⁷² which could be beneficial in atherosclerotic vascular disease.⁸¹ In spite of promising results, many candidate drugs have been abandoned because of unexpected clinically significant adverse events like excessive peripheral edema, volume overload, heart failure, cardiomyopathy, bone marrow haemopoietic changes and soft tissue neoplasm in rodent models. FDA guidelines suggest that at least 2 years of animal based carcinogenicity data must be accumulated prior to human trials of glitazars.

Stages of development: TAK-559, from Takeda is in phase 1 and 2 human trials. A product from Bristol – Myers – Squibb is in Phase 3 human trial Tesaglitazar – Phase 3, Muraglitazar (BMS-298585)- Phase 3.⁹ Glitazars may play the role of potent insulin sensitizers with potent hypolipidemic effects and possible weight neutrality. It will play a prominent role as an adjunct or monotherapy for subjects with early type 2 DM, who are obese and insulin resistant may and it also play a role in management of the metabolic syndrome and prevention of diabetes.

Combined PPAR γ and RXR agonists: PPAR γ exists as a heterodimer, with retinoid X receptor (RXR) and activation of PPAR γ normally requires co activation of RXR by retinoic acid. Stimulation of RXR alone shows a reduction in feeding, reduced weight gain and increased expression of part of PI3 K complex.⁸¹ Recently co administration of a PPAR- γ agonist with an RXR agonist has produced an additive or synergistic improvement of insulin action in skeletal muscle compared with PPAR γ used alone.¹³

Insulin and insulin modulating strategies: Insulin potentiating agents: potentiation of insulin action has been seen in N-terminal fragments of human growth hormone and with dopamine D2 agonist bromocriptine.⁸²

Analog of insulin with designer pharmacokinetics: insulin detemir, thyroxyl insu-

lin, insulin lispro, insulin glargine, insulin Aspart, Insulin glulisine are some examples.

Glargine: It relies on a change in amino acid sequence at 31, 32 position that shifts the isoelectric point close to neutrality. This makes the molecule soluble and stable in the acid solution of the formulation when injected, the relatively alkaline environment of interstitial fluid causes the insulin molecules to associate into hexamers. These crystallize and then dissociate slowly, giving a flatter, protracted and more reproducible circulating insulin concentration profile.¹⁰

Structures of insulin analogue for injection contain the following:

Rapid acting: Lispro (B28 Lys, B29 Pro), Aspart B29 Asp

Long acting: Glargine (HOE901) A2161Y, B31Arg, B32 Arg.

Detemir (NN304) B29, Lys, tetradecanoyl, des at B30.

Hepatoselective: thyroxyl – insulin bound to – L – thyroxine

Insulin detemir: There are various insulins available for use as a combination of basal and bolus insulin delivery to simulate physiologic insulin dynamics in diabetic subjects using mixed/split insulin injection regimens. Short acting bolus deliveries using regular human insulin, Lispro, aspart, glulisine are available but few options are available for basal insulin delivery (Glargine - only peak less locally acting insulin available). Miscibility is a limitation of glargine and detemir was developed to address this need.

Insulin Detemir (NN-304) insulin analog with the structure, Lys (B29) – tetradecanoyl des (B30) human insulin is produced by linking a fatty acid (myristic acid) to the end of Beta [B] chain. The fatty acyl group binds the insulin to albumin, slowing its absorption and prolonging circulation time.^{83,84} Other fatty acids (palmitic acids) are similarly being investigated. Glargine shows increased affinity for IGF-1 receptor and thus increased mitogenic potency, whereas Detemir shows decreased affinity.⁸⁵ Detemir has decreased po-

tency (when compared with NPH),⁸⁶ a more predictable pharmacokinetic profile, and smoothness of glycaemic control.^{87,88} It has higher molar concentration than NPH, so can be used with similar injection volumes but with different notation of units (U) than the typical international units (IU) of insulins.⁸⁹ Detemir exists predominantly as a hexamer in presence of zinc or phenol. Only the monomeric form is active and can affect its biological response when the 14-C fattyacyl moiety on B29 position is dissociated from plasma albumin.⁸⁹ Time to peak concentration appears to be ~ 4-6 hours with 12 hours duration of action. It shows a more plateau like pharmacodynamic profile unlike NPH (Peaks).⁹⁰ Detemir is associated with weight neutral or weight loss (~ 0.5 – 0.8 kg) status.^{91,92} Detemir is not approved to be mixed with short acting analogs like Lispro, aspart, and glulisine in pre-mixed formulations. Detemir has a neutral pH and is soluble (Glargine, has an acidic pH) making miscibility with other insulins a much better prospect. Results of an ongoing head – to head study⁹³ comparing add-on insulin glargine Vs Insulin detemir with oral agents in insulin-naive type 2 DM patients, are eagerly awaited. Even definite pharmacokinetic/ pharmacodynamic mixing studies have not yet been completed. No distinct or unique side effects beyond those known and characterized for insulin in general are seen.

Stages of development: Completed extensive phase 3 trials. Obtained approval for open market use in several European countries. Clinical approval has been applied for at FDA and in Canada.

Thyroxylin insulin: Preferential delivery of insulin to liver – the primary target of insulin secreted by the pancreas but not when injected subcutaneously has led to development of thyroxyl – insulin. The open sinusoids of liver allow free access to the hepatocytes for large insulin linked molecules that are excluded from peripheral tissues by normal endothelial barrier. Insulin linked to thyroxine is highly protein bound giving a long plasma

half-life and its limited transport across the endothelium reduces action in peripheral tissue i.e. increased glucose uptake (decreased risk of hypoglycaemia), reduced lipolysis and reduced hepatic glucose production.⁹⁶

Alternative routes of insulin delivery: Insulin administered orally has poor and variable bioavailability in spite of using various emulsions, polymer complexes and encapsulated formulations. To overcome these problems alternative routes of insulin delivery are being searched.

(HIM2- hexyl insulin monoconjugate 2: A non-encapsulated conjugate of insulin with alkyl – polyethylene glycol, which can withstand enzymatic degradation in the alimentary tract and enter the circulation.⁹⁸

Inhaled insulins: Inhaled insulins have been developed to provide an alternative route of insulin delivery that is more acceptable to the patient than the needle based delivery systems. The highly vascular and easily accessible mucosal tissue beds of the lungs are exploited by these delivery systems.⁹⁶ Effective insulin delivery is dependent on adequate aerosol generation appropriate particle size (<5 µm) and appropriate inhalation mechanics to ensure delivery of the particles to the alveolar bed.⁹⁷ Aerosols can be developed either by nebulisation of insulin solutions or pulverization of solid insulin particles / crystals to form mists. Technosphere is a dextro-piperazine derivative, able to reversibly bind insulin and other peptides. It self assembles in spherical lattice array (spherules) at low pH and then dissolves as the neutral pH of the alveolus rapidly releases the bound insulin.^{98,99} The Alkermes delivery system uses porous individual particles for delivery of long acting insulin.¹⁰⁰ Nektar therapeutics is involved in developing artificial particles for pulmonary insulin delivery (pulmospheres).⁹⁷ The newer inhaler systems do not depend on achieving sufficient airflow rates prior to inhalation, and are much smaller, more cosmetically acceptable; they do not require

spacer systems or cause patient irritation of the aerosol before inhalation. Major pulmonary insulin products have consistently shown a rapid onset of action, generally faster than SC regular insulin and Lispro in clinical trials.¹⁰¹⁻¹⁰³ They are now of acceptable size with acceptable clinical efficacy. The delivery is still largely inefficient with ~90% of administered insulin being lost.⁹⁷ Bioavailability remains a concern and has necessitated the use of significantly higher molar insulin amounts by inhalation routes.

Inhaled insulin when used as an adjunct with oral hypoglycemic agents was associated with HbA1C improvements, increased titres of insulin antibodies in type I DM (no clinically significant relevance) and no changes in FEV1 or diffusing lung capacity (DLCO). Bio equivalence is 1mg of inhaled insulin for each 3 IU of SC injected insulin. Technosphere insulin shows pharmacokinetics similar to IV insulin with more rapid onset of action. 100 IU of technosphere insulin has more rapid onset of action than 10 U of regular SC insulin and same time to onset of action (~ 14 minutes) as 5U of IV insulin.⁹ Its biopotency and bioavailability relative to SC regular insulin are ~ 26%.^{98,100} It also provides early meal related insulin akin to cephalic phase of insulin release. It can be increased in doses of 6IU (~ 2IU of SC dose). Aerodose inhaler uses liquid aerosol insulin with a biopotency of ~ 10% to that of SC insulin, faster clinical effects than SC regular insulin with short time to peak concentration and a shorter time to peak metabolic effect. It is still in phase I study.⁹ It has a role in management of postprandial hyperglycemia and as an alternative to present short acting insulins, in providing meal related insulin bolus (after combining with long acting glargine /

detemir). It can be an adjunct to oral hypoglycemic agents.

Potential effects on pulmonary function and mitogenic activity include lung irritation and inflammation, allergic reactions, development of insulin antibodies. Alteration in pulmonary functions includes airway functions like reversible airway obstruction and / or diffusion defects (decrease diffusion lung capacity, DLCO). Upper respiratory tract infections and airway diseases like chronic bronchitis and asthma, smoking and diabetes itself affect the delivery of these compounds to lung bed.⁹ Several long-term surveillance studies need to be done to find definitive answers to these problems.

Oral insulins: Oral insulin is an attractive idea for controlling meal-related hyperglycemia; the major obstacle to it is an effective means of insulin delivery that escapes the digestive gut enzymes and maintains therapeutic efficacy. Also, no selective insulin transport mechanism occurs in the bowel wall. High molar pharmacological doses may be required to enable even a small amount of systemic absorption.⁹⁷ To protect oral insulin from enzymatic degradation it has been coated with positively charged liposomes or impermeable polymers.¹⁰⁴⁻¹¹⁰ Nanospheres and nanocubicles as alternative delivery models are still being developed in animal models.^{111,112} The variable intestinal transit time and variable delay in absorption of encapsulated insulin are other problems that need to be overcome for effective delivery of oral insulins.

Agents HIM2: (insulin nobex / hexyl insulin monoconjugate 2)

Table1. Comparison of DPP-1V inhibitors and GLP –1 agonists.^{118,119}

Properties	DPP -1V INHIBITORS	GLP-1 AGONISTS
Administration	Oral	Injectable (IV/SC)
Effect on weight	Mild weight loss	Severe weight loss
Adverse effects	Pruritis, diarrhea, dizziness	Gastric emptying inhibition, Nausea, vomiting, anorexia.
Target	Multiple targets as it is ubiquitous enzyme	Single known GPCR target enhancing incretin hormones effects
Duration	Short vs. long acting. Twice daily/thrice daily	Longer acting days to weeks
Potency	Less potent	More potent glucose lowering agents
Drug overdose	Non toxic	Toxic
Patient compliance	Excellent	Good for non needle phobic patients
Hypoglycaemia	None	None
Concerns	Consequences of inhibiting ubiquitous enzyme in long term uncertain	None physiological effects and consequences are well studied

It is an insulin oligomer conjugate formed by covalent bonding of an amphiphilic polymer (alkyl polyethylene glycol) to the lysine moiety on position 29 of the insulin beta chain^{112,113,8} it is easily absorbed from the intestine because its amphiphilic side chain confers on it resistance to the enzymatic degradation and enhances absorption from the bowel wall. It is a semi solid preparation encased in hard gelatinous capsules. Oralin, a buccal spray insulin developed has unreliable pharmacokinetics and questionable outcomes. HIM2 insulin is in early phase 1 and 2 studies in subjects with type 1 diabetes and type 2 diabetes. It has some efficacy in controlling fasting and postprandial hyperglycemia. Poor palatability, unpredictable pharmacokinetics (especially poor bio-availability (1%-4%) if overcome could make oral HIM2 insulin a mainstay in type 2 DM as a whole, either as monotherapy or in combination with oral

agents. Diarrhea, gastroenteritis, malabsorption syndrome are seen as side effects.

Phase of development: HIM-2-early phase 1&2. oralin and emisphere insulin- preliminary stages of human investigation.¹¹⁴⁻¹¹⁷

Rectal Insulins: Rectal delivery of insulin using suppositories and micro-enema has shown good bioavailability with peak insulin levels 30-45 minutes after administration. Local side effects like diarrhea, rectal discomfort and route of administration are limitations for further use of this insulin clinically.⁹

Dermal insulins: Direct skin delivery of insulin using low grade current as a means of altering the cutaneous lipophilic barriers to peptides by ionizing the peptide of interest (insulin) [Iontophoresis] has shown promising kinetics in animal studies as a potential

basal insulin delivery method. Clinical utility needs to be established.⁹

β Cell expanders: INGAP (Islet neogenesis gene-associated protein)

Rationale: β cells are capable of growth, multiplication, replication and regeneration. Pancreatic islets develop predominantly from differentiation from progenitor cells derived from the ductal epithelium. Subsequent β-cell growth is a result of differentiation of existing β-cells (~12% of islets regenerative capacity) and differentiation of progenitor stem cells. Pancreatic islet neogenesis was initially serendipitously observed and then isolated from regenerating pancreata, shown to stimulate pancreatic neogenesis and reverse streptozocin – induced diabetes in animal models. These findings have spurred recent phase 1 and 2 human trials for safety and efficacy investigation.

INGAP: It is a 175-amino acid endogenous peptide isolated from pancreatic tissue stimulating β cell growth, multiplication and regeneration. Its core biologic activity resides in a 15 – amino acid stretch, which has been synthesized as the INGAP peptide. No published data of INGAP or INGAP peptide in humans (phase 1 & 2) is available. But in streptozocin induced diabetes in hamsters it has shown to stimulate β-cell regeneration within 10 days of dosing 5mg/kg I.P. The degree of β-cell growth induced correlated directly with dose of peptide administered and

duration of use. INGAP plays a critical role in normal fetal development of the pancreatic islets.⁹ INGAP, if it shows efficacy in Phase 1 and 2 trials, would become a standard addition to all therapies in type 1 & 2 DM, in halting and / or reversing the islet cell damage of diabetes. It may have a role in diabetes prevention in high-risk groups, thus becoming a cure for diabetes especially in type I DM with no insulin resistance. Various adverse effects seen are local site reactions to injections (local pain, lipoatrophy, lipohypertrophy, pruritis). Because of its viscid nature, INGAP administration requires large bore needles making it more painful, leading to poor patient compliance. Dose response studies are not available. Stage of development is the early phase 1 and 2 human trials.

Conclusions

Various molecules are being tried to find a cure for type 2 diabetes. Amylin and its analog pramlintide, an incretin mimetic and GLP1 agonists and exenatide, an analog of Exendin 4 are the currently approved drugs for type 2 diabetes. Newer insulins delivery methods are also being tried to replace animal insulins with oral insulins taking the early lead. Therefore there is hope that we will soon be able to fight the disease in a more effective way and prevent the co morbidities.

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