Review Article and Clinical Experience

RECENT ADVANCES IN DIABETES TREATMENT OPTIONS (CARDIOPROTECTIVE NOVEL OHA AND INSULIN GLARGINE)

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ABSTRACT

In clinical practice, Oral Hypoglycemic Agents (OHA_S) and Oral Antihyperglicemic Agents (OAA_S) can be categorized into 3 classes: 1. Insulin Secretagogues (Sulphonylureas = SU_S: Glimepiride, Glipizide XL, Glibenclamide, Gliclazide, Gliquidone, etc, and Non–SU_S: Meglitinide: Repaglinide, Nateglinide), 2. Insulin Sensitizers and Anti-hyperglycemic Agents (Thiazolidinedions: Pioglitazone, Rosiglitazone, Darglitazone, and Biguanides: Metformin, 3-Guanidinopropionic-Acid), and 3. Intestinal Enzyme Inhibitors: α-Glucosidase Inhibitors (Acarbose, Voglibose, Miglitol, Castanospermine, etc) and α-Amylase Inhibitor (Tendamistase). A powerful, endogenous mechanism for protecting the heart, "Ischemic Preconditioning" occurs when cardiac K^+_{ATP} Channels open during brief periods of mild myocardial ischemia to protect against a longer ischemic episode. Glimepiride (GLIM), which is thought to be a pancreatic-specific, non-cardiac K^+_{ATP} Channel, does not blunt the response to "Ischemic Preconditioning", hence, GLIM may show cardioprotective effect. In contrast, Glibenclamide abolishes such an effect of "Ischemic Preconditioning" by preventing the opening of cardiac K^+_{ATP} Channels. GLIM shows insulin-mimetic signaling events through molecular mechanism on the insulin receptor-independent activation of the IRS/P13-Kinase pathway via DIG (Detergent-Insoluble-Glycolipid-enriched rafts) and Caveolin through Non-RTK (Non-Receptor Tyrosine Kinase) pathway in which, normally via IRTK (Insulin Receptor Tyrosine Kinase); hence, GLIM has an Insulin Sparing Effect. Thus, it is suggested that GLIM may contribute to overcome Insulin Resistance. On the basis of clinical experiences and molecular mechanisms, GLIM can be summarized having 3B – 3A – 9D properties which mean: 3–fold higher rate of Binding to receptor (3B), 3-fold lower Affinity to receptor (3A), and 9–fold faster rate of Dissociation (9D). These effects (3B–3A–9D) may result in potential therapeutical benefits, including: rapid onset (due to 3-fold higher rate of Binding = 3B) and less hypoglycemic events due to lower Affinity (3A) and faster Dissociation (9D). By using therapeutic GLIM concentration (in contrast with Glibenclamide), GLIM (via PI3-Kinase Pathway) increases insulin – stimulated Glycogen Synthesis (GS) in human muscle cells (GS Effects). In addition, GLIM inhibits platelet aggregation which may in turn have a preventive effect on the development of diabetic vascular complications (more pronounced effect than Gliclazide). The ideal basal insulin should ideally have the following six characteristics: 1. mimics normal pancreatic basal insulin secretion, 2. long-lasting, 24-hour effect, 3. smooth, peakless profile, 4. reproducible and predictable effects, 5. reduces risk of nocturnal hypoglycemia, and 6. once-daily administration. Insulin Glargine (GLAR) is a novel peakless long-acting insulin analogue that is available for clinical use; it has a smooth profile and long, 24-hour duration of action. GLIM can be combined with insulin therapy (f.e. GLAR) in the treatment of T2DM. Based on the clinical experiences, such a combination can be performed by 3 Methods such as Method-A: both GLIM and GLAR can be given in the Morning, Method-B: GLAR is given in the morning and GLIM in the evening, and Method-C: GLIM is given in the morning and GLAR in the evening. Conclusions: Due to its pleiotropic effects (3B-3A-9D Properties, and Cardioprotective, Insulin Sparing, Glycogenic, and Antiplatelet Effects), GLIM may represent the state of the art in modern oral antidiabetic sulphonylurea treatment. Insulin GLAR which mimics normal pancreatic basal insulin secretion and shows smooth-peakless profile, can be safely administered once-daily, and it may reduce risk of nocturnal hypoglycemia. Three Methods (A, B, and C) for combined therapy of GLIM and GLAR can be practically and rationally applied (depends on the life style of diabetic patients)

Keywords: *Glimepiride, cardioprotective properties, insulin Glargine, combined therapy of Glimepiride and Glargine, Methods A, B, C*

INTRODUCTION

Sulphonylureas have been used since the 1950_S as first-line therapy for the treatment of Type 2 Diabetes Mellitus (T2DM) whose blood glucose levels were not effectively controlled by diet. In clinical practice, hypoglycemic and anti-hyperglycemic agents can be categorized into three groups (Tjokroprawiro, 2002).

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I. Insulin Secretagues
  A. Sulphonylureas
  B. Non-Sulphonylureas: Meglitinides (Repaglinide, Nateglinide), GLP-1 analogues, Extendin-4)

Sulphonylureas:
- Gen-I : Tolbutamid,Chlorpropamide, etc.
- Gen-II : Glibenclamide, Glipizide-IR, Glipizide-GITS, Gliclazide-MR, Gliquidone
- Gen-III : Glimepiride: No Effects at CV KATP Channels, 3B-3A-9D Properties, Insulin

Sparing, Glycogenic, Anti Platelet Effect

II. Insulin Sensitizer and Antihyperglycemic Agents
   A. Thiazolidinediones
      1. Ciglitazone
      2. Englitazone
      3. Trioglitazone (R/ Resulin)
      4. Rosiglitazone (R/ Avandia): FDA May 1999
      5. Pioglitazone (R/ Actos): FDA July 1999
      6. Darglitazone
   B. Biguanides
      1. Metformin: Glucophage, Glukotika, Diabex, Neodipar, etc
      2. 3-Guanidinopropionic-Acid

III. Intestinal Enzyme Inhibitors
      A. α-Glucosidase Inhibitors: Acarbose, Voglibose (AD-128), Miglitol, MDL-73945, Castanospermine.
      B. α-Amylase Inhibitor: Tendamistase

Glimepiride (GLIM) has a number of pleiotropic effects and clinical benefits over conventional sulphonylureas. Such specific properties of GLIM will be shortly described in this paper and on presentation. To date, Insulin Analogues (Recombinant Human Insulin, Since 1980_S) can be synthesised by means of the rDNA technique, and clinically can be differentiated into 2 groups (Bolli et al, 1999).

I. Short-Acting Insulin Analogues
1. Insulin Lispro: on the market by the year 1996 (Lys B28, Pro B29-Human Insulin)
2. Insulin Aspart (replacing Proline at posisition B28 by Aspartic Acids = Asp)
3. Insulin Asp B9
4. Insulin Asp B10
5. Insulin GLU B21
6. Insulin GLU B27

II. Long-Acting Insulin Anal ogues
1. Insulin Glargine: on the market by year 2000 (21 A-Gly-30Ba-L-Arg-30Bb-L-Arg-Human Insulin).
2. NovoSol Basal
3. NN-304
4. W99-S32
5. C-16-HI

Insulin Glargine (GLAR) is a long-acting peakless insulin analogue which may mimic normal pancreatic basal insulin secretion. On the basis of clinical experiences, 3 Methods for combined therapy of GLIM and GLAR will be introduced (Methods A, B, and C).

The aim of this paper and presentation is to introduce (in short) the pleiotropic effects of GLIM, Insulin GLAR, Combined Therapy and its clinical benefits with the GPs, Residents, Internists, and also with the associated Specialists.

GLIMEPIRIDE: A NOVEL INSULIN SECRETAGOGUE

There are several novel antidiabetic agents (hypoglycemic or antihyperglycemic agents) in development and in future that modulate blood sugar levels such as by delaying intestinal glucose absorption, increasing insulin concentration or mimicking insulin action, or by metabolic effect that enhance glucose uptake or reduce hepatic glucose production. Some agents are capable in lowering glucose levels into the hypoglycemic range, whereas others improve hypoglycemia but carry little risk of causing hypoglycemia. Oral or rectal administration of insulin delivery remain on trial.

Glimepiride (GLIM) is the 3rd Generation of Sulphonylurea, a Novel Insulin Secretagogue which has pleiotropic properties beyond glucose lowering (Műller et al 1994, 2000, Tjokroprawiro 2002A, 2002B), such as:

I. Cardioprotective Effect
II. Insulin Sparing Effect
III. Specific Properties: 3B–3A–9D Effects
IV. Glycogenic Effect
V. Anti platelet agregation

Hence, GLIM can be regarded as the 3rd Generation of Sulphonylurea with Quintuple Effects as mentioned above. Glimepiride acts at K_{ATP} channels on pancreatic β-cell to promote insulin release. It binds to 65 kD protein on β-cell, which appears to be a part of the some sulphonylurea receptor that binds Glibenclamide (140 kD). GLIM increases expression of glucokinase in RNA and the glucose transporter GLUT 2 in pancreatic cells in vitro.

The effects of GLIM (compared to placebo) on blood glucose and insulin levels in patients with T2DM appear during the first 4 hours after the dose. Over this 4-hour period, greater reduction in blood glucose occured on the 4th day of treatment with GLIM 2 mg/day than Glibenclamide 10 mg/day (Dills et al 1996). Glimepiride was also associated with greater reduction in insulinemia than Glibenclamide during exercise, despite similar reductions in blood glucose (Műller et al 1994). The drug appears to act within peripheral cells at a point after insulin receptor interaction, increasing glucose transport and glucose transporter expressions

(GLUT 1 and GLUT 4) lipogenesis, and glycogenesis. GLIM also appears to reduce insulin resistance and increase hepatic glucose disposal in animal models, but not in patients with T1DM. In a 1-Year US comparative study, hypoglycemia occurred in 10% of 289 GLIM recipients and 16.3% of 288 patients receiving Glibenclamide.

I. GLIMEPIRIDE: CARDIOPROTECTIVE EFFECT

The major site of activity of GLIM is thought to be membrane receptors on pancreatic β-cell, where it acts via the closure of K_{ATP} chanels. The closure of the chanels may result in reduced coronary blood flow. However, unlike glimepiride, GLIM is though to have no effects at cardiovascular K_{ATP} channels in humans (Bijlstra et al 1996). Furthermore, the ability of Norepinephrine, Serotonin, Potasium Chloride and $PGF_{2\alpha}$, to induce contractions in rat aorta in vitro was inhibited by GLIM. In contrast, Glibenclamide attenuated response to $PGF_{2\alpha}$ but not to Norepineprhrine, Serotonin, or Potassium Chloride. In vitro and in vivo studies in rats revealed that compared with Glibenclamide, GLIM showed the milder and fewer modest effects on K_{ATP} channels, blood vessels, or the heart. In Open-Chest anaesthetized dogs, GLIM had milder-effects than Glibenclamide or Gliclazide in inducing ST-Segment elevation, increasing coronary resistance, myocardial oxygen extraction and serum potassium levels, and reducing coronary blood flow and the mechanical activity of the heart. Conclusion: GLIM, the 3rd Generation Sulphonylurea shows cardioprotective effects beyond glucose lowering.

II. GLIMEPIRIDE: INSULIN SPARING EFFECT

As reported by Műller (2000), the molecular mechanism of decreases in blood glucose levels provoked by GLIM occured to early on β-cell on SURX, and it was associated with the K_{ATP} channels and different from SURX for Glibenclamide, in muscle and adipocytes. Such molecular mechanisms are:

1. the increased production of DAG and activation of PkC
2. the enhanced expression of GLUT
3. the insulin receptor-independent activation of the IRS/P13-Kinase Pathway.

The mechanism no. 3 involved a Non-RTK (Receptor Tyrosine Kinase) = Non-RTK and several components, such as Caveolin and GPI (Glycosyl Phosphatidyl Inositol) structures, which are assembled in Caveolae/DIG (Ditergent-Insoluble-Glycolipid)-enriched rafts of this target cell plasma membrane; hence, that pathway is different from IRTK activity. Conclusion: This insulin-mimetic/sensitizing activation of GLIM can be called Insulin Sparing Effect.

III. GLIMEPIRIDE: SPECIFIC EFFECTS 3B – 3A – 9D

Based on the results of many studies, compared with Glibenclamide, GLIM has a 3-fold higher rate of Binding to Receptor (3B), a 3-fold lower Affinity to Receptor (3A), and a 9-fold faster rate of Dissociation (9D). Hence, GLIM has 3B – 3A – 9D properties which may result in (Tjokroprawiro 2002A, 2002B):

1. rapid action (due to 3B-effect)
2. less hypoglycemic episodes (due to 3A and 9D)
3. minimal glucose levels fluctuations or spikes (3A and 9D)
4. not tightly closure of K_{ATP} channels; thus, reduced coronary blood flow can be minimized.

Conclusion: Specific properties (3B, 3A, 9D) of GLIM may be of great clinical benefits and therapeutically relevant.

IV. GLIMEPIRIDE: GLYCOGENIC EFFECT

It was recently reported that incubation of cultures human skeletal muscle cells derived from glucose tolerant subjects with GLIM caused a dose-dependent might increases insulin stimulated glycogen synthesis by using therapeutic GLIM concentration (Haupt et al 2001); this effect seems to be mediated via the PI3 Kinase Pathway. In contrast with GLIM, Glibenclamide had no significant effect on either basal or insulin-stimulated glycogenesis. Conclusion: In humans, GLIM has an extra pancreatic action as glycogenesis stimulator.

V. ANTI PLATELET EFFECT

GLIM affects key steps in thrombin-induced activation and aggregation. GLIM inhibits thrombine stimulated increase of intracellular Ca^{++}. GLIM inhibits selectively the cyclooxygenase enzyme, wheres Glibenclamide inhibits both cyclooxygenase an 12-lipooxygenase enzyme. Gliclazide has no effect on either cyclooxygenase or 12-lipooxygenase, GLIM inhibits platelet aggregation which may in turn have a preventive effect on the development of diabetic vascular complication in patients. GLIM has a more

pronounced effect than Gliclazide and a more specific effect than Glibenclamide.

INSULIN ANALOGUES: SHORT AND LONG ACTION (FOCUSED ON INSULIN GLARGINE)

A. Structure and Physicochemical Characteristics

Analogues of insulin which can be synthesis by means of the rDNA technique and they can be differentiated into Short and Long-acting Insulin Analogues (see Introduction). The description of insulin analogues will be focused on Insulin Glargine (GLAR). This insulin analogue (21A-Gly-30Ba-L-Arg-30 Bb-L-Arg-human insulin = HOE 901) produced by rDNA technology, is a human insulin analogue with prolonged action.

GLAR results from two modifications of human insulin. First, two positive charges (two Arginine Molecules) are added at the C-terminus of the B-chain. This result in a shift of the IEP (iso electric point) from a pH of 4.5 to 6.7 ± 0.2 making the molecule more soluble at slightly acidic pH and less soluble at the physiological pH of subcutanous tissue. Because the derivative is formulated at an acidic pH, a second modification is needed to avoid deamidation and dimerisation by the acid-sensitive Asparagine residue at position 21 in the A-chain. The replacement of A-21 Asparagine by Glycine is charge-neutral and associated with good stability of the resulting human insulin analogue.

Injected as a clear solution of pH 4.0, GLAR forms a microprecipitate at the physiologic, neutral pH of the s.c space. The stabilization of insulin hexamer and higher aggregates can influence the nature of he precipitate and the rate of its dissolution and absorption from the site of infection. Consequently, GLAR has a delayed and prolonged absorption from the injection site after s.c injection. Because GLAR is formulated as a clear, acidic solution, it cannot be mixed with insulin formulated at a neutral pH such as Regular Insulin

B. Example of Clinical Study

Several studies were done in T1DM treated for 4 weeks to evaluate the effectiveness and tolerability of GLAR compared with NPH (Pieber et al 1998, Rosenstock et al 1998), with FPG as the parameter. GLAR given once daily at bedtime reduced FPG statistically significantly more than NPH given once or twice daily. The improvement in glycemic control seen with GLAR compared with NPH in there 4-week studies were achieved with lower (Picker et al 1998) or similar (Rosenstock et al 1998) incidence of nocturnal hypoglycemia. These results have been confirmed in a 28-week randomized trial in 534 patients with T1DM on multiple daily insulin injection regimen allocated to bedtime GLAR or bedtime NPH or NPH b.i.d.. Fasting Plasma Glucose (FPG) was approximately 32.5 mg/dl lower and frequency of hypoglycemia (BG<36 mg/dl) was more than 50 % lower with GLAR (Ratner et al 1999). Similar Results have been observed in a 28 week randomized trial in 158 patients with T2DM (Rosenstock et al 1999). Taken together, these data suggest that the majority of patients with T1DM and perhaps also T2DM might benefit from GLAR. This is in line with the Clinical Experiences of the author (2002C) who manages 2 cases of T2DM who are treated with combined therapy of GLIM and GLAR.

COMBINED THERAPY OF GLIMEPIRIDE AND GLARGINE (Clinical Experiences)

As described before, 3 Methods (A, B, and C) can be chosen by patients with DM based on their conveniences and life style.

1. Method-A

GLIM-GLAR are both administered in the Morning (Morning and Morning). Glimepiride (GLIM) in maximal dose 3-6 mg (titrated dose) is given 30 minutes before breakfast, and then Glargine (GLAR) injection (s.c.) in a doses of 10-30 Units is administered precisely before breakfast (Figure 1).

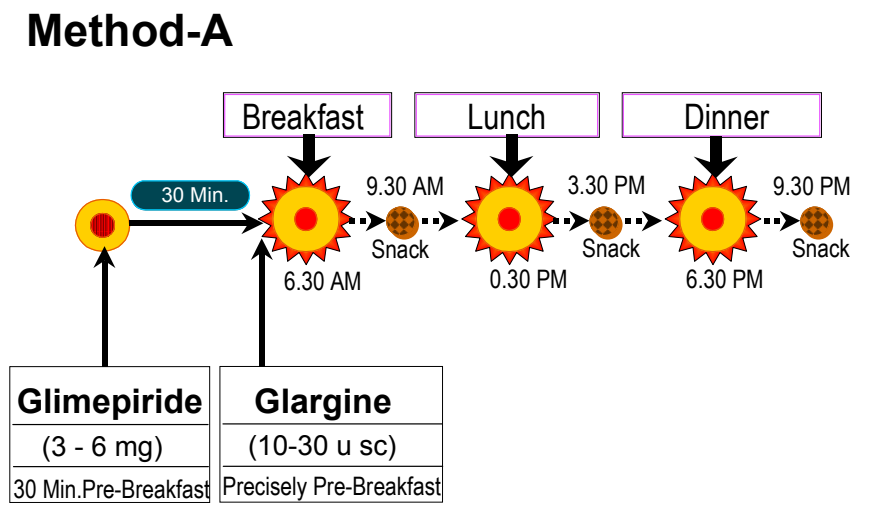

FIGURE-1: Method-A of Combined Therapy GLIMGLAR
(Clinical Experiences: Tjokroprawiro 2002B)

On the basis of clinical experiences, this Method (A) is the most frequent one accepted by the patients with Diabetes Mellitus. However, either Method A, B, or C shows the same glycemic control. For uneducated patients with autonomous diabetic neuropathy, Method-C may bring nocturnal hypoglycemic episode along with them.

2. Method-B

GLAR-GLIM are separately administered (Morning and Evening). By this Method, Glargine (10-30 Units) is subcutaneously injected 30 minutes before breakfast, and Glimepiride is given 30 minutes before dinner (Figure 2).

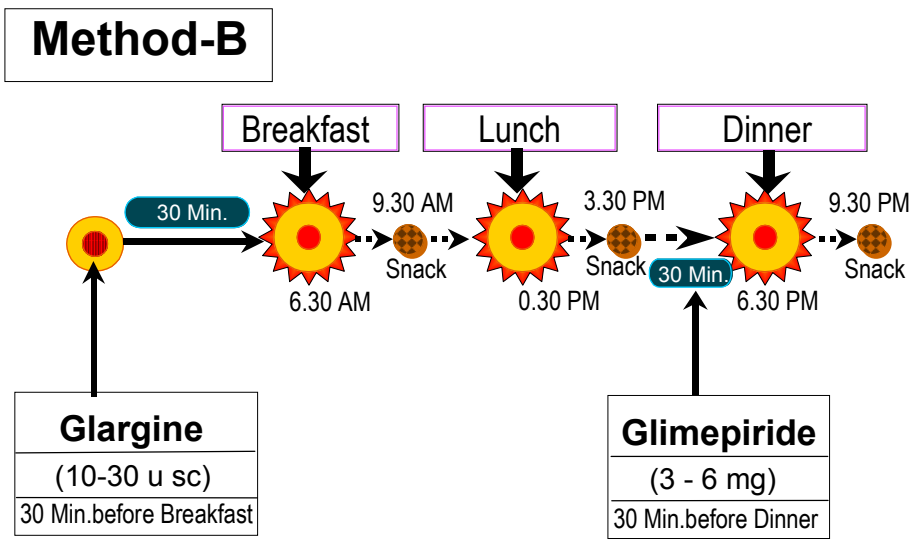

FIGURE-2: Method-B of Combined Therapy GLAR – GLIM
(Clinical Experiences: Tjokroprawiro 2002B)

3. Method-C

GLIM-GLAR are separately administered (Morning and Evening). Glimepiride is given 30 minutes before breakfast, and Glargine to be administered subcutaneously 30 minutes before dinner (Figure 3).

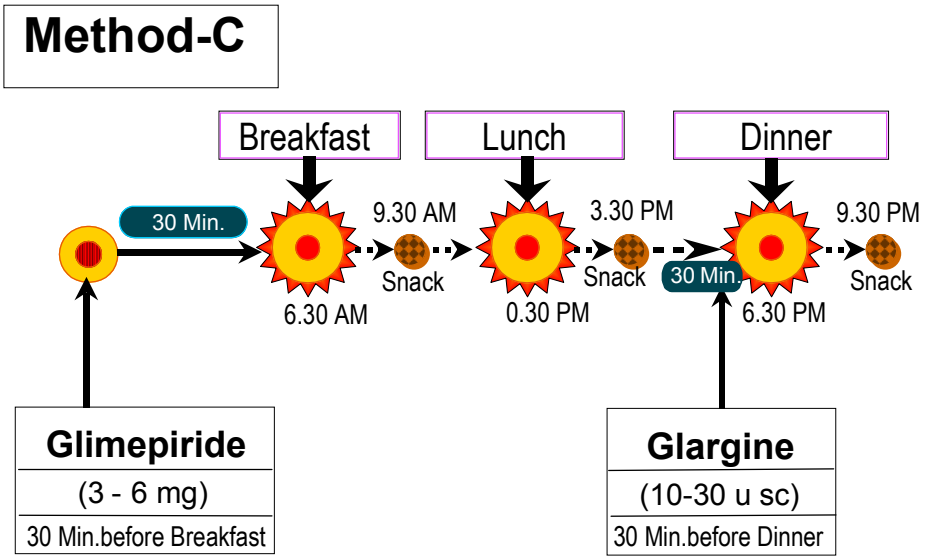

FIGURE-3: Method-C of Combined Therapy GLIM–GLAR
(Clinical Experiences: Tjokroprawiro 2002B)

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