VOLUME-9, ISSUE-3, MARCH-2020 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Medicine

INSULIN GLARGINE IN TYPE 2 DIABETES

Dr. Sanjay Mahajan	150 Duplex Apartments B-5 Vasundhara Enclave Delhi-110096
Dr. Shweta Bhanot Pandit*	Pandit Medical Near Mini Stadium Padmnabhpur Durg (Cg), 491001 *Corresponding Author
Dr. Sunil Shirsikar	Dwara Hospital, 101, Rajanvan Society Near Centreal Bank, N-9 Hudco Aurangabad, 431003
Dr Jitendra B Patel	Pruthvi Med. Nursing Home & Heart Centre, S. P. Colony, Naranpura, Ahmedabad
Dr M. G. Binu	Gknm, Avinashi Road, Coimbatore-641028

KEYWORDS :

Type 2 diabetes mellitus (T2DM) is characterized by relative insulin deficiency, decreased peripheral and hepatic sensitivity to insulin and raised plasma glucose levels[1]. T2DM treatment begins with lifestyle interventions, before progressing to pharmacological interventions with advancing disease. Despite the introduction of numerous anti-hyperglycemic medications, many patients with T2DM require insulin, and basal insulin continues to be frequently used either as first-line insulin treatment or as part of multiple daily injection regimens [2]. Oral hypoglycemic agents are effective agents for diabetes management, although secondary drug failure rates of 5-10% are bothersome. The disappointing results with monotherapy especially the worsening metabolic control is often seen within five years after the initiation of an oral hypoglycemic agent, with more than 50% patients requiring shifting to the insulin-based regimen to achieve optimal glycaemic control[3]. Basal insulin therapy is recommended if lifestyle modifications and oral antidiabetic agents fail to maintain HbA1c levels <7.5% and has been shown to improve glycemic control[4]. This highlights the fact that adequate basal insulin levels are an essential component of diabetes management. The ideal basal insulin should provide a sustained level of insulin, mimicking physiological basal insulin secretion, reproduce physiological basal insulin secretion, thereby restoring glycemic control, without hypoglycemia[1]. Such therapy should have relatively flat/constant insulin concentration profile over time, no pronounced peak, duration of action of at least 24 h, low within-patient variability in fasting plasma glucose (FPG), a favorable safety profile, including low risk of hypoglycemia and weight gain, and be easy to administer and titrate[2]. However, traditional insulin does not fully accomplish this goal. This stimulated the search for insulins with a more prolonged duration of action that could better replicate the physiological basal insulin secretory response[5]. This eventually led to the development of basal insulin-like, Neutral (porcine) protamine Hagedorn (NPH) insulin, Lente insulin, insulin detemir, etc. Still, all these variants are also not able to achieve the desired therapeutic insulin levels. For instance, NPH insulin, intermediate-acting insulin, has a duration of action that is considerably less than 24 h and an activity profile that peaks 3–5 h after administration. NPH insulin administered at bedtime results in high insulin levels when insulin requirements are low. This activity profile is not ideal as it increases the risk of nocturnal hypoglycaemia[1].

A greater understanding of the protein structure of insulin and the roles of key amino acids has opened up new avenues for the rational design of insulin analogs with more predictable absorption and time–action characteristics. Insulin glargine (IGlar) was the first long-acting basal analog to be introduced into clinical practice in 2000 and was a breakthrough in the field of insulin therapy. It continues to be a gold standard of basal insulin treatment and a benchmark for new injectable antihyperglycemic treatments, including newer basal insulin analogs[2]. IGlar is a biosynthetic, long-acting, clear human insulin analogue with an acidic pH. Upon subcutaneous injection, IGlar is neutralized and forms microprecipitates that release insulin in a constant profile over 24 h[6].

STRUCTURE OF IGLAR

IGlar differs from human insulin by the replacement of A21 asparagine with glycine and the addition of two arginine residues at B31 and B32 (GlyA21, ArgB31, and ArgB32). These mutations endow glargine with an isoelectric point of 6.4–6.8, implying that it is easily soluble at acid pH and less soluble at neutral pH. As a result, upon subcutaneous injection, IGlar forms an amorphous precipitate in the subcutaneous tissue, which slowly dissociates, providing a sustained release of insulin into the circulation[5].

Once injected, IGlar gets immediately metabolized into two main active metabolites M1 (GlyA21) and M2 (GlyA21, des-ThrB30). The M1 metabolite accounts for approximately 90% of the daily plasma insulin available. This protracted release of glargine from the subcutaneous depot translates into longer bioactivity than either human NPH or human ultra Lente insulin. Thus, IGlar can be administered once daily, unlike the earlier 'intermediate'/'long-acting' insulin preparations[5]. IGlar once daily has been shown to achieve superior glycemic control with equivalent or lower rates of hypoglycemia compared with NPH insulin in patients with T2DM[4].

CLINICAL EFFICACY OF IGLAR

Usage of NPH insulin is most often limited due to the high risk of nocturnal hypoglycemia when taken at bedtime, as its peak of the action occurs 4–6 h post-injection. In contrast, the smoother activity of the long-acting insulin analog, IGlar, allows more flexibility in dosing, and its administration is less strictly bound to the time of injection. This is especially important for certain patient populations where hypoglycemia poses a greater risk, such as the elderly[5]. Hence, IGlar is approved for administration at any time of day, provided it is at the same time each day[7]. To confirm the non-occurrence of hypoglycemia post-IGlar administration, Porcellati et al., carried out a study in T2DM insulin-treated patients[7]. The study was carried out in 10 T2DM insulin-treated persons were studied during 24-h euglycemic glucose clamp, after glargine injection (0.4 units/kg s.c.), either in the evening (2200 h) or the

morning (1000 h). It was concluded from the study that, the pharmacodynamics of insulin glargine differs depending on the time of administration. With morning administration insulin activity is greater in the first 0–12 h, while with evening administration the activity is greater in the 12–24 h period following dosing. However, glargine pharmacokinetics and plasma C-peptide levels were similar, when analyzed by 24-h clock time independent of the time of administration. Thus, insulin sensitivity in T2DM is affected by circadian rhythm rather than glargine per se[7].

Diabetic kidney disease is one of the most frequent microvascular complications related to diabetes mellitus and is the leading cause of end-stage renal disease. Kidneys play an important role in the regulation of glucose homeostasis, because they release a significant amount of glucose in the post-absorptive state, and they are responsible for approximately one-third of insulin degradation. The progressive loss of kidney function, and its consequent reduction in parenchyma and blood flow, has been associated with a lower capacity of renal glucose release, drug metabolism, and excretion and insulin extraction, resulting in prolonged half-life of some oral antihyper gl ycemic agents and insulin, besides an impaired response to hypoglycemia Thus, glycemic control in patients with chronic kidney disease (CKD) is particularly hard to achieve because of a slower insulin degradation by the kidney. It might modify the long-acting insulin analogue pharmacokinetics, increasing its time of action and the risk of hypoglycemia[8]. Betonico et al. examined the efficacy and safety profile of long-acting basal analogues in patients with significant loss of renal function. A comparison of the glycemic response to treatment with IGlar U100 or NPH insulin in patients with type 2 diabetes mellitus (T2DM) and CKD stages 3 and 4 was done in 34 patients. After 24 weeks, mean HbA1c was found to decrease on IGlar U100 treatment (−0.91%; P < 0.001), however, this benefit was not observed for NPH (0.23%; P ¼ 0.93). Moreover, the incidence of nocturnal hypoglycemia was found to be 3 times lower with IGlar than with NPH insulin (P ¼ 0.047). Thus indicating the potential of IGlar U100 in patients with T2DM and CKD stages 3 and 4[8]without resulting in significant hypoglycemia.

Traditionally, basal insulin is initiated on the failure of a standard therapeutic oral anti-diabetic regimen and is given as an additional hypoglycemic agent along with oral anti-diabetics. Eliaschewitz et al., compared the efficacy and safety of IGlar and NPH insulin, both in combination with a once-daily fixed-dose of glimepiride, in terms of glycemic control and incidence of hypoglycemia in an open-label, 24-week randomized trial in ten Latin American countries[4]. It was found that IGlar and NPH insulin achieved similar HbA1c reductions (adjusted mean difference 20.047; 90% CI 20.232, 0.138; per-protocol analysis). However, confirmed nocturnal hypoglycemia was significantly lower with IGlar vs. NPH insulin (16.9 vs. 30.0%; p<!0.01; safety analysis). Patients receiving IGlar were significantly more likely to achieve HbA1c levels <7.0% without hypoglycemia (27 vs. 17%; p =0.014; per-protocol analysis). There was a more pronounced treatment satisfaction improvement with insulin glargine vs. NPH insulin (p <0.02; full analysis). Thus, once-daily IGlar plus glimepiride is effective in improving metabolic control with a reduced incidence of nocturnal hypoglycemia compared with NPH insulin[4].

Another major complication of diabetes is the occurrence of cardiovascular complications. Cardiovascular disease is the leading cause of mortality in T2DM. Hyperinsulinemia has been reported to be associated with increased cardiovascular risk. Progression of atherosclerosis has been proposed to be associated with hyperinsulinemia. However, the effects of exogenous insulin on cardiovascular disease progression has not been well studied. The ORIGIN trial is the only study to date dedicated to investigate the effects of IGlar on cardiovascular outcomes. ORIGIN enrolled 12,537 patients with a mean age of 63.5 years, cardiovascular risk factors and impaired fasting glucose, impaired glucose tolerance or type 2 diabetes. Patients were randomized to receive IGlar with a target fasting glucose of less than 95 mg/dL or standard glycemic care. At the end of the study, 83.6% of patients in the glargine group were on insulin compared with 11.4% in the standard care group. The HbA1c in year 7 was 6.2% in the glargine group and 6.5% in the standard care group. However, the study found no difference in co-primary outcomes of nonfatal MI, nonfatal stroke or death from cardiovascular disease after a median follow-up of 6.2 years[9]. Further, a meta-analysis of outcomes from ACCORD, ADVANCE, and VADT found that intensive therapy of older adults with type 2 diabetes, the majority of whom were insulin-treated and followed for a mean 3.5–5.6 years, resulted in a 10% reduction in microalbuminuria, but no significant change in other microvascular complications[9]. Thus, although insulin has been shown to have both cardioprotective and athero scl erosis-promoting effects in laboratory animal studies, human trials have not shown insulin to increase cardiovascular events and need further in-depth study.

CONCLUSION

Hypoglycemia is considered to be one of the major barriers in initiating insulin therapy and is often a deciding factor while selecting an insulin regimen. Therefore, it makes clinical sense to adopt a treatment regimen that minimizes this risk. IGlar has been shown to result in fewer hypoglycemic events than NPH insulin, along with comparable glycemic control. Thus, IGlar-is the benchmark basal insulin and may continue to be an important part of treating T2DM.

REFERENCES

1. Kacerovsky-Bielesz G, Dressler A, Freunscht R. Long-term glycaemic control with insulin glargine in Type 2 diabetes. Diabetes Res Clin Pract. 2006;71(2):184-191. doi:10.1016/j.diabres.2005.06.007
2. Hirose T, Chen CC, Ahn KJ, Kilja ski J. Use of Insulin Glargine 100 U/mL for the Treatment of Type 2 Diabetes Mellitus in East Asians: A Review. Diabetes Ther. 2019;10(3):805-833. doi:10.1007/s13300-019-0613-7
3. Agarwal SK, Singh BK, Wadhwa R. Insulin glargine as add-on therapy to oral hypoglycaemic agents to achieve target fasting plasma glucose levels in type 2 diabetes patients in an Indian setup. Indian J Med Spec. 2014;5(2):89-92. doi:10.7713/ijms.2014.0002
4. Eliaschewitz FG, Calvo C, Valbuena H, et al. Therapy in Type 2 Diabetes: Insulin Glargine vs. NPH Insulin Both in Combination with Glimepiride. Arch Med Res. 2006;37(4):495-501. doi:10.1016/j.arcmed.2005.10.015
5. Owens DR. Optimizing treatment strategies with insulin glargine in Type 2 diabetes. Expert Rev Endocrinol Metab. 2012;7(4):377-393. doi:10.158 6 /ee m.12.29
6. Glargine I. Issues in Emerging Health Technologies Insulin Glargine for Type 2 Diabetes. 2004;(59).
7. Porcellati F, Lucidi P, Cioli P, et al. Pharmacokinetics and pharmacodynamics of insulin glargine given in the evening as compared with in the morning in type 2 diabetes. Diabetes Care. 2015;38(3):503-512. doi:10.2337/dc14-0649
8. Betônico CC, Titan SMO, Lira A, et al. Insulin Glargine U100 Improved Glycemic Control and Reduced Nocturnal Hypoglycemia in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease Stages 3 and 4. Clin Ther. 2019;41(10):2008-2020.e3. doi:10.1016/j.clinthera.2019.07.011
9. Gerstein HC BJ. The ORIGIN Trial Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia. N Engl J Med. 2012;367(4):319–328.