Efficacy of the Modern SU Glimepiride in Reducing Hyperglycemia in T2DM

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Abstract

Sulfonylureas (SUs) have been used for several decades for diabetes therapy, but the risk of severe hypoglycemia and weight gain associated with this class of drugs has rendered them a subject of controversy. In this context, modern SUs such as glimepiride have emerged as potentially safe and effective candidates for both monotherapy and combination therapy with other antidiabetic drugs such as metformin. Several clinical studies have validated the beneficial effects of glimepiride. A few such studies have established glimepiride as a relatively more potent antidiabetic drug vs. other SUs. Such studies indicate the potential of glimepiride as a preferred drug in the therapy of people with type 2 diabetes mellitus (T2DM). Here we will discuss the efficacy of glimepiride in reducing hyperglycemia in T2DM.

Introduction

Sulfonylureas (SUs) were the first available oral drugs used as glucose-lowering therapy. Indeed, metformin and SUs are the most widely prescribed drugs worldwide for the management of type 2 diabetes mellitus (T2DM).[1] The latest World Health Organization (WHO) guidelines recommend the use of SUs and metformin for control of blood glucose levels in people with diabetes.[2] Compared to conventional SUs, modern SUs such as glimepiride have several benefits, and their efficacy profiles are also better than those of conventional SUs.[2] The clinical efficacy of glimepiride in reducing hyperglycemia in people with diabetes mellitus will be discussed here.

Clinical Efficacy of Glimepiride in Reducing Hyperglycemia as Monotherapy

In a double-blind, randomized, placebo-controlled parallel group study of 14 weeks duration, Goldberg et al, evaluated the efficacy and safety of once daily administration of glimepiride in people with type 2 diabetes mellitus (n=304). At the endpoint (subject's last treatment evaluation) of the study, median reduction in FPG, in 1,4 and 8 mg glimepiride group, was greater by 2.4, 3.9, and 4.1 mmol/L respectively, compared to placebo group($p<0.001$). Overall, there was 1.2%, 1.8% and 1.9% more reduction in HbA_{1c} levels in the glimepiride 1 mg, 4 mg and 8 mg groups respectively, than placebo group. All these results were statistically significant ($p<0.001$). In addition, favorable safety profile of glimepiride was also observed in this study. Therefore, the study concluded that all three once-daily doses of glimepiride, were effective in glycemic control, and well-tolerated in people with type 2 diabetes. Figure 1 highlights the results obtained in this study.[3]

In a systematic review of 31 double-blind randomized controlled trials conducted for a median duration of 16 weeks (ranging from three weeks to three years), SU monotherapy (including glimepiride) lowered HbA_{1c} levels better than placebo, insulin, and other oral antidiabetic drugs (such as troglitazone) among 3956 patients. Another observation was that administration of higher doses of glimepiride than the relatively low effective dose (1 mg vs. 4, 8, or 16 mg daily) were not associated with increased efficacy.[4] In the Liraglutide Effect and Action in Diabetes 2 (LEAD-2) trial, which lasted 26 weeks, both liraglutide and glimepiride resulted in sustained glycemic control.[5]

As Add-On to Insulin

Previously reported studies were not completely in favor of the use of SU therapy in combination with insulin, since SUs reduce hyperglycemia by increasing insulin secretion from beta-cells. Therefore, when used in combination with insulin, they could possibly induce heightening of insulin secretion from beta-cells, thereby triggering apoptotic beta-cell death. However, despite that possibility, SUs continue to be used in combination with insulin therapy. In fact, several reports confirm that combination therapy with SU and insulin leads to better glycemic control vs. insulin alone.[6] A prospective comparative randomized study with 24-week duration revealed that addition of glimepiride to basal insulin resulted in improved efficacy than using basal insulin alone, with lowered weight gain and hypoglycemic effects.[7] In addition, such combination therapy also significantly reduced (by 4.01%) the required insulin dose and hence reduced the cost of therapy which is a significant issue in India. In another clinical trial lasting for 28-weeks, triple combination of insulin glargine, glimepiride and metformin was found to significantly improve overall glycemic control as compared to other therapeutic combinations. In addition, it was also found that decrease in HbA_{1C} was more significant with insulin glargine plus metformin and glimepiride combination, as compared to insulin glargine plus metformin combination (0.49% [CI,0.16%–0.82%];

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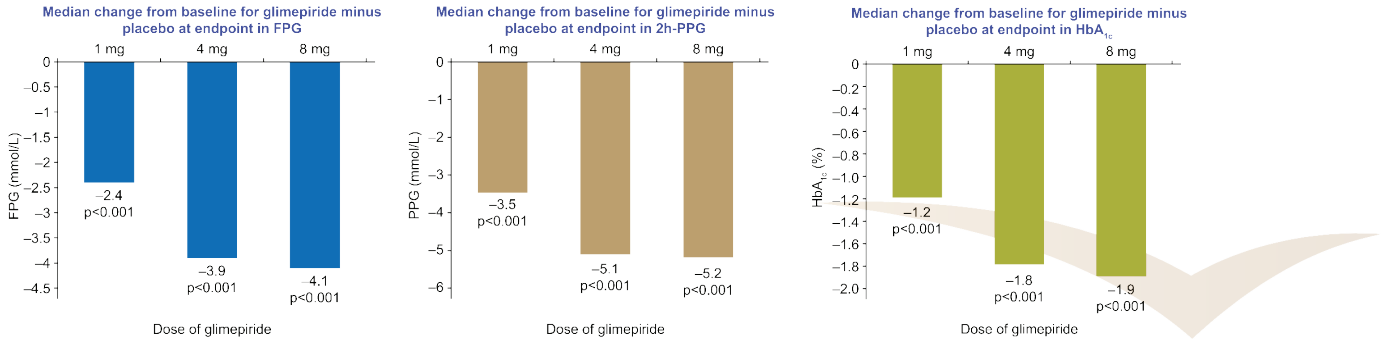

Fig. 1: Efficacy of once-daily dose of glimpiride proved in study by Goldberg et al[3]

P = 0.005) (5.10 mmol/mol [CI, 1.64–8.61]; P = 0.005) and insulin glargine plus glimepiride (0.59% [CI, 0.13%–1.05%]; P =0.012) (5.87 mmol/mol [CI, 1.10–10.64]; P = 0.012) (overall P = 0.02).[8] In another study by Yokoyama et al. conducted among people with type 2 diabetes, the efficacy of continuing glimepiride therapy in combination with basal prandial insulin therapy was investigated. The study revealed that continuing glimepiride in patients on basal-prandial insulin therapy offered sustained benefits in individuals with long-term diabetes.[6]

It has been recommended by the Expert panel of Basal Early Strategies to Maximize HbA_{1c} Reduction with Oral Therapy (BE-SMART), that while adding SUs to existing insulin therapy, it must be initiated with low dose of SUs. Subsequently, the SU dosage can be increased after 2-4 weeks interval, until the desired glycemic target is achieved. Additionally, modern SUs like glimepiride should be preferred over conventional SUs like glibenclamide, since modern SUs are associated with lower risk of hypoglycemia. The expert panel also recommended regular monitoring in case of combination therapy with basal insulin and insulin secretagogues like SUs.[9]

As Add-On to Metformin Therapy

Among the various options available for combination therapy with metformin, modern SUs such as glimepiride are considered ideal options for the treatment of T2DM due to their low cost, relative cardiovascular safety, and high efficacy. Hypoglycemia and weight gain are common side effects of conventional SUs; such effects can be minimized using modern SUs such as glimepiride. This advantage has contributed to their widespread use. Also, such combination therapies have been found to demonstrate better blood-glucose–lowering in several studies compared to monotherapy with individual components.[10]

The addition of SUs to ongoing monotherapy for diabetes with metformin has demonstrated satisfactory glycemic control in several meta-analyses and randomized controlled trials, with acceptable tolerability and safety.[10] When used as monotherapy, SUs are efficacious in enhancing short-term glycemic control.[1] Ahren et al. performed a placebo-controlled study for up to 104 weeks and compared the efficacy of metformin vs. glimepiride/metformin combination therapy. The study results favored combination therapy over metformin monotherapy.[11]

Comparative Efficacy of SU and Dipeptidyl Peptidase-4 Inhibitor (DPP4i) in Hyperglycemia Reduction

Addition of SUs to ongoing metformin monotherapy has demonstrated effective glycemic control with acceptable safety compared to DPP4i, in several clinical trials. Evidence from a systemic review and meta-analysis suggests that as compared to DPP4i, SUs when added to metformin, are associated with a significantly higher reduction in HbA_{1c} over 12 weeks.[12] In addition, accumulated evidence from 14 randomized controlled trials reveals that, as compared to DPP4i, SUs are associated with a greater decrease in HbA_{1c} (weighted mean difference [WMD]: 0.08, 95% CI: 0.03, 0.14, P = 0.001).[13] In a systematic review and meta-analysis, a 12% greater reduction in HbA_{1C}(WMD:-0.12;95% CI:-0.16,-0.07) was reported with addition of SUs to monotherapy as compared to DPP4i.[14] Findings from population-based cohort study, revealed that the reduction in HbA_{1c} with SU as second-line agents was more effective as compared to that with DPP4i(1.2% vs. 0.8%).[15]

Conclusion

The benefits and risks of SUs are now well understood, given the clinical and research experience of more than 60 years that favors their use. Sulfonylureas (SUs) are an asset in diabetes care and, owing to their unique characteristics—such as weight-neutralizing effects, cardiovascular safety, increased efficacy, and reduced episodes of hypoglycemia, modern SUs such as glimepiride can be preferred over conventional SUs.

Conflict of Interest

GP is an employee of Sanofi India. All other authors report no conflicts of interest.

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References

1. Khunti K, Chatterjee S, Gerstein HC, *et al*. Do sulphonylureas still have a place in clinical practice? *Lancet Diabetes Endocrinol* 2018; 6:821-832.
2. Kalra S, Das AK, Baruah MP, *et al*. Glucocrinology of modern sulfonylureas: Clinical evidence and practice-based opinion from an international expert group. *Diabetes Ther* 2019. doi:10.1007/s13300-019-0651-1. [Epub ahead of print].
3. Goldberg RB, Holvey SM, Schneider J. A dose-response study of glimepiride in patients with NIDDM who have previously received sulfonylurea agents. The Glimepiride Protocol #201 Study Group. *Diabetes Care* 1996; 19:849–56.
4. Hirst JA, Farmer AJ, Dyar A, *et al*. Estimating the effect of sulfonylurea on HbA1c in diabetes: a systematic review and meta-analysis. *Diabetologia* 2013; 56:973-84.
5. Nauck M, Frid A, Hermansen K, *et al*. Long-term efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: 2-year results from the LEAD-2 study. *Diabetes Obes Metab* 2013; 15:204-12.
6. Yokoyama H, Sone H, Yamada D, *et al*. Contribution of glimepiride to basal-prandial insulin therapy in patients with type 2 diabetes. *Diabetes Res Clin Pract* 2011; 91:148–153.
7. Kelwade J, Sethi B. Efficacy of glimepiride as an add on therapy to insulin in patients with high insulin requirement. Poster presented at IDF Congress 2017; 2017 Dec 4–8; Abu Dhabi, UAE.
8. Park CY, Kang JG, Chon S, *et al*. Comparison between the therapeutic effect of metformin, glimepiride and their combination as an add-on treatment to insulin glargine in uncontrolled patients with type 2 diabetes. *PLoS One* 2014; 9:e87799
9. Bajaj S, Das AK, Kalra S, *et al*. BE-SMART (Basal Early Strategies to Maximize HbA1c Reduction with Oral Therapy): Expert Opinion. *Diabetes Ther* 2019; 10:1189-1204.
10. Kalra S, Bahendeka S, Sahay R, *et al*. Consensus recommendations on sulfonylurea and sulfonylurea combinations in the management of type 2 diabetes mellitus - International Task Force. *Indian J Endocrinol Metab* 2018; 22:132–157.
11. Ahrén B, Johnson SL, Stewart M, et al. HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. *Diabetes Care* 2014; 37:2141-8.
12. Mishriky BM, Cummings DM, Tanenberg RJ. The efficacy and safety of DPP4 inhibitor compared to sulfonylureas as add-on therapy to metformin in patients with type 2 diabetes: A systematic review and meta-analysis. *Diabetes Res Clin Pract* 2015; 109:378-88.
13. Zhou JB, Bai L, Wang Y, *et al*. The benefits and risks of DPP4-inhibitors vs. sulfonylureas for patients with type 2 diabetes: Accumulated evidence from randomised controlled trial. *Int J Clin Pract* 2016; 70:132-41.
14. Amate JM, Lopez-Cuadrado T, Almendro N, *et al*. Effectiveness and safety of glimepiride and iDPP4, associated with metformin in second line pharmacotherapy of type 2 diabetes mellitus: Systematic review and meta-analysis. *Int J Clin Pract* 2015; 69:292-304.
15. Thomsen RW, Baggesen LM, Søgaard M, et al. Early glycaemic control in metformin users receiving their first add-on therapy: A population-based study of 4,734 people with type 2 diabetes. *Diabetologia* 2015; 58:2247-53.