

New oral diabetes drugs are more effective than older agents: real or a fraud?

Opinion

Recently, a question was raised in a debate regarding the utility of Sulfonylureas (SU) in comparison with new oral agents.^{1,2} Dr. Ganuth affirms that new agents are as or more effective than SUs.² Proponents of SGLT2 inhibitors claim similar assertions.³⁻¹² An equal or greater lowering of HbA1c by new agents compared to SUs and even Metformin in subjects with prolonged duration of diabetes may be attributed to several reasons. Many published clinical trials have compared the efficacy of the maximum daily dose of new agents; DPP4 Inhibitors, GLP1 analogs and SGLT2 inhibitors with either a minimally effective or sub maximal recommended daily dose of SUs.¹³⁻³⁰ The reason for administration of SUs in a minimally effective or sub maximal daily dose, e.g. Glimpiride, 1-6mg in these comparative trials may be explained by the selection of subjects with average baseline HbA1c between 8 to 8.5% prior to initiation of drugs because the maximal daily dose of new agents is established to lower HbA1c by 7-15% whereas the maximum daily dose of Glimpiride was documented to lower HbA1c by approximately 25%^{30,31} and therefore a much lower than the maximum daily dose is adequate to obtain a comparable reduction in HbA1c.

Moreover, many of these recent comparative clinical trials are conducted by using generic SU, e.g. Glimpiride, glipizide etc. probably with variable bioavailability and variable efficacy. Also, many of these studies are conducted in 'clinical trial mills' with same cadre of subjects in their collective databases as recently documented and hence the accuracy and validity of the results and conclusions derived from these studies has been recently questioned.^{32,33} These authors suggest that recycling of the same subjects hopping from one trial to another may have skewed the 'true and accurate' comparative efficacy in these studies. Alternatively, reduced efficacy of old drugs in these 'comparative efficacy' trials when compared to the efficacy documented in their 'premarketing' trials may be attributed to 'drug receptor interaction'. Previous long term or repeated exposure to old drugs is likely to induce 'down regulation' as well as decreased affinity of the receptors of old drugs resulting in decreased efficacy whereas lack of exposure causes 'up regulation' and maximal affinity of the receptors for the new agents at their initiation with consequential maximum efficacy. Finally, the efficacy in clinical trials with new drugs is determined by examination of the changes in glycemic parameters as compared to changes with placebo rather than the basal concentrations and therefore exaggerates the efficacy since rise in these parameters often occurs in the placebo group.³⁻²⁹ Moreover, these trials are conducted with the sponsorship and funding by the manufacturers of new drugs who are also fully cognizant of the reality that the old drugs are now 'generic' and pharmaceuticals producing the old agents are absolutely unlikely to conduct competitive trials to refute the findings of the trials with the new drugs.

Finally, the reliability and accuracy of the results of the comparative clinical trials conducted by the manufacturers of the new drugs are likely to be biased and hence need scrutiny and confirmation by independent investigators with no contact with these

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manufacturers. Therefore, the optimal and appropriate methodology is the comparative trials in drug naive subjects with the drugs being used as monotherapy conducted by independent investigators devoid of any sponsorship or funding by any pharmaceutical company. In fact, such an independent recent study documented a relatively superior efficacy of mono therapy with Glipizide over the regimen consisting of combination of Saxagliptin and Metformin thus exposing the biased nature of results provided by the studies conducted by the manufacturers of new drugs.³⁴ However, the findings of this study also need confirmation and it may be provided by the ongoing 'Grade' trial, in which the efficacies of the new and the old drugs as a second line agents added to Metformin are being examined.³⁵ Finally, even if the efficacies of new agents are noninferiority to old drugs, e.g. SUs and Metformin, the markedly lower costs are likely to render therapy with old drugs distinctly more cost effective than new agents.

The efficacy of old drugs reported in the recent comparative clinical trials sponsored and funded by the manufacturers of new drugs is in stark contrast to the data described in the original premarketing clinical trials with old drugs, SU and Metformin.^{3-12,36-46} These studies documented a markedly greater decline (25-30%) in HbA1c from baseline level in comparison to many new agents (7-12%) including DPP4 inhibitors and SGLT 2 inhibitors in drug naïve subjects.^{3-25,30,31,36-46} The greater efficacy of SUs in drug naïve subjects may be attributed to their ability to lower both the fasting and postprandial plasma glucose levels by stimulating both 1st and 2nd phase postprandial insulin secretion whereas DPP4 inhibitors and GLP1 analogs stimulate only the 1st phase insulin secretion and thus are devoid of a significant effect on fasting plasma glucose levels.^{19-25,47-54} Several studies suggest the major mechanism of lowering post prandial glycemia by DPP4 inhibitors to be the decrease in glucagon secretion rather than enhancement of insulin release by beta cells.^{19,22,24,54} Moreover, SUs improve post prandial glycemia to a greater degree when compared with DPP4 inhibitors and GLP 1 analogs because of their effect in lowering fasting plasma glucose and postprandial glycemia is closely correlated to fasting plasma glucose.⁵⁵ Therefore, therapy with SUs results in superior efficacy in lowering overall diurnal glycemia with a greater reduction in HbA1c as described previously.³¹ Finally, Glimpiride induces a rise in both 1st and 2nd phase postprandial insulin secretion as well as improvement in insulin sensitivity and therefore appears to be more effective than other SUs.^{31,52,53}

In conclusion, the old drugs are more effective and far less expensive than the new agents and therefore must remain in the armamentarium of choices in management of type 2 diabetes in 'developed' countries. Moreover, the old drugs remain the major therapy of choice in developing countries because of the easier availability and greater affordability.

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Conflict of interest

Author declares that there is no conflict of interest.

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