在 Metformin 使用後，口服降血糖藥物優先選--SU

What antidiabetic agents to choose after metformin?? The role of sulfonylureas

林時逸

台中榮總高齡醫學中心主任

The progressive nature of type 2 diabetes mellitus (T2DM) requires a range of treatment options. As oral antidiabetic therapy loses efficacy over time, polypharmacy with multiple mechanisms of action is usually necessary to achieve and maintain long-term glycemic control. The use of metformin as first-line therapy was supported by findings from a large meta-analysis, with selection of second-line therapies based on patient-specific considerations. However, there remains no clear consensus, however, regarding which drug is the most appropriate to add to metformin to achieve therapeutic goals. When first-line treatment with metformin proves ineffective or is not well tolerated, sulfonylureas (SUs) represent one of the most common second-line treatments in real world practice. SUs are certainly effective glucose-lowering agents, and in a recent meta-analysis of studies in which SUs were used as monotherapy or in combination with other medications, there was an average 1.5% reduction in HbA_{1c} in nine studies lasting up to 36 months (SU monotherapy vs. placebo) and a 1.6% decrease in HbA_{1c} in four large studies in which SUs were added to patients taking either metformin or thiazolidinediones (TZDs). In the Liraglutide Effect and Action in Diabetes 2 (LEAD 2) trial, 4 mg of glimepiride daily was as effective as liraglutide 1.2 or 1.8 mg daily in lowering HbA_{1c} in subjects taking metformin. Glimepiride also has been shown to be as effective as the dipeptidyl peptidase-4 (DPP-4) inhibitor linagliptin when added to metformin in patients suboptimally controlled on metformin alone. The results of the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE), currently under way, should help elucidate the comparative effectiveness of SUs, DPP-4 inhibitors, GLP-1 receptor agonists, and basal insulin as add-ons to metformin in subjects not achieving therapeutic goals with metformin alone, although the sodium–glucose cotransporter 2 (SGLT2) inhibitors are not included in the study as they had not been approved for clinical use when the study was initiated.

The belief that SU use may be associated with adverse cardiac events is first reported in 1970s that tolbutamide use in the University Group Diabetes Program (UGDP) was associated with a greater risk of adverse cardiac events. However, in the UKPDS, it is

shown that there was a nonsignificant 16% decrease in myocardial infarction rates in patients treated intensively with SUs at the end of the study but a significant 15% decrease in events in these subjects when evaluated 10 years after the end of the original study, despite the fact that they continued to take SUs and their metabolic control had been the same as the conventionally treated group within a year of completion of the original study.
Hypoglycemia is common in diabetes, and thus, an action is required when a sulfonylurea is used to minimize the risk of hypoglycemia taken by the diabetes health-care provider and the person to improve glycemic control more safely. Starting SU at a low dose and escalating the dose to submaximal doses that are as effective as maximal doses in those who warrant such escalations could help more people achieve therapeutic goals with reduced risk of hypoglycemia. In addition, SU use is associated with weight gain, which is recognized as an undesirable effect of treatment. However, there are no data that weight gain associated with use of some glucose-lowering medications (primarily insulin, TZDs, and SUs) is associated with worse outcomes when compared with medications that are associated with no change or loss in weight at equivalent reductions in HbA_{1c}.

Finally, if cost of medications needs to be considered when determining what drug to add to metformin, SU would be the preferred class of medication. SUs, when added to metformin, have been shown to be the most cost-effective medication, taking into account cost of drug, improvement in glycemic control associated with the drug, and low absolute risk of severe hypoglycemic episodes requiring medical intervention but more frequent episodes of mild hypoglycemia. The addition of SUs, pioglitazone, and DPP-4 inhibitors to metformin has similar effects on life-years gained. However, quality of life was adversely affected by hypoglycemia, greatest with SUs, and weight gain, greatest with SUs and pioglitazone.

In summary, SUs have been in clinical use for approximately 60 years. They are very effective glucose-lowering medications, and avoiding use of SUs as a class of medication as an add-on to metformin may not be appropriate as there are many patients whose glycemic control would improve with use of these drugs with minimal risk of adverse events. However, not every person with type 2 diabetes would be an ideal candidate for treatment with SUs when metformin alone provides insufficient glycemic coverage. As noted, such patients include the elderly who are at higher risk of deleterious consequences of hypoglycemic events, even mild ones. Choosing the most appropriate patients to use these medications is something that the practicing clinician needs to do.