Guiding the use of newer agents for blood glucose control

The National Institute for Health and Clinical Excellence has just published guidelines covering newer agents for blood glucose control in adults with type 2 diabetes (NICE, 2009a), and as such is a partial update of NICE's clinical guideline 66 for type 2 diabetes (National Collaborating Centre for Chronic Conditions [NCCCC], 2008). This now completes the guidance for type 2 diabetes in England, Wales and Northern Ireland, with SIGN guidance on the management of type 2 diabetes anticipated for Scotland in the first quarter of 2010.

The "newer agents" covered by this guidance include dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones (TZDs), the glucagon-like peptide-1 (GLP-1) receptor agonist exenatide, and the long-acting insulin analogues. Some of these agents will already be very familiar to primary care teams, but this published update places them in a wider context by setting clear guidance on their utility and where they fit into existing therapeutic pathways. Published in parallel to this guidance is a costing report estimating the cost impact from the implementation of the guidance (NICE, 2009b).

Underpinning the new document is the assumption that metformin will be offered first-line to people with type 2 diabetes with the addition of insulin secretagogues, preferably sulphonylureas, recommended as second-line therapy. The newer agents would then be used either in addition to these agents, when glycaemic control is inadequate, or instead of these agents where they are not tolerated or produce unacceptable side-effects.

DPP-4 inhibitors

With two DPP-4 inhibitors already licensed in the UK (vildagliptin and sitagliptin), and two more going through licensing in the USA, there is a recognition that these drugs are set to be important oral agents.

Sitagliptin has a marketing authorisation for combination with metformin and sulphonylurea together, and hence has a recommendation in the guideline for triple oral therapy, but otherwise both of the DPP-4 inhibitors are recommended for use in similar circumstances. For example, DPP-4 inhibitors may be used instead of a sulphonylurea as second-line therapy if sulphonylureas are not tolerated or are contraindicated or, importantly, the person is at significant risk of hypoglycaemia or its consequences (if it would be an occupational hazard or if a person lives alone). An important caveat is that they must only be continued if a beneficial metabolic response (a reduction in HbA_{1c} of at least 0.5 percentage points [5.5 mmol/mol] within 6 months) occurs and is maintained. There is also guidance suggesting when to choose a DPP-4 over a TZD: where weight gain is not desired or TZDs are not tolerated, contraindicated, or there has been a previous poor response.

GLP-1 receptor agonists

Exenatide is the first GLP-1 receptor agonist established in the UK. Liraglutide is under scrutiny from the licensing authorities and is expected to be launched later this year. Exenatide differs from the DPP-4 inhibitors, which enhance the effect of endogenous GLP-1, in that it is an injectable therapy associated with weight reduction.

The new NICE guidance is more circumspect in outlining the use of exenatide than it is for DPP-4 inhibitors, recommending that exenatide only be used as a third-line therapy in people with a BMI ≥35 kg/m^2 and specific psychological or medical problems associated with high body weight, or in people with a BMI <35 kg/m^2 where insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. The guidance adds that to continue with the therapy there must also be a demonstrated positive effect on HbA_{1c} and added weight loss. Presumably this is a reflection of exenatide's higher acquisition price than insulin, although this cost may be offset to some degree by the relative simplicity in initiating this newer therapy.

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The way that HbA_{1c} values are reported in the UK has now changed. To reflect this, as of this issue, all HbA_{1c} values will be dual reported both in percentages and mmol/mol.

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TZDs

The updated guidance also revisits the TZDs (pioglitazone and rosiglitazone). With the emerging DPP-4 inhibitors, the TZDs now have active competition as second- and third-line oral agents. Amongst other recommendations, like the DPP-4 inhibitors, the TZDs are recommended for use as second-line add-on to metformin if a sulphonylurea is not tolerated or contraindicated, or if a person is at risk of hypoglycaemia or its consequences. There is a suggestion that TZDs may be used in preference to a DPP-4 inhibitor if the person with diabetes has marked insulin insensitivity.

Only pioglitazone has a licence for use with insulin, and the guidance qualifies this by expecting that, if used in this way, there will have been a previous significant response to TZDs and recommends caution about fluid retention. There may be some people with diabetes for whom either a TZD or a DPP-4 inhibitor may be suitable and in this case, the guideline suggests that the choice of treatment should be based on patient preference.

Insulin therapy

The guidance outlines the utility of insulin when no other active agent has achieved the HbA_{1c} target of <7.5% (<53 mmol/mol). Rightly, the importance of initiating insulin as part of an agreed structured programme is reinforced. The guidance recognises that there are a number of potential insulin regimens, and it proposes, as with the 2008 guidance, that if insulin initiation is required, to begin with neutral protamine Hagedorn insulin at bedtime and then twice-daily as required.

The insulin analogues are popular with primary care teams because of their ease of initiation, and NICE makes recommendations on the circumstances and patient groups in which they should be used. The place of biphasic pre-mixed insulin and basal–bolus regimens is also outlined.

Conclusion

An important element of this guidance is a new algorithm outlining when and where these antidiabetes agents should be used. It is a flow diagram with agreed HbA_{1c} targets for each step. Primary care teams faced with a burgeoning population of people with type 2 diabetes, and who wish to achieve new indicators set under the recent QOF changes, will want to actively consider this new guidance to help individuals to work towards these ambitious goals. ■

National Collaborating Centre for Chronic Conditions (2008) *Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update).* NICE, London. Available at: http://guidance.nice.org.uk/CG66/Guidance/pdf/English (accessed 27.05.09)

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