PostScRxipt
from the
NHSGGC Area Drug & Therapeutics Committee
Issue 43 January 2008

NEW AGENTS IN THE MANAGEMENT OF TYPE 2 DIABETES

Recent years have brought much activity in the development of new drugs for the management of type 2 diabetes. Many of these agents come with both novel mechanisms of action and favourable effects on some of the associated abnormalities present in patients with the metabolic syndrome. This summary of new agents has been contributed by Dr Marion Devers and Dr Isabel Howat, Specialist Registrars in diabetes and Dr Andrew Gallagher, lead clinician for the Diabetes Managed Clinical Network. You can find a more detailed article on our website.

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Website
http://www.ggcformulary.scot.nhs.uk

Thiazolidinediones

Pioglitazone and rosiglitazone are currently approved for use in the management of type 2 diabetes in combination with metformin and/or sulphonylurea and, more recently, in combination with insulin. These are attractive candidates for the treatment of type 2 diabetes in that they increase insulin sensitivity, increase glucose utilisation and decrease glucose production. Three large randomised controlled clinical trials have shown beneficial effects on glycaemic control, cardiometabolic parameters and cardiovascular outcomes. One of these, the DREAM study, considered progression from impaired glucose tolerance to diabetes rather than treatment of existing diabetes.

The PROactive Study hypothesised that pioglitazone would reduce total mortality and macrovascular morbidity in type 2 diabetes when added to current oral hypoglycaemic therapy. There was a non significant 10% reduction in the primary endpoint, a composite of death, MI, stroke, revascularisation procedures and amputation. There was a significant reduction of 16% in the main secondary endpoint, a composite of death, MI and stroke only. A significant fall in HbA1c and improvement in triglycerides, HDL-cholesterol and LDL:HDL ratio were noted in subjects treated with pioglitazone.

The Adopt study compared rosiglitazone, metformin and glibenclamide as initial oral therapy for maintaining long-term glycaemic control in type 2 diabetes. Rosiglitazone was associated with a significant reduction in monotherapy failure, however the glycaemic improvement in terms of HbA1c reduction after four years was modest when compared to the other agents.

Caution continues to surround the glitazones due to the consistent association with weight gain, fluid retention and heart failure; a significant finding in the PROactive study. A meta-analysis published in the *New England Journal of Medicine* in May 2007 suggested an increased risk of myocardial infarction in patients treated with rosiglitazone. This study has been the subject of intense debate with criticism of the methods used and the conclusions drawn. The same association has not been identified with pioglitazone.

From a practical perspective, the glitazones continue to have a role in type 2 diabetes. They should be avoided in patients with heart failure and discontinued in those who develop significant fluid retention on treatment. Pioglitazone and rosiglitazone are both in the Preferred List restricted to initiation by clinicians experienced in the treatment of diabetes. See the *Formulary* for full details.

DPP-4 inhibitors

Incretins are hormones produced from the gastrointestinal tract that act to enhance the normal release of insulin after the oral ingestion of carbohydrates. They also delay the absorption of nutrients and act to promote a feeling of satiety that can lead to weight loss in overweight individuals. Incretins are normally rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4). Sitagliptin inhibits DPP-4 so augmenting the incretin response. It has been shown to improve glycaemic control in combination with metformin. It appears to be weight neutral and well tolerated with no major adverse events and no hypoglycaemia. Sitagliptin is the first DPP-4 inhibitor available in the UK; a second drug, vildagliptin, is expected shortly.

Sitagliptin was approved by the SMC in October 2007 for use in the treatment of type 2 diabetes, in combination with metformin, when diet, exercise and metformin do not achieve adequate glycaemic control. It has been added to the Total Formulary, restricted to specialist initiation only when the addition of sulphonylureas is not appropriate.

Exenatide

Exenatide is an analogue of glucagon-like-peptide-1, which is the most well characterised incretin. It is administered by twice daily subcutaneous injection. It was associated with a reduction in HbA1c of 0.9%, and a weight loss of 2.1 kg after 30 weeks in patients inadequately controlled with sulphonylurea and/or metformin. After 82 weeks there was a reduction in HbA1c of 1.1% and weight loss of 4.4 kg. Exenatide was well tolerated, the most frequent adverse events were nausea and hypoglycaemia, the latter occurring predominantly in association with sulphonylurea therapy.

Exenatide was approved by the SMC in June 2007. It has been added to the NHSGGC Total Formulary restricted to specialist initiation as an alternative to insulin in patients who

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For all article references, check our website
http://www.ggcformulary.scot.nhs.uk

Alphabetical list of most recent ADTC decisions

For full details of SMC advice, visit **www.scottishmedicines.org** For NICE advice, visit **www.nice.org.uk** For previous ADTC decisions, visit **www.ggcformulary.scot.nhs.uk**

Drug	Indication under consideration (There may be other licensed indications)	Glasgow decision	
Adalimumab (Humira®)	Severe, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.	Non-*Formulary* for this indication.	x
Bevacizumab (Avastin®)	Unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.	Non-*Formulary*.	x
Calcium Carbonate 1.25g and colecalciferol 10microgram (400 units) (Calceos®) (ADTC Appeal)	Calcium and vitamin D supplementation	*Formulary*. (Preferred List).	✓
Ciclesonide (Alvesco®)	High dose use (up to 640mcg daily for up to 12 weeks) to control persistent asthma in adolescents and adults (12 years and older).	Non-*Formulary*.	x
Conjugated oestrogen (Premarin®)	Hormone replacement therapy for oestrogen deficiency symptoms in postmenopausal women.	*Formulary*. (Total Formulary). Acknowledge new presentation	✓
Dasatinib (Sprycel®)	Chronic myeloid leukaemia in adults with resistance or intolerance to prior therapy including imatinib mesylate.	*Formulary*. Total Formulary for this indication. Restricted to specialist use only for CML in accordance with regional protocol. Use for all other indications should be considered non-Formulary.	✓R
Dexrazoxane (Cardioxane®)	Prevention of chronic cumulative cardiotoxicity caused by doxorubicin or epirubicin use in advanced and/or metastatic cancer patients after previous anthracycline containing treatment.	Non-*Formulary*.	x
Docetaxel (Taxotere®)	Induction treatment of patients with unresectable locally advanced squamous cell carcinoma of the head and neck in combination with cisplatin and 5-fluorouracil.	*Formulary*. (Total Formulary). Acknowledge new indication. Restricted to specialist use in accordance with regional protocol.	✓R
Eculizumab (Soliris®)	Paroxysmal nocturnal haemoglobinuria.	Non-*Formulary*.	x
Epoetin delta (Dynepo®)	Anaemia in patients with chronic renal failure.	*Formulary*. (Total Formulary). Darbepoetin remains the preferred Formulary agent for this indication	✓
Erdosteine (Erdotin®)	Expectorant for the symptomatic treatment of acute exacerbations of chronic bronchitis in adults.	Non-*Formulary*.	x
Esomeprazole (Nexium®)	Zollinger-Ellison Syndrome.	Non-*Formulary*.	x
Fondaparinux (Arixtra®)	Unstable angina or non-ST segment elevation myocardial infarction (NSTEMI) in patients for whom urgent invasive management is not indicated.	Add to Total Formulary restricted to use in the treatment of unstable angina or NSTEMI only in accordance with agreed local protocols.	✓R
Formoterol (Atimos® Modulite®)	Relief of broncho-obstructive symptoms in patients with chronic obstructive pulmonary disease.	*Formulary*. (Preferred List). Acknowledge new indication.	✓
Fosamprenavir (Telzir®)	HIV-1 infected adolescents and children of 6 years and above in combination with other antiretroviral medicinal products.	Non-*Formulary* for this indication.	x
Imatinib (Glivec®)	Relapsed or refractory Philadelphia chromosome position acute lymphoblastic leukaemia as monotherapy in adults.	Non-*Formulary* for this indication.	x
Imatinib (Glivec®)	Newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia in combination with chemotherapy in adults.	Non-*Formulary* for this indication.	x
Imatinib (Glivec®)	Myelodysplastic / myeloproliferative diseases associated with platelet-derived growth factor receptor gene rearrangements in adults.	Non-*Formulary* for this indication.	x
Imatinib (Glivec®)	Advanced hypereosinophilic syndrome and/or chronic eosinophilic leukaemia with FIP1L-PDGFRa rearrangement in adults.	Non-*Formulary* for this indication.	x
Imatinib (Glivec®)	Unresectable dermatofibrosarcoma protuberans (DFSP) and patients with recurrent and/or metastatic DFSP who are not eligible for surgery.	Non-*Formulary* for this indication.	x
Risedronate (Actonel®)	Osteoporosis in men at high risk of fractures.	Non-*Formulary* for this indication.	x
Rivastigmine (Exelon®) patch	Moderately severe Alzheimer's dementia.	Deferred for consultation with specialists and protocol development.	?
Rufinamide (Inovelon®)	Adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients four years and older.	Non-*Formulary*.	x
Sevelamer (Renagel®)	Control of hyperphosphataemia in adult patients receiving peritoneal dialysis.	Non-*Formulary* for this indication.	x
Tiotropium respimat inhaler (Spiriva-Respimat®)	Maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease.	*Formulary*. (Preferred List). Acknowledge new presentation. Restricted to patients with poor manual dexterity who have difficulty using the Handihaler® device.	✓R
Topotecan (Hycamtin®)	Carcinoma of the cervix recurrent after radiotherapy and for patients with stage IVB disease.	Deferred to Regional Cancer Advisory Group for development of protocol.	?

✓= *Formulary* ✓R = *Formulary* (restricted) **x** = non-*Formulary* **?** = awaiting final decision

Low molecular weight heparins (LMWH) for patients with malignant disease

The ADTC has recently agreed a protocol for the use of LMWH for the treatment and secondary prophylaxis of venous thromboembolism (VTE) in patients who have malignant disease and those who are unable to tolerate oral anticoagulants. The full protocol can be found in the guidelines store on our website. It is intended for use in patients who have active cancer, eg recent diagnosis, undergoing chemotherapy, liver metastases and those in whom there are likely to be problems with maintaining a stable INR if warfarin is used. It is envisaged that LMWH will be administered by the patient or carer.

The physician diagnosing the DVT or PTE will initiate therapy with enoxaparin or dalteparin and ensure initial monitoring is undertaken. The responsibility for ongoing monitoring and completion of therapy will rest with the doctor managing the patient's cancer - usually the oncologist but possibly a specialist physician, palliative care consultant or GP. This individual will be identified and consulted prior to patient discharge. Details of the proposed treatment plan should be clarified in the discharge letter to the clinician responsible for on-going care and supervision of LMWH therapy.

Patients should receive therapy for a minimum of six months, and longer if the cancer or cancer treatment is still active. Any decision to shorten or lengthen duration of treatment should be made in discussion between GP, treating oncologist and the patient.

Survey of GPs and consultants on the *Glasgow Formulary* and Drug of Choice scheme

A survey investigating the opinions and attitudes of GPs and consultants towards the *Glasgow Formulary* and Drug of Choice scheme was completed in 2007 as part of an MSc research project. It was sent to 50% of randomly selected Glasgow GPs (n=311) and consultants for adult services (n=465). The project started before the merger with Clyde so considered Glasgow only.

Just over half of recipients responded. Some of the main results are listed here.

- 72% agreed that the *Formulary* was a useful prescribing resource.
- 74% agreed that it should contain short practical prescribing notes.
- 81% agreed that the *Formulary* should contain recommendations for first and second line therapies.
- 64% thought that the *Formulary* should cover 80-90% of all prescribing.
- 40% were aware of the Drug of Choice (DoC) scheme and 53% of those named *PostScript* as the source of DoC information.

There were several key recommendations made as a result of the responses given in the survey. Some of these have already been implemented while others are in development.

1 The NHSGGC *Formulary* should be developed to contain more short practical guidance notes.

√ Since the introduction of the Preferred List in August 2007, the NHSGGC *Formulary* has been further developed to ensure the inclusion of short practical guidance notes.

2 A hard copy of the NHSGGC *Formulary* should remain in place for the foreseeable future.

√ This has been agreed by the Formulary and New Drugs Committee.

3 Hospital Electronic Prescribing and Medicine Administration systems (HEPMA) should include information on *Formulary* drugs.

- There are plans to introduce HEPMA systems across Scotland. Local needs must be balanced with national needs for a single system. Issue raised with local decision makers.

4 Future editions of the *Formulary* should, where possible, highlight first and second line therapies and should cover 80-90% of all prescribing. However, reference to specialist medicines should still be made.

√ The Total Formulary is included in the hard copy as an appendix to the Preferred List.

5 For specific first choice medicines, the development of Patient Information Leaflets should be considered to inform patients of the reasoning behind the drug choice.

- This has been passed to the Medicines Utilisation and Prescriber Education sub-group of ADTC and agreed that this will be considered.

6 Educational materials should be widely circulated to prescribers in both primary and secondary care to reinforce prescribing messages. In addition, the opinions of GPs, consultants, nurses, pharmacists and other healthcare professionals should be sought when developing such materials.

√ Future *PostScript Extra* bulletins (often used as educational tools) will ensure that stakeholder opinions are sought during the development stages. They will be distributed to a wider group and published on the *Formulary* website.

Thanks to the GPs and consultants who took part in this research. Your views are important and have helped to shape the development of the NHSGGC *Formulary.* For a full copy of the report, contact Laura Hendry at laura.hendry@ggc.scot.nhs.uk

New agents in the management of Type 2 diabetes

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have failed treatment on metformin and/or sulphonylureas and in whom insulin would be the next treatment option.

Inhaled insulin (Exubera®)

The manufacturers have announced their intention to withdraw marketing of this product due to poor uptake. It will, however, be available for existing patients who meet criteria developed by NICE for up to one year from January 2008 to allow transition to other therapies.

Glycaemic pathway and new hypoglycaemic agents

The latest NHSGGC guidelines for the glycaemic control in type 2 diabetes are in preparation and will incorporate these new agents. At present, the early introduction of metformin is indicated, in combination with diet and exercise, when the HbA1c is greater than 7.0%. The choice of additional therapy should be tailored to the individual patient, with the emphasis on weight management as well as glycaemic control. In overweight patients, the addition of a glitazone or sulphonylurea to metformin monotherapy can improve glycaemic control with significant further weight gain. The advantage of the newer agents could be to improve glycaemic control without weight gain, or even to aid weight loss. The optimum use of these new agents will become more clearly defined as we gain experience with their use in routine clinical practice.

NHS Greater Glasgow and Clyde

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Published by the Communications Sub-group to reflect the views of the Area Drug & Therapeutics Committee but not necessarily those of NHS Greater Glasgow and Clyde.

PostScRipt

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Strathcashel Publications Project Management (01505 850 344)
Printed by: Mackay & Inglis, Glasgow