Focus on Avandamet

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Avandamet – a fixed dose combination therapy of rosiglitazone and metformin – is now available for treating patients with type 2 diabetes.

Type 2 diabetes accounts for over 90% of diabetes in Australia. Although glycaemic control can be improved with a healthy diet and physical activity, many patients find long term adherence to these lifestyle measures difficult. Oral hypoglycaemic medications and then insulin are usually required. In the UK Prospective Diabetes Study (UKPDS), most participants progressed steadily from lifestyle modification alone to tablets and then to insulin in order to keep their glycosylated haemoglobin (A_{1c}) on target; after nine years, most were taking oral hypoglycaemic medications and/or insulin (Figure 1).[1] Most patients with type 2 diabetes require multiple medications to keep their ABCss on target (the ABCss of diabetes care are listed in the Table). These medications are over and above those for coexisting medical conditions, such as arthritis, reflux, depression and insomnia.

Fixed dose combination therapy, in which pharmacological agents are coformulated in a single tablet or capsule, is increasingly being used to enhance patient adherence and gain the benefits of different medications. Common examples include the coformulation of either an ACE inhibitor or angiotensin receptor antagonist with a thiazide diuretic for the treatment of hypertension.

For glycaemic control in type 2 diabetes, a combination of metformin and glibenclamide (Glucovance) is already available. This article focuses on the new coformulation of metformin and rosiglitazone, which is marketed as Avandamet.

Metformin and glitazones

Metformin is a biguanide antihyperglycaemic agent. It has been used since the late 1950s and remains first line pharmacotherapy when glycaemic control is not achieved with lifestyle modification alone. Metformin lowers fasting and postprandial blood glucose by decreasing hepatic gluconeogenesis and glucose output.

Rosiglitazone and pioglitazone are thiazolidinediones ('glitazones'), which reduce insulin resistance in skeletal muscle, liver and adipose tissue. Glitazones stimulate an intracellular (nuclear) protein (the peroxisome proliferator activator receptor gamma) and reduce levels of circulating free fatty acids that otherwise increase insulin resistance in type 2 diabetes. By reducing insulin resistance, glitazones increase tissue response to insulin and increase glucose utilisation and fatty acid uptake.

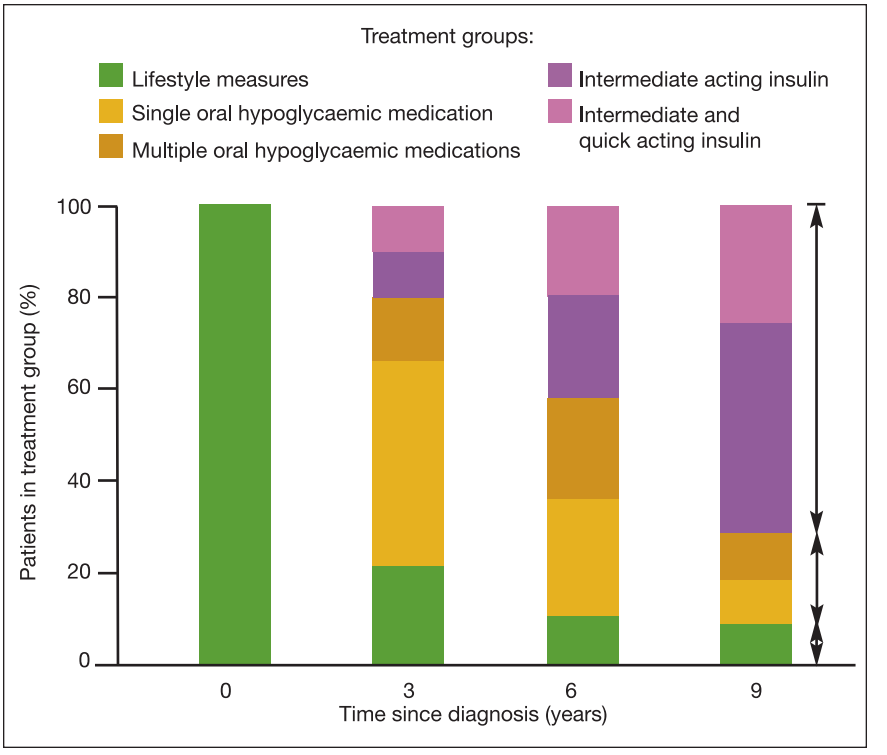

Figure 1. In UKPDS, a progressive increase in requirements for medication (oral hypoglycaemics and insulin) was demonstrated in the majority of patients with type 2 diabetes in order to maintain A_{1c} below 7%.[1] Arrows on the right-hand side of the graph indicate the proportion of patients using insulin, oral hypoglycaemic medications and lifestyle measures at nine years.

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Table. The ABCss of diabetes care

Risk factor	Target
A_{1c} (glycosylated haemoglobin)	<7%
Blood pressure	<130/80 mmHg (<125/75 mmHg if proteinuria >1 g/day exists)
Cholesterol	<4 mmol/L (corresponding to LDL cholesterol <2.5 mmol/L)
smoking	Cessation
salicylates	Aspirin 75 to 150 mg/day

Metformin and glitazones can be considered 'insulin sensitisers' (as opposed to sulfonylureas and glitinides, which stimulate insulin release from pancreatic beta cells). Their actions are shown in Figure 2.

At present, the recommended sequence for prescribing oral hypoglycaemic medication is to start with metformin (unless contraindicated by renal impairment, risk of hypoxia or side effects) and then to add a sulfonylurea (unless contraindicated by risk of hypoglycaemia or side effects) and then to consider triple therapy by adding rosiglitazone.[2] (Pioglitazone is not currently authorised for use in triple therapy.) However, if sulfonylureas or metformin cannot be used then either of the glitazones can be added as double therapy.[2]

Avandamet

Avandamet is approved in the USA, European Union and now Australia for use in patients with type 2 diabetes that is inadequately controlled by metformin in addition to a healthy lifestyle. However, the glitazones are only available on the PBS (authority required) as double therapy with metformin when:

- sulfonylureas are contraindicated
- there is documented intolerance to sulfonylureas, or
- use of sulfonylureas is not appropriate in the opinion of the prescriber.

Avandamet is also available on the PBS (authority required) for use in triple combination therapy with a sulfonylurea for patients with type 2 diabetes.

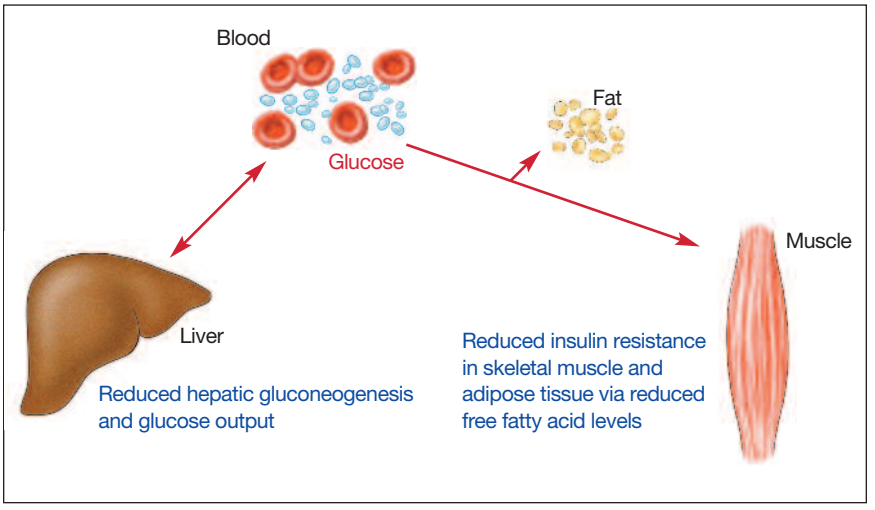

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Figure 2. Actions of metformin and a glitazone such as rosiglitazone.

A fixed dose combination of rosiglitazone and metformin has been shown to be bioequivalent to the two separate components given concomitantly.[3] The fixed dose and free combination schedules were equally well tolerated in clinical trials, with the likelihood of adverse effects to metformin or rosiglitazone being similar in both groups. A retrospective analysis suggested that adherence is greater for the fixed dose combination than for the two separate medications.[4]

Starting treatment

Avandamet is available in four formulations of rosiglitazone/metformin: 2/500, 4/500, 2/1000 and 4/1000 (mg/mg). For patients who are already receiving metformin (with or without a sulfonylurea), Avandamet can be introduced at the same daily dose of metformin (up to 2000 mg), with up to 8 mg of rosiglitazone given in the same divided doses prescribed for metformin alone.

For patients who are already receiving rosiglitazone with a sulfonylurea, Avandamet can be introduced at the same daily dose of rosiglitazone, plus metformin 1000 mg/day (usually in two divided doses with the main meals). The dose of metformin may be increased further by changing the formulation of Avandamet (e.g. from 4/500 twice daily to 4/1000 twice daily). The dose of the rosiglitazone component of Avandamet could be doubled (e.g. from 2/1000 twice daily to 4/1000 twice daily) after six to eight weeks if significant improvement in glycaemic control is not achieved.

To switch from a schedule of rosiglitazone and metformin as separate tablets, the nearest daily dose of Avandamet should be used (up to a maximum of rosiglitazone 8 mg, metformin 2000 mg).

Precautions, contraindications and adverse reactions

The precautions and contraindications for Avandamet are the same as for the separate components. These include:

- metformin – renal impairment, risk of hypoxia
- rosiglitazone – congestive cardiac failure (especially New York Heart Association Class III and IV), active liver disease.

Avandamet should not be used in pregnancy, lactation or type 1 diabetes. It can be used in elderly patients, but they should be monitored regularly for adverse effects.

The adverse event profile for Avandamet is also similar to that of its components. For example:

- metformin – gastrointestinal upset
- rosiglitazone – fluid retention, possible exacerbation of heart failure and weight gain, although the latter may be less likely when coadministered with metformin.

Full lists of precautions, contraindications and potential adverse effects can be found in the product information leaflets.

Summary

- Avandamet combines two insulin sensitisers, rosiglitazone and metformin, in clinically appropriate dosage combinations.
- The doses of rosiglitazone and metformin in the combined preparation are bioequivalent to the same medication doses given separately at the same time.
- Adherence may be improved by using the combined preparation rather than the two medications separately.
- The same indications, contraindications and precautions apply to the combined preparation as to the two separate components. MT

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