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CONTENTS

EDITORIAL

Medicine shortages in Australia – what are we doing about them?

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drug industry, drug regulation, medicine shortages, Therapeutic Goods Administration

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The first objective of the Australian National Medicines Policy is to provide 'timely access to the medicines that Australians need, at a cost individuals and the community can afford'.[1] However, even developed countries such as Australia can experience shortages of medicines. These can lead to patient harm due to a result of non-treatment, undertreatment, the use of less appropriate alternatives and medicines safety issues.[2,3] Addressing these shortages consumes significant clinical effort and there are financial and logistical impacts on healthcare systems and all stakeholders.[3]

In a 2017 survey of Australian hospitals the five most common medicines in short supply were antibiotics, anaesthetics, cardiology drugs, endocrinology drugs and chemotherapy. Such shortages can have a significant impact on patient care with little or no notice.[2] In 2018 there was a shortage of the EpiPen device for emergency self-administration of adrenaline (epinephrine). Vaccines and even water for injections have been in short supply.

Medicine shortages are not a new problem but the extent and scope has worsened over recent years.[4] The causes of medicine shortages could be described as a spider's web of diverse interacting and connected factors including regulation, manufacturing, procurement, global acquisitions, financial viability, political instability and even natural disasters.[2,3] Medicine shortages are inherently an international issue. However, as Australia accounts for only 2% of the global market and imports over 90% of its medicines, it is potentially more vulnerable than bigger markets which may be prioritised by suppliers in periods of shortage.[4,5] Although international efforts should continue to focus on increasing the resilience of the global pharmaceutical supply chain, we have to consider how the potential consequences for Australian patients can be minimised.

In 2014, recognising the problems relating to medicine shortages, the Therapeutic Goods Administration (TGA) established the Medicines Shortage Information Initiative (MSII).[6] This was an attempt to provide information and clarity to prescribers and pharmacists via a voluntary sponsor reporting scheme.[6] However, this initiative has had major failings with some critical shortages not being reported. Also, few clinicians were aware of the initiative.[4,5] This has led to instances in which a prescriber only becomes aware of a shortage after prescribing when they are informed by a community pharmacist or when hospitals receive notification from a wholesaler after placing an order.[2,5]

The current system leads to duplication of effort, inconsistency and creates a vicious cycle of local stockpiling leading to shortages of therapeutic alternatives within the wider health system and potential inequity of access to critical drugs across Australia.[2,4] The lack of inclusive, robust and timely information prevents effective system-wide strategies from being put in place. Effective strategies should discourage local stockpiling and minimise the impact on patients and the health system.

The strategies adopted to date have focused on anticipating, identifying and managing shortages.[2,5] Strategies to extend existing supplies have included minimising waste and prioritising patient need in addition to providing a different formulation or a therapeutic alternative. This is in some respects a form of local rationing. The TGA can approve the temporary supply of a substitute medicine during a medicine shortage, and temporary listing of unregistered medicines on the Pharmaceutical Benefits Scheme (PBS) can be facilitated. However, this may not cover all medicine shortages and an alternative drug without PBS listing has obvious financial impacts on patients.

In response to these problems, in 2017 the Australian Health Minister called for the development of a strategy to support better management of shortages. The TGA has consulted on some proposals.[4] These proposals are in line with the principles of transparency, coordination and communication between stakeholders articulated by the World Health Organization.[7] One fundamental component of the proposals is that drug companies will be mandated to report shortages and the reporting will be made public for those drugs with the potential for extreme impacts on patients. Systematic, timely and transparent reporting is the foundation of a patient-centred approach to medicine shortages. Without this reporting, securing alternative drugs from overseas or rationing and prioritising the use of available medicines will not be possible. The proposals include a process for centralised systematic assessment and management of shortages including the establishment and maintenance of a medicine watchlist. Supply problems would be escalated

to a National Medicines Action Group to provide advice on possible rationing or alternative therapies when needed. It is intended that comprehensive communication strategies will be evolved to inform all stakeholders about shortages and solutions.

The Australian Health Minister introduced the Therapeutic Goods Amendment (2018 Measures No. 1) Bill 2018 into the House of Representatives on 28 June 2018.[8] The Bill encapsulates the core of the proposals in legislation and will come into effect on 1 January 2019. Successful implementation will require all stakeholders to embrace the principles of transparency, coordination and communication. Health professionals will need to understand the systems in place to address shortages and how they can stay informed.

The TGA website will be a critical primary source of information supplemented by health professional organisations and local mechanisms. The provision of information to aid both the prescribing of alternative drugs and the advice given to patients on the impact of a therapeutic change needs to be practical, understandable and timely.

In addition to national processes facilitated by the TGA, local health systems including hospitals will need to develop fair, legitimate and effective strategies for managing shortages and communicating effectively. This should include adopting practice standards such as those developed in Scotland.[9] Robust governance mechanisms should be in place clarifying accountabilities and providing an ethical framework for decision making.[10] Any proposed therapeutic alternatives need to be both accessible and affordable for patients.

Medicine shortages will continue to impact on patient care for the foreseeable future. It is simplistic to believe that there are straightforward solutions. However, the proposals outlined by the TGA, and now adopted in legislation, provide an important road map in moving towards a genuine patient-centred approach to medicine shortages in Australia to minimise potential harm. <

Steve Morris became Chief Executive Officer of NPS MedicineWise in September 2018.

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LETTERS

Letters to the Editor

Automated adverse drug reaction detection

Aust Prescr 2018;41:138
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The recent article 'Pharmacovigilance and expedited drug approvals' by Matthew Linger and Jennifer Martin,[1] provided a timely summary of issues and pressures around our national adverse drug reaction reporting program, particularly in a changing Australian regulatory environment.

One factor not raised, but that I would like to highlight, is the potential for automated data analytic techniques to screen for significant (i.e. moderate, severe or fatal) adverse drug reactions. I am referring to events that would have gone otherwise undocumented to the Therapeutic Goods Administration (TGA) by usual reporting routes – manufacturers, clinicians or consumers.

In the tertiary hospital sector, there is interest in achieving this through tools such as International Statistical Classification of Diseases (ICD-10) coding (collected routinely through medical records departments), and Natural Language Processing. These are described as complementary adverse drug reaction reporting tools, which could work to greatly supplement current standard practice.

Tertiary hospitals manage patients with complex care needs. Hospital pharmacists frequently dispense medicines when there is limited global experience with use, but where local prescribers feel their benefit outweighs the risk. Access routes to these medicines can include clinical trials, patient familiarisation programs without Pharmaceutical Benefits Scheme listing, or importation.

Practical examples where these automated adverse drug reaction detection techniques may be useful include:

- severe immune adverse effects to cancer checkpoint inhibitors (nivolumab, ipilimumab and pembrolizumab)
- perioperative drug-induced anaphylaxis
- drug-induced angioedema.

I would be keen to hear the authors' comments on automated detection, particularly in the context of expedited approvals. The Austin Health pharmacovigilance team would look forward to further research funding and TGA collaboration in this area. When serious adverse drug reactions can be detected with greater precision early in the regulatory process, there is potential for the entire patient community to benefit, minimising medicine-related harm.

Claire Keith
Senior medicines information pharmacist,
Austin Health, Melbourne

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Jennifer Martin and Matthew Linger, the authors of the article, comment:

Thank you for raising the excellent point regarding the potential for automated data analytic techniques to screen for significant events. We agree this would be a helpful source of data collection for new drugs, those using the provisional approval process and those with added significant new concerns, such as medicines blocking major cell regulatory pathways like the checkpoint inhibitors. The changes around the electronic medical record will be a step in this regard. However there are issues with some of these automatic techniques in that they still require clinicians to consider that a patient symptom, presentation or disease might be drug related, or even dose related. Research has found that this link is quite commonly missed in clinical practice.[1]

Further, the systems around publicly and timely reporting of this collated data by the TGA still require systems updating to enable clinicians to become aware as soon as there is a signal that a drug might have unknown or unexpected toxicity. Support to get such upgrades before the provisional approval pathway is rolled out is encouraged.

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The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

Reducing medicine waste in aged care

Aust Prescr 2018;41:139
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In response to your article on returning unwanted medicines to pharmacies,[1] there is an additional source of wasted medication in nursing homes. These facilities have contracted pharmacies that supply medicines to residents. Most of these pharmacies will not use or pack medicines that they have not dispensed (for economic and protocol reasons). Therefore, when a resident arrives from hospital (new or returning resident) or the community, the medicines they arrive with are incinerated rather than administered to them. Private hospitals in particular dispense medicines in full packs even if a patient is only admitted for one or two days.

When a patient comes from home there is the risk that their medication has been improperly stored and may not be 100% reliable. However, when they are transported via ambulance from one health facility to another I find that argument hard to swallow. The lack of dispensing fee or equivalent packing or checking fee at the pharmacy seems more to the point.

I tried to collect such medication to give to a charity (i.e. refugees without Medicare or Pharmaceutical Benefit Scheme rights) but it was declined on logistical grounds.

Is there a way to reduce waste either by redirecting the medicines or facilitating the packing and use of existing medicines? I'd love to see less waste within the medical system and the redirection of funds to where they are needed most.

Leah Curtis
General practitioner, Melbourne

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Amanda Wheeler and Fiona Kelly, two authors of the article, comment:

We thank Leah Curtis for raising the issue of medicine waste in aged care. The reason that medicines provided at hospital discharge, or purchased by the resident before admission, are not used is commonly a logistic issue related to the type of dose administration aids used in residential facilities. Packing medicines for these dose administration aids is typically an automated process done in a remote facility, and only certain brands of medicines are used.

Reducing the supply of unwanted medicines could be addressed at the hospital, for example by encouraging doctors, nurses and pharmacists to be mindful about medicines actually required at discharge. Rather than dispensing a full supply of (unneeded) medicines, timely discharge planning, including appropriate conversations with the residential facility, would identify what the patient needs. This may only be a prescription and discharge summary.

This approach aligns with the UK 'Only order what you need' campaign introduced specifically to reduce medicines waste,[1] and the 'Choosing Wisely Australia' initiative which highlights the use of unnecessary tests, treatments and procedures in our health system.[2]

Redirecting unwanted medicines to those less able to access them has been raised by the Australian public in a recent study.[3] Medicine reuse schemes are well established in the US (SafeNetRx since 1997) and in Greece (GIVMED, 2016). While re-dispensing returned or donated medicines is another option to reduce medicines waste, it is challenged by logistic, quality, safety and cost-effectiveness issues. These challenges often seem insurmountable, however there are currently calls in the UK that medicines reuse should be publicly debated.[4]

In the absence of a reuse scheme in Australia, making health professionals and consumers more aware of medicines waste, particularly oversupply at the point of prescribing and dispensing, is vital. When medicines wastage does occur, the Australian Return Unwanted Medicines Project provides a safe and cost-effective method of unwanted medicines disposal.

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LETTERS

Safer dispensing labels and paediatric prednisolone

Aust Prescr 2018;41:140
https://doi.org/10.18773/austprescr.2018.055

We thank Adam La Caze for his article on safer dispensing labels for prescription medicines.[1] As pharmacists working at the Queensland Poisons Information Centre, we fully support the introduction of patient-centred labels. In particular, we refer to the specific example of paediatric dosing errors involving prednisolone.[2]

In 2017, our centre alone received 70 calls about paediatric therapeutic errors involving prednisolone. We classify a therapeutic error as administration of a medicine at the wrong dose, the incorrect frequency, the incorrect route or a patient inadvertently receiving the incorrect medication. Of these 70 cases, most involved errors in interpretation of instructions on the label. Most commonly, prednisolone liquid was given to children three times daily instead of once daily for three days. This seems to be a recurring theme as noted by our colleagues at the Victorian Poisons Information Centre in 2016.[2]

Along with verbal counselling, we endorse Adam La Caze's recommendation of patient-centred instructions for prednisolone as – 'For 3 days: Give 3 mL in the morning for asthma (or croup)'. As the author notes our patients are often confused and worried following the initial consultation and with the additional stress of having a sick child. We believe these changes to medicine labels will reduce dosing errors, especially when prednisolone liquid is involved.

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Specialist in poisons information

Carol Wylie
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Adam La Caze, author of the article, comments:

Thank you to Genevieve Messina and Carol Wylie for sharing their experience. The frequency of calls regarding paediatric dosing errors for prednisolone illustrates the importance of improving communication on dispensing labels.

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ARTICLE

Second steps in managing type 2 diabetes

SUMMARY

In type 2 diabetes, diet, exercise and attaining a healthy weight should be encouraged at every opportunity.

Metformin is the usual first-line drug management.

Sulfonylureas are appropriate as second-line drugs for many patients. Other oral drugs are preferable if weight gain or hypoglycaemia are significant problems.

If a combination of metformin and a sulfonylurea is not suitable, either a dipeptidyl peptidase-4 inhibitor or sodium-glucose co-transporter 2 inhibitor can be prescribed. The patient characteristics and the beneficial and adverse effects of the drug should be considered when selecting second-line therapy.

Due to their adverse-effect profiles, thiazolidinediones and acarbose should be reserved for patients with contraindications to all other oral drugs, and those who will not tolerate injectable drugs.

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Keywords
incretin mimetics, metformin, oral hypoglycaemic drugs, sodium-glucose co-transporter 2 inhibitors, sulfonylureas, type 2 diabetes

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Introduction

Type 2 diabetes is a common medical condition, with the prevalence increasing to 1 million people in Australia in 2014–15.[1] The goals of therapy should be individualised, based on patient characteristics, including age and comorbidities. Diet, exercise and a healthy weight are important components of the management.

The range of drugs for type 2 diabetes (see Table) has increased in recent years, delaying the need for insulin therapy, but adding complexity to treatment algorithms. Metformin is first line for drug therapy.[2] Sulfonylureas have a major role as second-line drugs, however there are a number of alternative options that should be considered when weight gain and hypoglycaemia are to be avoided. The choice of second-line drug should be individualised, based on the degree and timing of hyperglycaemia, comorbid conditions and the drug's beneficial and adverse-effect profile.

The Pharmaceutical Benefits Scheme (PBS) has placed some limitations on the prescribing of second- and third-line drugs for type 2 diabetes. These restrictions need to be considered when prescribing, especially as they change from time to time.

Treatment targets

The treatment targets relating to overall glycaemic control, glycated haemoglobin (HbA1c) and glucose monitoring for patients with type 2 diabetes are an important consideration when selecting a second-line drug. These should be individualised, with age, comorbidities, diabetes-related complications, and the person's preferences among a number of factors to be considered. The risk of hypoglycaemia should always be balanced against the benefits of tight glycaemic control.

The Australian Diabetes Society has created a website that includes an algorithm for the management of type 2 diabetes and provides case studies to assist with setting targets. Once a target has been set, treatment should be escalated if the concentration of HbA1c is above the target, or has not improved by at least 0.5% after three months.

Monitoring

The recommended frequency of self-monitoring of glucose depends on the drugs prescribed. For people taking insulin, more frequent monitoring is required, compared to drugs that do not pose a significant risk of hypoglycaemia. However, when starting a second-line drug, it is important to be able to both assess the efficacy of the treatment, as well as ensure that there is no significant hypoglycaemia. Glucose should be monitored at least daily and at varied times across the day to provide a picture of the overall glycaemic profile, in particular the effect of meals and activity on glycaemic control. Once someone is stable on a new drug, with the exception of insulin, monitoring frequency can be reduced.

Management

It is essential to counsel people on the importance of diet, exercise and a healthy weight for improving control of type 2 diabetes. These should be discussed regularly to optimise glycaemic control and minimise the dose or number of drugs required to

Table **Second-line drugs for type 2 diabetes**

Class	Approximate HbA1c reduction*	Benefits in addition to glucose-lowering	Adverse effects	Precautions
Sulfonylureas	0.5–1.3%	Nil	Hypoglycaemia, weight gain	Kidney impairment (dose reduction may be required), severe liver disease, elderly
Dipeptidyl peptidase-4 inhibitors	0.7–1%	Minimal hypoglycaemic risk	Pancreatitis	Pancreatic disease, kidney impairment (dose reduction may be required)
Glucagon-like peptide-1 analogues	0.8–0.9%	Weight loss	Nausea and vomiting	Kidney impairment (contraindicated if CrCl <30 mL/min), pancreatic disease, gallbladder disease, pre-existing gastrointestinal symptoms, family or personal history of thyroid cancer (based on animal models)
Sodium-glucose co-transporter 2 inhibitors	0.5–0.7%	Lowering of blood pressure, cardioprotection, weight loss	Genitourinary infections, euglycaemic ketoacidosis	Fasting or peri-operative state, acute intercurrent illness, taking loop diuretics, kidney impairment (contraindicated if CrCl <45 mL/min)
Insulin	Superior to other diabetes drugs	Nil	Hypoglycaemia, weight gain	Inability to safely administer insulin or monitor glucose
Acarbose	0.8%	Nil	Gastrointestinal symptoms	Gastrointestinal disease, kidney impairment (contraindicated if CrCl <25 mL/min), note glucose (not sucrose) must be administered to treat hypoglycaemia
Thiazolidinediones	0.7–0.8%	Nil	Worsening of heart failure, increased fracture risk, macular oedema, cardiac ischaemia, bladder cancer	Osteoporosis, macular oedema, heart failure, liver disease

CrCl creatinine clearance
* The approximate glycated haemoglobin (HbA1c) reduction is based on studies using the class of drug as adjuvant therapy to metformin.

maintain control. Non-drug management is of equal importance in people of healthy weight, as it is in those who are overweight or obese.

Metformin

Metformin is typically prescribed as the first-line drug for type 2 diabetes.[2] It improves insulin sensitivity and is effective in improving glycaemic control. There is no weight gain and a limited risk of hypoglycaemia.

There are some situations in which metformin is contraindicated, such as end-stage kidney disease (creatinine clearance <15 mL/min), or not tolerated, for example, because of gastrointestinal adverse effects. If metformin was not used as the initial drug to manage type 2 diabetes, and no contraindications or previous intolerance exist, then it could be considered as a second-line drug. A dose reduction is required for metformin if the patient's creatinine clearance is less than 90 mL/min. Conditions that alter kidney function may increase the risk of lactic acidosis.

Sulfonylureas

Sulfonylureas such as gliclazide and glibenclamide have traditionally been used as second-line oral drugs, as add-on therapy to metformin. They are effective drugs that should be considered when metformin therapy does not achieve the target for glycaemic control. The reduction in HbA1c is 0.5–1.3% when used in addition to metformin.[3] Sulfonylureas are particularly recommended as second-line drugs if it is anticipated that the patient is likely to need a glucagon-like peptide-1 (GLP-1) analogue as a third-line drug in the relatively near future, for example in an overweight or obese person whose HbA1c is significantly above target.

Sulfonylureas act as insulin secretagogues, so there is a risk of hypoglycaemia and weight gain. Hypoglycaemia is a significant risk in patients with kidney impairment and the elderly, particularly because of the long duration of action.

Incretin mimetics

Incretins are neuroendocrine hormones produced by the gastrointestinal tract in response to food. They are involved in stimulating insulin secretion and suppressing glucagon secretion. Incretins also suppress appetite and inhibit gastric emptying. The major incretin hormones are glucagon-like peptide and glucose-dependent insulinotropic polypeptide (GIP). These hormones are metabolised by dipeptidyl peptidase-4 (DPP-4).

There are currently two types of incretin mimetic drugs that are effective in the management of type 2 diabetes. These are the oral DPP-4 inhibitors and the injectable GLP-1 analogues. The choice between a DPP-4 inhibitor and a GLP-1 analogue may be influenced by a number of factors including patient preference regarding route of administration, desired weight loss (more likely with GLP-1 analogue), and the magnitude of improvement needed for glycaemic control (tends to be greater with GLP-1 analogue when weight loss and appetite effects are also factored in).

Dipeptidyl peptidase-4 inhibitors

DPP-4 inhibitors, also known as gliptins, are effective in reducing postprandial glucose, without a risk of hypoglycaemia. DPP-4 inhibitors are weight neutral, and are generally well tolerated. As adjuvant therapy to metformin, they result in a modest reduction in HbA1c, in the order of 0.7–1%.[4-7] They have been associated with pancreatitis, so should not be prescribed to people with a previous history of pancreatic disease. Regular monitoring of pancreatic function is not required, however the drug should be stopped if people develop symptoms consistent with pancreatitis and this is confirmed on blood tests.

Glucagon-like peptide-1 analogues

GLP-1 analogues are given by subcutaneous injection. These drugs predominantly target postprandial glucose, without a risk of hypoglycaemia. They have the beneficial effects of increasing satiety, thereby reducing dietary intake and causing weight loss. The expected HbA1c reduction from GLP-1 analogues is 0.8–0.9%.[8,9]

An expected adverse effect is nausea and vomiting, in particular triggered by certain food types and large portion sizes. Like DPP-4 inhibitors, GLP-1 analogues have an increased risk of pancreatitis and pancreatic malignancy, but no routine monitoring of pancreatic function is required.

Several GLP-1 analogues are approved by the Therapeutic Goods Administration, however only exenatide and dulaglutide are currently listed on the PBS. Exenatide is available in a standard-release formulation administered as a twice-daily injection and an extended-release formulation injected weekly. Dulaglutide is administered as a weekly injection. Current PBS authority criteria restrict GLP-1 analogues to use as third-line drugs, prescribed in combination with both metformin and a sulfonylurea, or with either metformin or a sulfonylurea if there is a contraindication to a combination of both oral drugs.

Sodium-glucose co-transporter 2 inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors, or gliflozins, are the latest class of oral hypoglycaemic drugs. They work by blocking the renal sodium-glucose co-transporter, resulting in an increase in urinary glucose excretion. In combination with metformin they reduce HbA1c by 0.5–0.7%. SGLT2 inhibitors, such as dapagliflozin and empagliflozin, have the beneficial effect of mild weight and blood pressure reduction, due to the diuretic action. Another significant benefit is the cardioprotective effect reported in the EMPA-REG trial,[10] which makes the drugs a good choice for people with or at high risk of cardiovascular disease.

SGLT2 inhibitors can cause a number of adverse effects, which may make them intolerable. The glycosuria results in an increased risk of genital candidiasis and urinary tract infections, which can be severe and recurrent. SGLT2 inhibitors can cause kidney impairment, which is often transient. It is usually due to hypovolaemia as a consequence of the diuretic effect of the SGLT2 inhibitor, and those with pre-existing kidney impairment are at particular risk. There is also a small but clinically significant risk of euglycaemic ketoacidosis,[11] particularly in the perioperative period, when it is recommended that SGLT2 inhibitors are withheld for three days pre- and postoperatively.

Insulin

The role of insulin as a second-line drug is predominantly in people with hyperglycaemia who do not respond adequately to oral hypoglycaemic drugs or incretin mimetics, or in those who have significant symptomatic hyperglycaemia requiring immediate glucose-lowering. Insulin comes in a number of forms, with the frequency of subcutaneous injections ranging from once daily to five times a day. A variety of regimens can be prescribed. These include:

- basal insulin alone
- a basal-plus regimen (basal insulin with a rapid-acting insulin analogue with one meal)
- a basal-bolus regimen (rapid-acting insulin analogue administered with each meal)
- pre-mixed insulins injected one to three times daily.

When insulin is prescribed in type 2 diabetes, it is usually taken in addition to, not instead of, the other hypoglycaemic drugs, minimising the insulin doses required. In particular, metformin should

always be continued. Sulfonylureas are an exception, however, and should be stopped once rapid-acting or pre-mixed insulin is commenced, as they will not provide any additional improvement in glycaemic control. They can, however, provide ongoing benefit in those taking only long-acting insulin. The other exception relates to PBS prescribing – the extended-release formulation of exenatide, and dulaglutide are not currently PBS-approved in combination with insulin. If appropriate, these can be switched to the immediate-release formulation of exenatide, which is approved for use in combination with insulin.

The HbA1c reduction varies depending on dosage and regimen, but it is superior to all other drugs for diabetes.[11] Adverse effects include hypoglycaemia and weight gain. Access to refrigeration is needed to store insulin before use.

Acarbose

Acarbose is an oral hypoglycaemic drug, which has a limited role in the management of type 2 diabetes. It acts by delaying the intestinal absorption of carbohydrates, which causes the undesirable adverse effects of flatulence and other gastrointestinal symptoms. As an adjuvant to metformin, acarbose lowers HbA1c by 0.7%,[11] however this was based on only a few studies with small numbers of patients. Acarbose is generally considered to be less effective at improving glycaemic control than other oral hypoglycaemic drugs, which should be prescribed in preference.

Thiazolidinediones

Thiazolidinediones, also known as glitazones, act as insulin sensitisers, and reduce HbA1c by 0.7–0.8% when used with metformin.[11] These drugs are no longer commonly used because of their adverse effects. Rosiglitazone was associated with an increase in the risk of cardiac ischaemia, and pioglitazone with an increase in the risk of bladder cancer. Both these thiazolidinediones are associated with worsening heart failure, increasing the risk of fracture in people with osteoporosis, and worsening diabetic macular oedema.

Conclusion

There are a number of drugs that are suitable for use as second-line therapy in the management of type 2 diabetes. However, there is no single drug that is consistently superior as adjuvant therapy to metformin and, as a result, treatment algorithms are complex. The choice of second-line therapy should be based on the individual, considering the treatment goals, comorbidities, degree and timing of hyperglycaemia, and the beneficial and adverse effects of each class of drug.

Many people will progress to require more than two drugs to adequately manage their type 2 diabetes. There are a number of possible combinations, the most common being metformin, a sulfonylurea and one of a DPP-4 inhibitor, SGLT2 inhibitor or GLP-1 analogue. The combination of metformin, a DPP-4 inhibitor and an SGLT2 inhibitor has recently gained PBS approval, and is also an effective management option. Specialist advice should be sought if appropriate glycaemic control is unable to be achieved with these combinations, if hypoglycaemia is preventing overall adequate glycaemic control, or if there are significant diabetes-related complications. ◀

Conflict of interest: none declared

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ARTICLE

Treatment of irritable bowel syndrome

SUMMARY

Irritable bowel syndrome is a chronic functional gastrointestinal disorder that presents with abdominal pain, related to defecation, accompanied by a change in stool frequency or form. Despite its impact on a patient's quality of life, it has no effect on mortality.

A positive clinical diagnosis should be made if the characteristic symptoms are present and red flags are absent. Red flags should prompt specialist referral.

Consultations should be provided in an empathetic manner, addressing the concerns of the patient while providing reassurance.

Manipulating diet, with the assistance of a dietitian, is an appropriate initial treatment for irritable bowel syndrome. A low-FODMAP diet is an effective therapy.

Low-dose antidepressants improve symptoms but can be accompanied by adverse effects. Antispasmodic drugs have a limited role.

Psychological therapies and gut-focused hypnotherapy are effective if patients are willing to try them.

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constipation, diarrhoea, irritable bowel syndrome, low-FODMAP diet, psychological therapy

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Introduction

Irritable bowel syndrome is a functional gastrointestinal disorder meaning there are no biochemical or structural abnormalities on investigation.[1] However, it is treatable and it is among the most common complaints presenting to GPs[2] affecting about 9% of Australians.[3]

The syndrome is characterised by recurrent abdominal pain, related to defecation, and is associated with a change in stool frequency or form.[4] It is subtyped by the predominant stool form as follows:

- diarrhoea predominant (IBS-D)
- constipation predominant (IBS-C)
- mixed subtype (IBS-M).

The diagnostic criteria, referred to as the Rome criteria, are based on an expert consensus governed by the Rome Foundation (see Box 1).[5]

Given the broad definition of irritable bowel syndrome, it is likely to represent multiple different conditions, each developing from unique pathophysiological mechanisms.[6] These include intolerance to particular foods, hypersensitivity to pain and psychosomatic manifestations of anxiety or stress. Other associated mechanisms include low-grade inflammation, altered microbiota, genetic factors and altered 5-HT (5-hydroxytryptamine) metabolism.

Irritable bowel syndrome can result in significant disability, reduced quality of life and impaired workforce productivity.[7] Fortunately, it is not directly associated with mortality[8] or an increased risk of gastrointestinal malignancies.[9]

Diagnosis

Irritable bowel syndrome is not a diagnosis of exclusion. A positive diagnosis should be based on the presence of characteristic symptoms[4] (Box 1), and the absence of red flags. Patients with red flags should be referred for further investigation, including imaging or specialist review (Box 2).[6] A significant proportion of patients with irritable bowel syndrome may have symptoms that overlap with another functional gut disorder.

Initial testing should be minimally invasive. Full blood counts, urea and electrolytes, C-reactive protein and liver function tests would constitute reasonable initial investigations.

Box 1 The Rome IV diagnostic criteria* for irritable bowel syndrome

Recurrent abdominal pain, on average, at least one day per week in the last three months associated with two or more of the following criteria:

1. Related to defecation
2. Associated with a change in the frequency of stool
3. Associated with a change in the form (appearance) of stool

* Criteria fulfilled for the last three months with symptom onset at least six months before diagnosis.

Source: reference 5

Box 2 **Red flags that require further testing or specialist assessment**

Age over 50 years, no previous colon cancer screening and presence of symptoms
Recent change in bowel habit in people over 50 years of age
Evidence of overt gastrointestinal bleeding (i.e. melaena or haematochezia)
Nocturnal pain or passage of stools
Unintentional weight loss
Family history of colorectal cancer or inflammatory bowel disease
Palpable abdominal mass or lymphadenopathy
Evidence of iron deficiency anaemia on blood testing
Positive test for faecal occult blood

Adapted from reference 6

Coeliac serology should be considered as there is a significantly increased risk of coeliac disease among patients with symptoms that fit the Rome criteria for irritable bowel syndrome.[10] Genetic testing for coeliac disease is not recommended – it is unlikely to discriminate between irritable bowel syndrome and coeliac disease because more than 30% of the population share the HLA-DQ2/8 gene.[11]

The symptoms of irritable bowel syndrome share similarities with inflammatory bowel disease and gastrointestinal malignancies. The concern of organic gastrointestinal pathology, even in the absence of red flags, may prompt many clinicians to recommend an endoscopic assessment. There is no role for a faecal occult blood test to exclude gastrointestinal malignancy in patients with symptoms of irritable bowel syndrome.[12] A normal faecal calprotectin test result, which measures intestinal inflammation, reduces the need for endoscopy to rule out inflammatory bowel disease.[13]

Understandably, many clinicians are not confident to make a diagnosis of irritable bowel syndrome without specialist assessment. However, clinicians should be reassured that patients presenting with symptoms of irritable bowel syndrome in the absence of red flags are extremely unlikely to be affected by serious organic illness.[14]

Treatment

The treatment for irritable bowel syndrome should involve addressing the patient's concerns, and prescribing treatments that tackle the mechanisms underpinning their symptoms.

The consultation

An appropriately conducted consultation can be therapeutic for a patient with irritable bowel syndrome. However, only a minority of patients consult their GP, and an even smaller proportion seek specialist care.[15]

Clinicians should therefore recognise that patients who present with irritable bowel syndrome require a holistic consultation. A positive diagnosis and reassuring explanation of irritable bowel syndrome should be delivered in an empathetic manner, while allowing time for the patient to discuss their concerns. A randomised controlled trial showed patients who were given sham acupuncture were less likely to have adequate relief of irritable bowel syndrome symptoms compared with patients who received sham acupuncture combined with a 'warm empathetic' consultation (44% vs 62%, $p<0.001$).[2]

Diet

Many patients with irritable bowel syndrome report aggravated gastrointestinal symptoms related to specific foods.[16] This perception lends itself well to a therapeutic manipulation of diet. However, clinicians should be mindful of overly restrictive eating patterns,[17] and dietary manipulation should be supervised by a dietitian.

General dietary advice

The UK's National Institute of Health and Care Excellence (NICE) recommends eating smaller frequent meals, avoiding trigger foods, and avoiding excess alcohol and caffeine. This diet has been found to be as effective as a low-FODMAP diet (low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols) for the diarrhoea-predominant irritable bowel syndrome.[16]

Fibre

Insoluble fibres are more likely to worsen abdominal pain and bloating in patients with irritable bowel syndrome.[6] However, soluble fibres such as psyllium improve symptoms, especially in patients with the constipation subtype.[18]

Low-FODMAP diet

Foods containing FODMAPs (which are short-chained carbohydrates) are poorly absorbed by the small intestine. This leads to an osmotic effect in the colon and excess gas production causing pain and diarrhoea. A low-FODMAP diet has been proven to significantly reduce symptoms related to irritable bowel syndrome compared to a regular Australian diet.[19] Patients with irritable bowel syndrome, especially those with the diarrhoea subtype, should consider a low-FODMAP diet as their initial therapy. Individual symptoms of pain and bloating seem to respond to this diet.

A dietitian-supervised low-FODMAP diet involves an exclusion phase where patients reduce FODMAP-containing foods over six weeks. If the patient reports a significant reduction in symptoms, FODMAP-containing foods can be carefully re-introduced over

subsequent weeks. Remaining on an exclusively low-FODMAP diet in the long term has been shown to transform the intestinal microbiota to a potentially negative profile,[19] and therefore is not recommended.

General lifestyle advice

Symptoms of irritable bowel syndrome can be mitigated by regular exercise[20] which should be recommended in conjunction with dietary advice. The importance of sleep should also be discussed as improved quality of sleep has been found to control symptoms.[21]

Medicines

Drugs exclusively developed for irritable bowel syndrome are not available in Australia, unlike the USA and Europe. Most of the drugs used here were designed for other indications.

Mebeverine and hyoscine

Antispasmodic drugs have only modest effects in irritable bowel syndrome and have a limited role.[22] Although hyoscine has greater evidence for symptom relief,[23] it is associated with significant adverse effects including constipation and dry mouth.

Peppermint oil

Peppermint oil acts as an antispasmodic through smooth muscle calcium channel antagonism.[24] A systematic review found that it significantly reduces symptoms compared with placebo.[25]

Antidepressants

Antidepressants can significantly reduce symptoms of irritable bowel syndrome.[26] They are purported to work by manipulating visceral hypersensitivity and abnormal central pain sensitisation.[24] Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) have both demonstrated benefit.[26] Tricyclics are ostensibly used for the diarrhoea subtype due to their known adverse effect of constipation. Similarly, SSRIs may be better used for the constipation subtype due to their adverse effect of diarrhoea. Although SSRIs have been shown to be of benefit,[26] the exact dose and their use are not universally accepted for the treatment of irritable bowel syndrome.

It is important to advise patients that antidepressants are used for their neuropathic-pain-modulating effect, rather than for an antidepressant effect. Patients should take a low dose of the antidepressant every day for 4–6 weeks before assessing efficacy.

Rifaximin

Rifaximin has a limited role in irritable bowel syndrome and it is not subsidised by the Pharmaceutical Benefits Scheme for this indication. It is a non-absorbed antibiotic that modestly reduces symptoms of non-constipating irritable bowel syndrome compared to placebo.[27] Despite theoretical concerns of developing persistent bacteria that are resistant to rifaximin, studies have not demonstrated this to be the case.

Probiotics

Probiotics possibly have a role in irritable bowel syndrome but the dose and strain needed for benefit is not clear. Of the products available in Australia, the strains and doses are too varied to provide a meaningful recommendation based on evidence.[28]

Psychological therapies

There are many psychological therapies that have been shown to improve or resolve symptoms in irritable bowel syndrome. These include cognitive behavioural therapy, multi-component psychological therapy and dynamic psychotherapy.[26]

Some patients recognise that their symptoms arise or are aggravated by stress and anxiety. For these patients, offering psychological therapies as a direct method to treat irritable bowel syndrome is a reasonable solution. A carefully timed and formulated referral to a psychologist with expertise in functional gastrointestinal disorders improves the chance of a successful outcome.[29]

Many patients do not associate their symptoms with psychological disturbance, even if there appears to be an obvious clinical correlation. Offering psychological therapy for these people is unlikely to be therapeutic.

Gut-focused hypnotherapy

Hypnotherapy has been proven to reduce symptoms of irritable bowel syndrome with sustained benefit for greater than five years.[30] A recent Australian trial showed that gut-directed hypnotherapy is as effective as a low-FODMAP diet.[31]

Patients should be advised that hypnosis is not as theatrical as it is portrayed in popular culture. It usually incorporates cognitive behavioural therapy and relaxation exercises administered by a psychologically trained hypnotherapist, typically over 10 weekly sessions.

Physical and behavioural therapies

Pelvic floor dysfunction is underdiagnosed among patients with irritable bowel syndrome, especially those with the constipation subtype.[32] These patients either fail to relax the pelvic floor or paradoxically contract the pelvic floor muscles causing obstructed defaecation.[33] Through a technique referred to as biofeedback, physiotherapists with expertise can retrain patients to use their pelvic floor muscles appropriately. Patients are given visual or tactile

awareness of involuntary bowel function in order to learn voluntary control.[34] Behavioural aspects that contribute to symptoms such as incorrect toileting posture, prolonged time spent in the toilet and the use of inappropriate cues to trigger the need to defecate are also addressed with exercises and biofeedback.[35] Selecting patients for this therapy is best determined by specialists with expertise in the diagnosis of irritable bowel syndrome.

Severe disease

Some patients can present with a severe form of irritable bowel syndrome, resulting in multiple admissions to hospital and repeated investigations.[15] Despite what may appear to be debilitating symptoms, clinicians should avoid prescribing opioids for pain as it can cause narcotic bowel syndrome. These patients are best managed by a single gastroenterologist working with a multidisciplinary team including a psychologist.[6]

Conclusion

Irritable bowel syndrome is a common chronic gastrointestinal condition. A positive clinical diagnosis is made using the Rome criteria, in the absence of red flags. Patients with red flags should be referred for further testing or specialist assessment.

Once the diagnosis is made, consultations should provide reassurance in an empathetic manner with time allocated to address the patient's concerns. There are multiple therapeutic modalities that benefit patients with irritable bowel syndrome, including medicines, diet and psychologically based therapies. <

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ARTICLE

Drugs for benign prostatic hypertrophy

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SUMMARY

Benign prostatic hyperplasia is a common condition. It can cause problems with urine storage and voiding, and the severity of symptoms may be unrelated to the size of the prostate.

When drug treatment is required, benign prostatic hyperplasia can be managed with monotherapy or combination therapy. Most patients are managed with selective alpha blockers.

Patients with larger prostate volumes may benefit from a 5-alpha-reductase inhibitor, usually in combination with an alpha blocker.

Introduction

Lower urinary tract symptoms are common and can be classified into either storage (e.g. urinary frequency, nocturia and urgency) or voiding symptoms (weak stream, intermittency of flow, hesitancy).[1] Voiding symptoms in men are usually due to bladder outflow obstruction, of which benign prostatic hyperplasia is the most common cause. It is managed by Australian GPs on over 200 000 occasions each year.[2] While benign prostatic hyperplasia is the histological definition, the term benign prostatic hypertrophy is commonly used when describing the clinical syndrome.[3,4] Although medical or structural complications from benign prostatic hyperplasia are relatively uncommon, bothersome symptoms can affect the patient's quality of life.

The treatment depends on the severity of symptoms. These can be assessed by the International Prostate Symptoms Score (I-PSS).[5] This score quantifies incomplete emptying, frequency, intermittency, urgency, weak stream, straining and nocturia, as well as overall bother, using a 5-point Likert scale.[6]

Management approaches range from observation only, to medical therapy, to minimally invasive, endoscopic or open surgery.[5,7] Men with bothersome lower urinary tract symptoms without complications from benign prostatic hyperplasia, such as urinary retention, hydronephrosis or impaired kidney function, are often good candidates for medical therapy.[8]

Medical therapy

Lower urinary tract symptoms due to benign prostatic hyperplasia are caused by three main factors:[3,4,7]

- dynamic – tone of the prostatic smooth muscle and bladder neck
- static – enlarging prostatic adenoma causing mechanical obstruction
- compensatory – hypertrophy and irritability of the bladder muscle (detrusor).

Medical therapy for benign prostatic hypertrophy largely works by reducing dynamic and static components. In the last decade, clinical trials have shown that drug therapy is beneficial, however the currently available drugs vary in their efficacy depending on the patient's profile.

Alpha blockers

Alpha$_{1a}$ adrenergic receptor inhibition with selective (tamsulosin, silodosin, terazosin, alfuzosin) or non-selective (prazosin) drugs treat the dynamic component of benign prostatic hyperplasia by relaxing smooth muscle in the prostate and bladder neck. This causes the urethral lumen to widen so improving urinary flow.[3] Alpha blockers can improve symptoms and increase the maximal urinary flow rate.[3,5,9-12]

Prazosin was previously the most commonly used alpha blocker, but it requires multiple daily dosing. There are limited efficacy data therefore international guidelines no longer recommend prazosin for lower urinary tract symptoms.[4] Studies have also shown that prazosin has an average discontinuation rate of 17%, due to systemic adverse effects such as dizziness and headaches, presumably caused by postural hypotension.[3]

Tamsulosin is a selective blocker for the alpha$_{1a}$ receptor subtype. It is available in a slow-release formulation, which reduces the systemic adverse effects such as postural hypotension and the need for dose titration.[12] Tamsulosin is a commonly prescribed drug in Australia but reimbursement is only covered by the Repatriation Pharmaceutical Benefits Scheme.

Silodosin is a newer drug that is highly selective for alpha$_{1a}$ receptors. It has demonstrated a similar efficacy to tamsulosin.[13,14]

Adverse effects

Although systemic adverse effects are less frequent with the more selective alpha blockers, they increase the risk of ejaculatory dysfunction.[3] Other adverse effects of alpha blockers include retrograde

ejaculation, erectile dysfunction, nasal congestion, hypotension, dizziness and tachycardia.[3-5,7,14]

Alpha blockers, particularly tamsulosin, have been associated with intra-operative floppy iris syndrome. This increases the technical difficulty of cataract surgery and increases the incidence of complications such as posterior capsule rupture, iris trauma and vitreous loss.[15] The incidence in patients taking tamsulosin can be 40–90%.[15] If an alpha blocker is being considered for a patient awaiting cataract surgery, it is essential that the ophthalmologist is informed, ideally before the drug is prescribed.

5-alpha-reductase inhibitors

The enzyme 5-alpha-reductase converts testosterone to dihydrotestosterone in the prostate.[16] Inhibition of this enzyme reduces androgenic dihydrotestosterone and subsequently reduces prostatic tissue volume and the static contribution to symptoms.[3,17-19] Dutasteride inhibits both the type 1 and type 2 isoenzymes of 5-alpha-reductase, while finasteride only inhibits the type 2 isoenzyme.[20]

The 5-alpha-reductase inhibitors reduce the progression of benign prostatic hypertrophy, manifested as acute urinary retention or the need for surgery.[21] Compared to alpha blockers, dutasteride and finasteride are more effective in men with larger prostate volumes (>40 mL) or prostate specific antigen (PSA) concentrations above 1.4 ng/mL.[19-21] Finasteride or dutasteride monotherapy is likely to have minimal to no difference for the I-PSS and urinary flow rates compared to placebo among men with prostate volumes less than 40 mL.[8,21-23] Overall the changes in I-PSS and flow rate are less than those with alpha blockers.[3]

The symptomatic benefit can take 3–6 months to emerge.[3,5] The drugs can reduce PSA concentrations by 57–66%.[24,25]

Adverse effects

The most common adverse effects of 5-alpha-reductase inhibitors are erectile dysfunction, decreased libido, decreased ejaculate and decreased semen count.[26] These adverse effects can be irreversible and debilitating, therefore counselling is strongly recommended before prescribing.[26,27]

Combination therapies

The MTOPS trial[28] studied a combination of doxazosin and finasteride (vs monotherapy with placebo, doxazosin or finasteride) and the CombAT trial studied a dutasteride and tamsulosin combination (vs monotherapy with dutasteride or tamsulosin).[7,29] Both of these trials consisted of large cohorts (over 3000 patients each). They found that combination therapy with an alpha blocker and 5-alpha-reductase inhibitor provided a greater improvement in lower urinary tract symptoms compared to monotherapy.[7] Both studies confirmed a reduced relative risk of urinary retention or benign prostatic hyperplasia-related surgery with combination therapy.[28,29] A fixed-dose combination of tamsulosin and dutasteride is now available on the Pharmaceutical Benefits Scheme (PBS) with an authority streamlined listing. However, combination therapy also has an increased risk of adverse effects such as sexual dysfunction, and this needs to be balanced against potential benefits for urinary symptoms.[30]

For select men with bladder outlet obstruction secondary to benign prostatic hyperplasia and concomitant storage symptoms such as urgency and frequency, the combination of an alpha blocker with anticholinergic drug can be helpful.[31] Anticholinergic drugs inhibit acetylcholine-mediated bladder contraction and thus can reduce detrusor overactivity, a compensatory factor contributing to lower urinary tract symptoms. However, anticholinergic therapy in patients with elevated residual urine volume or a history of spontaneous urinary retention should only be considered with a urological opinion.[3]

Phosphodiesterase-5 inhibitors

Phosphodiesterase-5 inhibitors are more commonly used to treat erectile dysfunction. They can be effective in the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia, however they are less effective than alpha blockade therapy according to measures such as I-PSS and maximum urinary flow rate.[32] Phosphodiesterase-5 inhibitors reduce smooth muscle tone in the detrusor, prostate and urethra by increasing intracellular cyclic guanosine monophosphate.[3] As erectile dysfunction is a common adverse effect of 5-alpha-reductase inhibitors, they are sometimes used in combination to counteract it and also to reduce lower urinary tract symptoms.[33]

The combination of phosphodiesterase-5 inhibitors with an alpha blocker results in greater reductions in I-PSS, post-void residual volumes and quality-of-life scores, and greater increases in maximum urinary flow rate than both drugs used as monotherapy.[32] Tadalafil has an indication for benign prostatic hypertrophy and erectile dysfunction. Headache is a common adverse effect of phosphodiesterase-5 inhibitors. They should be avoided in patients receiving nitrates for ischaemic heart disease or those with poor cardiac function.

Referral

Urological referral is indicated for patients who have ongoing symptoms despite medical therapy. It is also indicated for complications including hydronephrosis, deteriorating kidney function, recurrent urinary tract infections, progressive deterioration of residual volume or macroscopic haematuria.

Surgery has a role in the management of benign prostatic hyperplasia. The options range from minimally invasive therapies (e.g. prostatic urethral lift, transurethral needle ablation) to the more invasive transurethral resection of the prostate, and enucleation prostatectomy in select cases.

Conclusion

In the last decade, selective alpha blockers have become the mainstay of drug therapy for uncomplicated benign prostatic hypertrophy. In the absence of contraindications, the first-line therapy for all men is an alpha blocker. In men with larger prostate volumes, combination therapy with an alpha blocker and 5-alpha-reductase inhibitor has been shown to have increased efficacy.

Patients must be informed about the adverse effect profile of these drugs to make a collaborative and holistic decision about which drug to use. Combinations of drugs are likely to have more adverse effects than monotherapy. ◀

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

1. Phosphodiesterase-5 inhibitors should not be used to treat erectile dysfunction in men with benign prostatic hypertrophy.
2. Flopsy iris syndrome is an adverse effect of alpha blockers.

Answers on page 173

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ARTICLE

Medical management of metastatic prostate cancer

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SUMMARY

Androgen deprivation therapy has an important role in the medical treatment of advanced and metastatic prostate cancer.

The treatment of metastatic prostate cancer is influenced by whether the patient's disease has progressed on androgen deprivation therapy or not. It is considered to be castrate-resistant disease if the cancer has progressed despite adequate suppression of androgens.

Chemotherapy using docetaxel or cabazitaxel and anti-androgen drugs such as abiraterone and enzalutamide can be used to treat castrate-resistant disease. Radium-223 is an option for patients with bony metastases.

Metastatic castrate-resistant prostate cancer is now considered a chronic illness as the life expectancy of patients has almost doubled due to the new treatments. General practitioners are therefore more likely to encounter patients with disease- and treatment-related complications.

Introduction

Prostate cancer is the second most common cause of cancer death in Australian men. When localised, it can be cured with surgery or radiotherapy, but some patients will relapse with either overt metastases or an isolated rise in prostate specific antigen (PSA). A proportion of these patients are found to have a local relapse and can have salvage therapy (generally radiation), but the remainder of cases are considered to have incurable advanced disease. There is also a proportion of men who have metastases when the prostate cancer is first diagnosed.

The management of advanced disease is predominantly medical. While the cancer is incurable, it is not untreatable.

Androgen deprivation therapy

Androgen deprivation therapy underlies prostate cancer therapy at all stages of disease. It aims to reduce the growth of cancer cells in the prostate by reducing the testosterone concentration.

Surgical castration is effective but not commonly used mainly due to a perceived risk of psychological distress. Medical castration can be achieved with gonadotrophin-releasing hormone (GnRH) analogues such as goserelin or leuprorelin and GnRH antagonists such as degarelix. It works by suppressing luteinising hormone and therefore testicular testosterone production.

Androgen deprivation therapy is usually started when metastatic disease is diagnosed. However, delaying treatment until the onset of symptoms does not decrease overall survival. Either approach can be used.[1]

Intermittent versus continuous therapy

The common complications of androgen deprivation therapy include sexual dysfunction, mood disturbance, change in body composition and osteoporosis.[2,3] In view of these adverse effects intermittent dosing has been considered. This is a period of androgen deprivation therapy followed by a break until disease progression, if a good response was attained. The optimal duration of androgen deprivation therapy is fairly arbitrary as the studies have looked into various periods ranging from three months to three years.

In patients with PSA relapse only (no overt metastases), intermittent therapy has been shown to be non-inferior to continuous dosing. There was also a better quality of life with intermittent dosing.[4]

In patients with objective metastases, intermittent androgen deprivation therapy had numerically worse outcomes than continuous treatment, but the study was statistically inconclusive. There was less sexual dysfunction and better mental health in the intermittent group, but this effect disappeared by 15 months when most people were back on continuous treatment.[5] If short-term quality of life is important, even at the risk of possible worse survival, intermittent therapy is a reasonable approach.

Metastatic castration-resistant prostate cancer

Prostate cancer is termed 'castrate resistant' when the disease progresses despite continuous androgen deprivation therapy. After this, further treatment is needed to maintain disease control. Androgen deprivation therapy is continued as patients who continue it survive longer than those who stop.[6]

Micro-levels of peritumoural androgen have been shown to persist despite castration levels of serum testosterone.[7] Anti-androgens are therefore added to androgen deprivation therapy.

'First-generation' anti-androgens

The early anti-androgens included non-steroidal drugs (such as bicalutamide, nilutamide and flutamide) and the steroidal drug cyproterone acetate. Even though these drugs have less benefit compared to the newer drugs, they are widely used in castrate-resistant disease as first-line drugs to achieve combined androgen blockade. This is for several reasons – current prescribing rules state that new anti-androgens are only subsidised in Australia for patients who are unfit for, or have already progressed after, chemotherapy and many men wish to delay having chemotherapy. In addition, because of the longitudinal nature of prostate cancer treatment, these anti-androgens allow additional time on oral treatments. Many men will respond and these drugs can delay the time to progression and the need for newer drugs which can then be used later in the disease course. Bicalutamide is most widely used due to its once-daily dosing and better tolerability.[8]

Common adverse effects of first-line anti-androgens are similar to those of androgen deprivation therapy (hot flushes, sexual dysfunction). Nilutamide causes changes in light accommodation (reversible on cessation). Cyproterone acetate increases cardiovascular risk and is not widely used.

These drugs can also be used sequentially as second-line therapy after progression on another anti-androgen as there may be a brief response in a selected cohort of patients. For example, flutamide could be tried after a patient progresses despite taking bicalutamide.[9] However, in the current era, the older anti-androgens are rarely used in second- or third-line settings.

New anti-androgens

The new anti-androgens target various steps of the androgen production pathway which is crucial in tumour growth. They are added to androgen deprivation therapy. These anti-androgens are used in men not fit for chemotherapy, and in those whose disease has progressed on previous chemotherapy. In men who are fit for chemotherapy the drugs are usually reserved until after the disease progresses on first-line docetaxel chemotherapy. This is due to the current prescribing restrictions and also due to the ability to give the drugs later when these men may no longer be well enough for further chemotherapy.

Abiraterone acetate

The cytochrome P450 17 alpha-hydrolase and C17,20-lyase are enzymes involved in testosterone synthesis. They mediate conversion of pregnenolone-like steroids into androgens. Abiraterone is an oral inhibitor of these enzymes so it halts both extragonadal and testicular androgen synthesis.[10]

Abiraterone improves the survival of patients with metastatic castrate-resistant prostate cancer whether they are chemotherapy (docetaxel) naïve or have cancer that has progressed post chemotherapy.[11,12] Co-administration of prednisone is important to minimise the abiraterone-induced reduction of serum cortisol and increase of mineralocorticoid. Patients need to be monitored for hypertension, hypokalaemia and peripheral oedema as well as the elevation of hepatic aminotransferases which may require a temporary suspension of treatment.

Enzalutamide

Enzalutamide is an androgen-receptor signalling inhibitor.[13] It improves survival in metastatic castrate-resistant prostate cancer, and is significantly more effective than the older drug, bicalutamide.[14,15] Enzalutamide has activity both before and after chemotherapy.[15,16] Adverse effects include hypertension, fatigue, memory impairment, falls and, less commonly, seizures.

Chemotherapy

Anthracyclines and taxanes have been used to treat metastatic castrate-resistant prostate cancer.

Mitoxantrone

Mitoxantrone is an anthracycline compound. It was the first approved cytotoxic drug for the treatment of metastatic castrate-resistant prostate cancer and was widely used before docetaxel was available. Mitoxantrone significantly improved cancer symptoms and quality of life, but did not improve survival.[17] A small number of patients may benefit from mitoxantrone and other older cytotoxic drugs such as cyclophosphamide and etoposide in third- and fourth-line settings.

Docetaxel

Docetaxel is a taxane that has been studied in a variety of cancers. It was the first cytotoxic drug to show a survival benefit for patients with prostate cancer.

It became the standard of care for metastatic castrate-resistant disease after a phase III trial reported a median survival benefit of 2.4 months over mitoxantrone (18.9 vs 16.5 months). Although adverse events were more common with docetaxel, some patients had a better quality of life.[18] Adverse effects include neutropenia, fatigue, diarrhoea, hair loss, nail changes and sensory neuropathy.

Cabazitaxel

Cabazitaxel is a newer taxane. In patients with cancer that has progressed following or during docetaxel chemotherapy it improved survival by 2.4 months compared with mitoxantrone (15.1 vs 12.7 months).[19]

Cabazitaxel is generally better tolerated than docetaxel with the common adverse effects of myelosuppression, diarrhoea, nausea and fatigue. A recent study evaluating a lower dose of cabazitaxel (20 mg/m^2 every three weeks) reported non-inferiority in overall survival compared to the standard dose (25 mg/m^2 every three weeks). There was less myelosuppression and infection which may benefit frail older patients.[20]

Metastatic hormone-sensitive prostate cancer

Studies of the optimal sequence of treatment have found that early introduction of the drugs previously reserved for castrate-resistant disease can improve overall survival in other patients with metastases. This has been proven for both abiraterone and docetaxel. The studies introduced these drugs shortly after the diagnosis of metastatic disease, at the time androgen deprivation therapy was commenced. The survival benefit for both drugs was highly significant, with an additional survival of more than one year.[21–24] At present, only the prescribing of docetaxel is not restricted for this condition. Abiraterone is not reimbursed. A study into upfront enzalutamide is ongoing.

Radiopharmaceuticals

Radiopharmaceuticals, such as radium-223, mimic calcium and are incorporated into bone growth around bony metastases. Radium-223 emits alpha particles. These emit more energy, yet have a much shorter range than beta or gamma particles and therefore provide more targeted radiation without causing significant collateral damage to surrounding bone marrow.

Radium-223 is a well-tolerated treatment when added to standard androgen deprivation therapy. It resulted in a 30% improvement in overall survival and the delay of the onset of first skeletal-related events when compared to placebo in patients with bony metastases.[25] Lutetium-177-prostate-specific membrane antigen therapy has also been shown to be active in metastatic castrate-resistant prostate cancer.[26]

Supportive care

Modern therapies have prolonged survival (see Table) so now advanced prostate cancer is akin to a chronic disease. The median survival in metastatic disease can be more than five years with best available treatment.[23,24] In biochemical relapse (raised PSA), median survival in the modern era is around nine years.[4] As more treatments become accessible, it is likely that the duration of survival will continue to extend. As a result, men with prostate cancer have more time to accumulate physical and psychological adverse effects.

Bone health

Long-term androgen deprivation therapy increases the risk of osteoporosis. Indirect evidence suggests that there is a role for smoking cessation and weight-bearing exercise in reducing the risk of osteoporosis and fractures.[27] Bisphosphonates and denosumab can reduce the risk of fracture in men on long-term androgen deprivation therapy.[28,29] It is important for these men to have regular measurements of bone mineral density to assess their risk of fractures.

Bisphosphonates and denosumab prevent skeletal events (e.g. fracture, need for radiotherapy or surgery) in patients with bony metastases. Denosumab is more effective than bisphosphonates.[30] Both therapies are associated with hypocalcaemia and a very small risk of osteonecrosis of the jaw. It is therefore recommended that patients should take calcium supplements and have dental reviews before starting these drugs.

Vitamin D supplementation is recommended in patients with vitamin D deficiency and in all patients taking denosumab or bisphosphonates.

Mental health

Common treatments for prostate cancer including prostatectomy and androgen deprivation therapy have significant risks of sexual, urinary and bowel dysfunction which impair health-related quality of life.[31] There is an increased risk of depression in men on androgen deprivation therapy.[32] Using intermittent androgen deprivation therapy improves short-term, but not long-term, mental health outcomes.[4,5]

Physical function

Loss of lean muscle mass is a known adverse effect of androgen deprivation therapy. A randomised trial of an aerobic and resistance exercise program showed a benefit in muscle mass, strength, physical function and balance in men on androgen deprivation therapy.[33]

Table **Summary of survival data for metastatic prostate cancer treatments**

Intervention	Comparator	Study design	Survival benefit	Median survival duration	Comment
Hormone-sensitive disease					
Docetaxel (at start of androgen deprivation therapy)	Androgen deprivation therapy alone (standard of care)	CHAARTED Phase III RCT 792 men, unblinded, dual arm[23]	13.6 months (metastatic only)	57.6 months (docetaxel) vs 44 months	
		STAMPEDE Phase III RCT 2962 men, unblinded, multiarm[24]	10 months (metastatic and non-metastatic)	81 months (docetaxel) vs 71 months	Study included patients with local recurrence as well as metastatic disease
Abiraterone (at start of androgen deprivation therapy)[21]	Androgen deprivation therapy alone (standard of care)	Unblinded phase III RCT 1917 men	3-year survival of 83% compared with 76% in the androgen deprivation therapy alone group		Median overall survival not reached in study follow-up Not PBS-funded in Australia
Castrate-resistant disease					
Docetaxel chemotherapy[18]	Mitoxantrone	Unblinded phase III RCT 1006 men, 3 arms (2 docetaxel arms – weekly or 3-weekly)	2.4 months	18.9 months (3-weekly docetaxel) vs 16.5 months (mitoxantrone)	Weekly docetaxel was less effective than 3-weekly
Cabazitaxel chemotherapy[19]	Mitoxantrone	Unblinded phase III RCT 755 men	2.4 months	15.1 months (cabazitaxel) vs 12.7 months (mitoxantrone)	The men in this study had already progressed after docetaxel, hence the shorter overall survival than in the other docetaxel study
Abiraterone after chemotherapy[11]	Prednisone	Blinded phase III RCT 1195 men	3.9 months	14.8 months (abiraterone) vs 10.9 months (placebo/ prednisone)	
Abiraterone before chemotherapy[12]	Prednisone	Blinded phase III RCT 1088 men	4.4 months	34.7 (abiraterone) vs 30.3 months (prednisone alone)	
Enzalutamide after chemotherapy[15]	Placebo	Blinded phase III RCT 1199 men	4.8 months	18.4 months (enzalutamide) vs 13.6 months (placebo)	
Enzalutamide before chemotherapy[16]	Placebo	Blinded phase III RCT 1717 men	65% vs 14% had not progressed at 1 year, 29% risk reduction for death at close of study (medians not reached)		Need more mature data for accurate survival benefit
Enzalutamide before chemotherapy[14]	Bicalutamide	Unblinded RCT 396 men	Median time to progression 19.4 months with enzalutamide vs 5.7 months with bicalutamide		Data is for progression of disease, not survival – follow-up not long enough for survival yet
Radium-223[25]	Placebo	Blinded RCT 921 men	3.6 months	14.9 (radium-223) vs 11.3 months (placebo)	Not PBS-funded in Australia

PBS Pharmaceutical Benefits Scheme RCT randomised controlled trial

Note: Survival duration in each trial is measured from when the trial intervention started. In some cases this is from diagnosis of prostate cancer and in other cases this is after all standard therapies have failed. Care should be taken in interpretation of absolute survival duration as it is highly context specific.

Body composition changes

Androgen deprivation therapy results in increased fat deposition and loss of lean body mass. As a result, the incidence of type 2 diabetes increases.[34] There have also been concerns about an increase in cardiovascular risk, but this has not been consistently shown. It appears that men with recent cardiovascular events are at an increased risk of further events during androgen deprivation therapy,[35] whereas in other men with prostate cancer the risk does not seem to increase.[34]

Stopping treatment

Eventually, prostate cancer evolves to the point that it is no longer sensitive to the treatment currently available. This is usually when androgen deprivation therapy, new anti-androgens and chemotherapy have all been tried but the disease continues to progress. At this point, if the patient is well enough and wishes to persist with treatment, they could be referred for a clinical trial. Alternatively, different combinations of older anti-androgens or less effective but broad-spectrum cytotoxic drugs can be tried. Ultimately, the success rate of these approaches is low and palliative care should be instigated in parallel. Equally, it is appropriate to stop active treatment when the major drugs with proven survival benefit have been exhausted. In practice it is usually a combination of patient preference and patient fitness that are the deciding factors.

Conclusion

Advanced prostate cancer is a complex disease with an often prolonged course. There are many treatment options which are used sequentially and should be tailored for each patient. There is a significant need for GPs to provide high-quality supportive care alongside the specialist care in what is now a chronic disease. ◀

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

3. Androgen deprivation therapy is ceased once prostate cancer metastasises.

4. Docetaxel improves survival in hormone-sensitive metastatic prostate cancer.

Answers on page 173

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ARTICLE

Dry eye disease: when to treat and when to refer

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SUMMARY

Dry eye disease affects one in five adults, and can significantly impair quality of life. Most patients have mild disease.

This condition is multifactorial, with an inflammatory component which can markedly worsen the impact on the ocular surface. Meibomian gland dysfunction is extremely common in dry eye disease, and contributes to the inflammatory process.

Management of mild disease includes identifying and removing precipitants, and symptomatic treatment with artificial tear supplements.

More advanced disease requires management of underlying ophthalmic and systemic conditions, as well as more aggressive therapies to protect the ocular surface.

Introduction

Dry eye disease, or keratoconjunctivitis sicca, is highly prevalent, and can have significant adverse effects on quality of life. It is 'a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play aetiological roles'.[1]

As a leading cause of patient visits to both optometrists and ophthalmologists, it is a substantial burden on the healthcare system. While most patients have mild disease and need only simple treatment, complex interventions in severe disease aim to prevent progression to corneal ulceration and conjunctival scarring. It should be noted that dry eye disease is worsened by contact lens wear and refractive laser surgery.

Dry eye disease subtypes

There are two main subtypes of dry eye disease – aqueous deficiency and evaporative. These may co-exist.[2]

Aqueous deficiency

Aqueous deficiency occurs because of reduced aqueous production from the lacrimal glands. It accounts for only a tenth of dry eye disease. Aqueous deficiency can be further separated into Sjögren's syndrome-related and non-Sjögren's syndrome-related.

Evaporative

Evaporative dry eye is due to a deficient tear film lipid layer, which increases tear evaporation. It is caused by meibomian gland dysfunction, which occurs in over 85% of dry eye disease. Blepharitis, or lid margin inflammation, is both a cause and an effect of meibomian gland dysfunction. The differential diagnosis of blepharitis includes ocular rosacea and atopy, seborrhoeic dermatitis, staphylococcal infection and *Demodex* mite infestation. Tear deficiency is thought to alter resistance to infection, so dry eye disease is both a cause and an effect of blepharitis.

Risk factors

Multiple factors contribute to the development of dry eye disease (Box 1). Female gender is the most consistently identified risk factor, with the prevalence in women being almost double that in men. Advancing age is also a major risk factor, possibly due to decreased androgen levels, since androgen up-regulates meibomian gland function in animal models. While oestrogen is thought to down-regulate it, there is uncertainty as to whether hormone replacement therapy exacerbates or improves dry eye disease.[3]

Diagnosis and assessment

Accurately diagnosing dry eye disease and determining its severity is confounded by the variability in clinical presentation. Patients often report non-specific symptoms, such as visual disturbance, photophobia and ocular discomfort, including foreign body sensation, grittiness and burning.

Paradoxically there may be excessive wateriness, as discomfort triggers reflex tearing. The severity of symptoms does not correlate well with the severity of signs seen at the slit lamp, especially if there is a low pain threshold (symptoms exceed signs), or if there is reduced corneal sensation (signs exceed symptoms).

All of these symptoms may be present in other unrelated eye conditions such as ocular allergy, corneal erosion and foreign body. Differential diagnoses must be considered when symptoms are severe or unilateral. Box 2 outlines when referral for specialist assessment is needed.[4]

Dry eye questionnaires such as DEQ-5 or OSDI have been developed and validated for screening and/or measuring severity and response to treatment. However, they are not in common use. Clinical assessment and various tests are required to diagnose dry eye disease.

Ocular surface staining

In dry eye disease, there is loss of the protective glycocalyx barrier, due to increased shedding of the corneal and conjunctival epithelial cells.[5] The new underlying cells are able to absorb vital dyes, with the degree of pathological staining matching disease severity. Areas of epithelial cell loss are readily seen using sodium fluorescein drops under cobalt blue light at the slit lamp.

Tear film break-up time

Tear film break-up time is reduced in dry eye disease. Again using sodium fluorescein drops under cobalt blue light at the slit lamp, the time it takes for the first dark spot to appear in the fluorescein-stained tear film since the last complete blink is measured. A tear break-up time less than 10 seconds indicates tear film instability, and a measurement less than five seconds diagnoses dry eye disease.

Tear lake

The tear meniscus seen at the inferior lid margin is reduced in dry eye disease. Less than 0.2 mm is diagnostic.

Blepharitis

Debris is seen on the lashes and there may be reddening, telangiectasia and thickening of the lid margins.

Meibomian gland assessment

Objective meibomian gland assessment is important for diagnosing evaporative dry eye disease. Healthy meibomian glands should discharge a transparent liquid oil under gentle pressure to the lid margin, whereas thick or discoloured meibum indicates gland dysfunction. 'Pouting' of the gland orifices at the lid margin may be seen due to retained meibum.

Box 1 Causes and risk factors for dry eye disease

- Female gender and advancing age, possibly hormone replacement therapy
- Blepharitis/meibomian gland disease – rosacea, seborrhoeic dermatitis, staphylococcal infection, *Demodex* mite infestation
- Lagophthalmos – facial nerve palsy, proptosis, vertical lid shortening
- Decreased blinking – prolonged computer use or other visual task, Parkinson's disease
- Ocular autoimmune disease – atopy, cicatricial pemphigoid
- Systemic autoimmune disease – Sjögren's syndrome, lupus, scleroderma, chronic graft-versus-host disease, rheumatoid arthritis
- Other medical causes – vitamin A deficiency, hepatitis C, thyroid disorders
- Antihypertensives, antihistamines and antidepressants
- Exogenous factors – radiation therapy, chemical injuries
- Low-humidity environments e.g. air conditioning or heating
- Low intake of omega-3 fatty acids

Box 2 NICE guidelines for referral to an optometrist or ophthalmologist

- Patients with moderate–severe eye pain, photophobia, marked redness in one eye or reduced visual acuity (same day referral)
- Deteriorating vision
- Ulcers or signs of corneal damage
- Persisting or worsening symptoms despite appropriate treatment for four weeks
- Associated disease requiring specialist treatment e.g. Sjögren's syndrome, eyelid deformities

Source: reference 4

Schirmer's test

Schirmer's test is used to diagnose aqueous deficiency dry eye disease. It is more invasive than the tests above, as a Schirmer strip composed of filter paper is placed into the lower fornix for five minutes. Anaesthetic drops are instilled first, to prevent reflex tearing due to irritation by the paper. A measurement less than 5 mm is consistent with low aqueous tear production.

Other tests

Tears can also be analysed for hyperosmolarity, and for the cytokine MMP-9 as a marker of inflammation and dryness.[6]

Management

Treatment of dry eye disease aims to relieve symptoms, and to reduce any risk of ocular surface damage. Tear film homeostasis should be restored as much as possible.

Mild disease

Box 3 provides a summary of first-line treatments for mild dry eye disease. Many of the treatments for mild symptoms are available from the pharmacy (Table).

Box 3 First-line treatments for mild dry eye disease

- Apply ocular lubricants – drop, gel or ointment depending on severity of symptoms, preferably unpreserved. Consider adding a lipid layer stabiliser.
- Treat blepharitis – lid wipes, rosacea management, eradication of infection e.g. one-week course of chloramphenicol ointment to lid margins.
- Optimise meibomian gland function – warm compresses, warming eye masks.
- Modify the environment to decrease evaporation of tears – increase air humidity, reduce computer use, increase frequency of breaks for eye rest, 'conscious blinking'.
- Review drugs that may exacerbate eye symptoms e.g. antihistamines, beta blockers, tricyclic antidepressants, selective serotonin reuptake inhibitors, isotretinoin, eye drops with preservatives.

Table Examples of pharmacy treatments for dry eye disease

Main lubricant	Presentation	Preserved
'Aqueous' tear supplements		
Carmellose sodium (Cellufresh, Celluvisc)	Single-use vial	No
Polyethylene glycol or propylene glycol (Systane drops or gel drops)	Single-use vial	No
	Multi-dose bottle	Yes
Sodium hyaluronate (Hylo-Fresh, Hylo-Forte)	Multi-dose bottle	No
Carbomer (Poly Gel)	Single-use vial	No
Carboxymethylcellulose sodium, hypromellose (Genteal gel)	Multi-dose tube	Yes
'Lipid' tear supplements		
Propylene glycol, emulsified mineral oil (Systane Balance)	Multi-dose bottle	Yes
Soya lecithin (Optrex ActiMist)	Multi-dose spray (closed lids)	Yes
Perfluorohexyloctane (NovaTears)	Multi-dose bottle	No
Lid cleansers		
Foam solution containing plant oils (Sterilid)	Pump bottle	No
Lid wipes (Systane)	Wipes	No

Lubricants

Artificial tear drops to supplement the aqueous component of the tear film are the first-line therapy for patients with mild symptoms. For moderate symptoms, gels are used during the day. Lubricating ointment is only applied at night, as it causes blurring of vision. The regular use of artificial tears, gels and ointment increases tear film break-up time, and reduces signs of corneal damage – a month's treatment produces improvement of around 25%.[7] An insert retained by the lower lid (Lacrisert) provides a slow-release alternative to conventional lubricants. Newer preparations seek to stabilise the lipid layer of the tear film, and can be used in conjunction with lubricants augmenting the aqueous layer.

Preservatives

Preservatives such as benzalkonium chloride are commonly found in eye drops, including artificial tears, corticosteroids, antibiotics and glaucoma medicines. These can cause irritation and exacerbate dry eye disease. However, because preservatives are diluted in the tear film, they remain suitable for patients with mild dry eye. In more severe disease, the dilution effect is attenuated due to reduced tear volume, so preservative-free eye drops are recommended.

Meibomian gland dysfunction

Every effort must be made to treat blepharitis and meibomian gland dysfunction. Strategies include using lid wipes or foam cleansers, doxycycline for ocular rosacea, warm compresses or eye masks, and expression of blocked glands.

Extrapolating from its use in facial rosacea, some optometrists and ophthalmologists now offer intense pulsed light therapy to improve meibomian gland function. Treatment is applied across the zygomatic arches, lower lids and bridge of the nose, while the patient is wearing opaque goggles. A variety of treatment mechanisms are proposed,[8] but there are limited studies to date. A thermal/pulsation system (LipiFlow) provides an automated method of lid margin heating and massage, and is also aimed at improving meibomian gland function.

Refractory disease

Certain patient populations have more refractory disease and require more aggressive intervention to reduce the risk of permanent ocular surface injury. This includes patients with rheumatoid arthritis or Sjögren's syndrome, and those with cicatrising disease of the conjunctiva, such as severe atopy or ocular pemphigoid. Here the foundation of care is optimal treatment of the underlying systemic disease, with co-management of the patient by both an ophthalmologist and an immunologist or rheumatologist.

Medical treatments

Topical anti-inflammatory drugs are used by ophthalmologists for more severe cases. However, topical corticosteroids are sparingly prescribed, due to the risk of glaucoma, infection and keratolysis.

Immunomodulatory drugs with anti-inflammatory effects such as ciclosporin eye drops (0.05–0.1%) have been shown to reduce symptoms and corneal surface damage.[9] Tacrolimus eye drops (0.02–0.03%) are a viable alternative for patients who are unable to use ciclosporin, or do not benefit from it.[10] Testosterone eye drops (0.03%) have shown promise in very limited settings,[11] but like tacrolimus can only be obtained from a compounding chemist.

Autologous serum eye drops, containing growth factors, vitamin A and fibronectin, are effective in severe dry eye disease. However preparation is laborious, and the procedure is only available in hospitals.[12]

Surgical treatments

Reduction of tear drainage by punctal occlusion, with dissolvable or permanent plugs, has been shown to provide symptomatic improvement, particularly in aqueous deficiency dry eye disease and when combined with other treatments. Permanent surgical closure is offered if clinical benefit is obtained from temporary plugs.

Severe lagophthalmos may need to be addressed with botulinum toxin-induced ptosis if temporary, or tarsorrhaphy if permanent.

Referring appropriately

GPs and pharmacists are well placed to recommend the interventions in Box 3 for mild disease. For more severe symptoms it is appropriate to refer a patient to an optometrist before an ophthalmologist.

An optometrist can perform a specialised eye examination, including a comprehensive dry eye disease evaluation, using equipment that is not normally available in general practice. The National Institute for Health and Care Excellence provides concise recommendations on when to refer patients (Box 2).[4]

Conclusion

Dry eye disease is common, and particularly prevalent in older women. Management of mild disease consists of tear supplements from the pharmacy as first-line treatment, and techniques to manage meibomian gland dysfunction. Patients with more severe symptoms or risk factors for ocular surface damage can be assessed by an optometrist, then referred to an ophthalmologist as needed for more advanced interventions. ◀

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FURTHER READING

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NEW DRUGS

New drugs

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Benralizumab

Approved indication: asthma

Fasenra (AstraZeneca)
pre-filled syringe containing 30 mg in 1 mL
Australian Medicines Handbook section 19.1.6

Benralizumab is a humanised IgG1 monoclonal antibody. It is indicated as an add-on therapy for people with severe eosinophilic asthma aged 12 years and over. It binds to the interleukin-5 receptor which is expressed on eosinophils and basophils. Antibody binding leads to apoptosis of these cells through cell-mediated cytotoxicity and aims to reduce eosinophilic inflammation.

The approval of benralizumab is based on three main placebo-controlled trials. The SIROCCO[1] and CALIMA[2] trials assessed the effect of benralizumab on asthma exacerbations over 48 and 56 weeks respectively. A third trial – ZONDA[3] – investigated whether benralizumab reduced the need for oral corticosteroids over 28 weeks.

The SIROCCO and CALIMA trials enrolled people (aged 12 and over) who had asthma requiring high-dose inhaled corticosteroids plus long-acting beta agonists (with or without oral corticosteroids). They must have had at least two exacerbations in the previous year requiring systemic corticosteroids or an increase in their usual dose of oral corticosteroids. Participants were given subcutaneous benralizumab 30 mg every four weeks, or every four weeks for the first three doses then every eight weeks, or placebo. The primary outcome was the annual exacerbation rate at the end of treatment. In patients with a baseline blood eosinophil count of at least 300 cells/microlitre (≥0.3 x 10^9/L), both trials found that benralizumab significantly reduced the exacerbation rate and improved the forced expiratory volume in one second (FEV_1) compared to placebo (see Table).[1,2]

In a pooled analysis of the two studies looking at predictors of treatment response, lower baseline blood eosinophil counts (less than 300 cells/microlitre or <0.3 x 10^9/L) and age less than 18 years seemed to be associated with a poorer response to benralizumab treatment.[4]

The ZONDA trial enrolled adults with severe asthma who had been taking high-dose inhaled corticosteroids plus long-acting beta agonists

Table **Efficacy of benralizumab in severe eosinophilic asthma**

Trial (duration)	Annual exacerbation rate	FEV_1 change from baseline (L)
SIROCCO (48 weeks)		
Placebo	1.33 (267 patients)	0.239 (233 patients)
Benralizumab (every 4 weeks)	0.73 (275 patients)	0.345 (236 patients)
Benralizumab (every 8 weeks)	0.65 (267 patients)	0.398 (235 patients)
CALIMA (56 weeks)		
Placebo	0.93 (248 patients)	0.215 (244 patients)
Benralizumab (every 4 weeks)	0.60 (241 patients)	0.340 (238 patients)
Benralizumab (every 8 weeks)	0.66 (239 patients)	0.330 (238 patients)

Subcutaneous injections of benralizumab 30 mg were added to patients' usual therapy of high-dose inhaled corticosteroids plus long-acting beta agonists.
Participants in the analysis had blood eosinophil counts of at least 300 cells/microlitre (≥0.3 x 10^9/L) at baseline. (The normal reference range for blood eosinophils is around 0–0.6 x 10^9/L.)
FEV_1 forced expiratory volume in 1 second
Source: references 1, 2

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

and oral corticosteroids for at least six months.[3] Participants had a median baseline blood eosinophil count of 437–535 cells/microlitre (0.44–0.54 x 10^9/L). As with the other trials, they were randomised to subcutaneous benralizumab 30 mg every four weeks (72 patients) or every four weeks for the first three doses then every eight weeks (73 patients), or placebo (75 patients). The trial period was preceded by an eight-week run-in phase (–8 to 0 weeks) to establish the minimum oral corticosteroid dose for each participant. This was followed by an induction phase of four weeks (0 to 4 weeks) in which patients continued to receive their established corticosteroid dose, then a dose-reduction phase of 20 weeks (4 to 24 weeks) in which the oral corticosteroid dose was gradually reduced at regular intervals. This was followed by a four-week dose maintenance phase (24 to 28 weeks).

At 28 weeks, the median reduction in the oral corticosteroid dose was 75% in those given benralizumab (every 4 or 8 weeks) compared with 25% in those who were given placebo. Of those taking a 12.5 mg daily dose of corticosteroid or less at baseline, more people in the benralizumab groups were able to stop their corticosteroid dose than people in the placebo group: 56% (22/39, 4-weekly dosing) and 52% (22/42, 8-weekly dosing) versus 19% (8/42, placebo). The corresponding annual asthma exacerbation rates at the end of the trial were 0.83 and 0.54 versus 1.83. Improvements in FEV_1 were significantly higher with benralizumab than with placebo at 20 weeks. However, by 28 weeks, there was no significant difference between groups.[3]

The most common adverse events with benralizumab in the exacerbation trials included headache (8.6%), pharyngitis (4%), arthralgia (3.9%) and cough (3.3%). They all occurred more frequently with benralizumab than with placebo. Injection-site reactions were reported in 2.2% of those receiving eight-weekly benralizumab and 1.9% of those receiving placebo. Similar results were seen in the ZONDA trial. Hypersensitivity reactions such as urticaria and rash have occasionally been reported with benralizumab.

In the exacerbation trials, 13% of participants treated with benralizumab developed anti-drug antibodies. High antibody titres were associated with increased clearance of benralizumab, but this did not appear to affect efficacy or safety.

As benralizumab reduces eosinophils, it may impair the immune response to helminth infections. Pre-existing infections should be treated before the start of therapy. If someone develops a helminth infection during therapy and does not respond to antihelmintics, benralizumab should be stopped.

Benralizumab is available as a single-dose pre-filled syringe. The recommended dose is 30 mg given subcutaneously (upper arm, thigh or abdomen) by a health professional every four weeks for the first three doses then every eight weeks. The drug's elimination half-life is around 15.5 days. As it is catabolised, renal and hepatic impairment are not expected to affect clearance. Drug interactions are also not expected.

Although there have been no studies in pregnant women, IgG antibodies can cross the placenta particularly in the third trimester of pregnancy. This could deplete eosinophils in the fetus and poses risks in the newborn. Antibodies can also be excreted in breast milk.

Adding benralizumab to usual treatment seems to reduce exacerbations, improve lung function and decrease the reliance on chronic corticosteroid use in people with poorly controlled asthma and elevated eosinophils. However, its efficacy beyond 56 weeks is unclear. It is not known how benralizumab will compare to mepolizumab, another antibody that targets interleukin-5 in eosinophilic asthma.

TT manufacturer provided additional useful information

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.

NEW DRUGS

Aust Prescr 2018;41:166–8
https://doi.org/10.18773/austprescr.2018.052
First published 11 September 2018

Dulaglutide

Approved indication: type 2 diabetes
Trulicity (Eli Lilly)
pre-filled pens and syringes containing 1.5 mg/0.5 mL solution
Australian Medicines Handbook section 10.1.4

When drug treatment is needed for type 2 diabetes, patients are usually prescribed metformin. If this does not control blood glucose, a second drug may need to be added.[1] This includes the glucagon-like peptide-1 (GLP-1) analogues, such as exenatide and liraglutide. Like these drugs, dulaglutide acts as an agonist at the GLP-1 receptor. It therefore increases the secretion of insulin when glucose concentrations are high.

Dulaglutide is a genetically engineered protein. It therefore has to be given by subcutaneous injection. The way the molecule is engineered slows its absorption and clearance. Peak plasma concentrations are reached in 48 hours and the half-life is 4.7 days. This makes dulaglutide suitable for once-a-week injections. It takes 2–4 weeks to reach a steady state. The molecule is catabolised and no dose adjustment is required for hepatic impairment or mild–moderate kidney impairment.

There have been multiple studies of dulaglutide as monotherapy and in combination with other drugs. Its approval in Australia is based on five main trials (Table).[2-6] Although the recommended weekly dose is 1.5 mg, these AWARD trials also studied 0.75 mg.

Monotherapy

Dulaglutide was compared with metformin in a double-blind trial involving 807 patients with type 2 diabetes of less than five years duration. At the start of the AWARD-3 study the mean concentration of glycated haemoglobin (HbA1c) was 59.6 mmol/mol (7.6%). After 26 weeks this had reduced by 8.5 mmol/mol (0.78%) with dulaglutide 1.5 mg and by 6.1 mmol/mol (0.56%) with metformin. A target HbA1c concentration below 53 mmol/mol (7%) was achieved by 62% of the patients taking dulaglutide and 54% of those taking metformin. These statistically significant advantages for dulaglutide 1.5 mg were still present after 52 weeks of treatment.[2]

Added to metformin

In the AWARD-5 trial, 1098 patients treated with metformin were randomised to add dulaglutide, sitagliptin 100 mg daily or placebo. After 26 weeks the patients taking placebo changed to sitagliptin. At the start of the study the mean HbA1c was 65 mmol/mol (8.1%). After 26 weeks this reduced by 13.3 mmol/mol (1.22%) with dulaglutide 1.5 mg, 6.7 mmol/mol (0.61%) with sitagliptin and 0.3 mmol/mol (0.03%) with placebo. The reductions from baseline at 52 weeks were 12 mmol/mol (1.1%) for dulaglutide and 4.3 mmol/mol (0.39%) for sitagliptin. Dulaglutide therefore had a significant advantage over sitagliptin. A target concentration under 53 mmol/mol (7%) was achieved by 58% of patients injecting dulaglutide and 33% of those taking sitagliptin.[3]

Table **Pivotal efficacy trials of dulaglutide in type 2 diabetes**

Trial (comparator)	Total number of patients (number treated with dulaglutide 1.5 mg weekly)	Total duration	Time of primary endpoint assessment	Reduction in HbA1c from baseline in mmol/mol (%) at primary end point		Proportion of patients achieving an HbA1c below 53 mmol/mol (7%) at primary end point
AWARD-1[4] (exenatide)	976 (279)	52 weeks	26 weeks	Dulaglutide	16.5 (1.51%)	78%
				Exenatide	10.8 (0.99%)	52%
AWARD-2[5] (insulin glargine)	810 (273)	78 weeks	52 weeks	Dulaglutide	11.8 (1.08%)	53.2%
				Insulin glargine	6.9 (0.63%)	30.9%
AWARD-3[2] (metformin)	807 (269)	52 weeks	26 weeks	Dulaglutide	8.5 (0.78%)	62%
				Metformin	6.1 (0.56%)	54%
AWARD-4[6] (insulin glargine)	884 (295)	52 weeks	26 weeks	Dulaglutide	17.9 (1.64%)	68%
				Insulin glargine	15.4 (1.41%)	57%
AWARD-5[3] (sitagliptin)	1098 (304)	104 weeks	52 weeks	Dulaglutide	12.0 (1.1%)	58%
				Sitagliptin	4.3 (0.39%)	33%

HbA1c glycated haemoglobin

Added to metformin and a thiazolidinedione

Patients in the AWARD-1 trial were stabilised on a combination of metformin and pioglitazone. The 976 patients were then randomised to have weekly injections of dulaglutide or exenatide. There was also a group of patients who injected a placebo for 26 weeks then switched to dulaglutide. From a mean baseline of 65 mmol/mol (8.1%), the HbA1c had fallen by 16.5 mmol/mol (1.51%) with dulaglutide 1.5 mg and by 10.8 mmol/mol (0.99%) with exenatide at 26 weeks. The reduction in the placebo group was 5 mmol/mol (0.46%). At 52 weeks the reduction from baseline was statistically significantly greater with dulaglutide than exenatide (14.9 vs 8.8 mmol/mol (1.36% vs 0.89%)). The goal of an HbA1c concentration below 48 mmol/mol (6.5%) was achieved by 57% of the dulaglutide group and 35% of the exenatide group.[4]

Added to metformin and a sulfonylurea

Dulaglutide has been compared to insulin when treatment with metformin and glimepiride has been insufficient to control type 2 diabetes. In the open-label AWARD-2 trial 810 patients with an average HbA1c of 65–66 mmol/mol (8.1–8.2%) were randomised to inject dulaglutide weekly or insulin glargine daily. After 52 weeks the HbA1c had reduced by 11.8 mmol/mol (1.08%) with dulaglutide 1.5 mg and 6.9 mmol/mol (0.63%) with insulin glargine. This gave dulaglutide a statistical advantage. There was also a significant difference in the proportion of patients who achieved a target HbA1c below 53 mmol/mol (7%) (53.2% dulaglutide, 30.9% insulin). The statistical superiority of dulaglutide 1.5 mg over insulin was still present after 78 weeks of treatment.[5]

Added to insulin

The open-label AWARD-4 trial involved 884 patients who were using insulin lispro with or without metformin. They were randomised to receive weekly dulaglutide or a bedtime injection of insulin glargine. From a baseline concentration of 68.95 mmol/mol (8.46%), HbA1c reduced by 17.93 mmol/mol (1.64%) after 26 weeks with dulaglutide 1.5 mg. With insulin glargine it reduced by 15.41 mmol/mol (1.41%) from a baseline of 69.72 mmol/mol (8.53%). This statistically significant difference was still present at 52 weeks. At that time, 59% of the patients injecting dulaglutide 1.5 mg had an HbA1c below 53 mmol/mol (7%) compared with 49% of those injecting insulin glargine.[6]

Safety

In studies lasting up to 104 weeks 8.4% of the patients injecting dulaglutide discontinued it because of adverse effects. Nausea, vomiting and diarrhoea are very common, particularly at the start of therapy. Pancreatitis is a possibility, but enzyme concentrations can be unhelpful for making the diagnosis as they rise during treatment with dulaglutide.

Hypoglycaemia can occur particularly in patients who are also taking insulin or a sulfonylurea. A meta-analysis of 12 trials of dulaglutide reported that with monotherapy 7.8% of patients developed hypoglycaemia compared with 10.6% of those in control groups.[7] In the study of patients taking metformin and glimepiride (AWARD-2), 55.3% of those given dulaglutide for 52 weeks developed hypoglycaemia compared with 69.1% of those who added insulin glargine. This difference was significant.[5]

The meta-analysis reported that dulaglutide reduced body weight less than metformin, but more than sitagliptin, exenatide and insulin glargine.[7] Across the studies the reduction from baseline was 0.35–2.88 kg.

Dulaglutide increases the heart rate and slightly lowers systolic blood pressure. It is also associated with atrioventricular block. The risk of cardiovascular events does not appear to differ from that of control treatments.

Some patients develop antibodies to dulaglutide. This does not appear to make them more prone to hypersensitivity reactions.

Place in therapy

As the clinical outcomes for some of the newer drugs for type 2 diabetes are not yet clear, the optimum combination is uncertain.[1] If a GLP-1 analogue is selected, there are few differences between them. Dulaglutide appears to have a greater effect on HbA1c than exenatide[4] and is non-inferior compared to liraglutide.[8] Although the absolute differences are small, dulaglutide appears to reduce weight more than exenatide,[4] but less than liraglutide.[8] As liraglutide is given daily, patients who want to minimise injections may prefer weekly dulaglutide.

T manufacturer provided the AusPAR

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

Glecaprevir/pibrentasvir

Aust Prescr 2018;41:169–70
https://doi.org/10.18773/austprescr.2018.050
First published 2 August 2018

Approved indication: hepatitis C

Maviret (Abbvie)
100 mg/40 mg tablets
Australian Medicines Handbook section 5.5

This fixed-dose combination tablet is indicated for people with hepatitis C genotypes 1–6. It contains two new antiviral drugs – glecaprevir, which is an NS3/4A protease inhibitor, and pibrentasvir, which inhibits the NS5A protein involved in viral replication.

Approval of the combination is based on several trials in approximately 2300 treatment-experienced and treatment-naïve patients, with and without cirrhosis. The primary efficacy outcome in the studies was the proportion of patients with a sustained virologic response 12 weeks after the end of the treatment course. Following 8, 12 or 16 weeks of glecaprevir/pibrentasvir (300 mg/120 mg), 91–100% of patients in the trials responded (see Table).[1-5] Most of the trials were open label and did not include an active comparator. However, in the Endurance-3 study, the efficacy of glecaprevir/pibrentasvir was comparable to sofosbuvir plus daclatasvir (95% vs 97%) in treatment-naïve participants (see Table).[2]

The combination has also been investigated in patients who had experienced treatment failure or relapsed after treatment with an NS3/4A protease inhibitor or an NS5A inhibitor, or both (Magellan-1 study). Participants did not have cirrhosis. In part 1 of the study, 86% (19/22) of patients with genotype 1 infection had a sustained response to 12 weeks of treatment.[6] In part 2 of the study, which enrolled patients with genotype 1 or 4 infection with or without cirrhosis, 89% (39/44) and 91% (43/47) responded to 12 and 16 weeks of treatment respectively.[7]

The combination has also been assessed in 104 people with severe chronic kidney disease with hepatitis C genotypes 1–6 (Expedition-4 study). Almost 20% of them had cirrhosis. After a 12-week course of treatment, 98% had a sustained virologic response 12 weeks later.[8]

Of all patients who participated in the trials, 0.1% discontinued treatment because of an adverse event. The most commonly reported events were headache (13.2%), fatigue (11.4%) and nausea (7.6%). In the severe kidney disease trial, 20% (21/104) of patients developed pruritis.[8]

As with other direct-acting antiviral drugs, there is a risk of hepatitis B reactivation with this combination. There have been no studies in pregnant or lactating women, however in preclinical studies there were no adverse outcomes in pregnant animals. Both glecaprevir and pibrentasvir were excreted in the breastmilk of rats.

Both drugs inhibit P-glycoprotein and BCRP (breast cancer resistance protein), and glecaprevir is a substrate of OATP1B1/3. The combination has the potential for many drug interactions and concomitant use of atazanavir, atorvastatin, simvastatin, dabigatran, contraceptives containing ethinylestradiol, and rifampicin are contraindicated.

The recommended treatment course for patients who have not previously been treated for hepatitis C and do not have cirrhosis is eight weeks. Longer courses (12 or 16 weeks) are recommended for people who have received previous hepatitis C regimens or who have compensated cirrhosis (Child Pugh A).

This combination is not recommended for those with moderate hepatic impairment and it is contraindicated in severe impairment. However, it can be used in patients who have had a liver transplant. Dose adjustment is not needed in renal impairment or for patients on dialysis.

The combination of glecaprevir and pibrentasvir seems to offer most people with hepatitis C a tolerable, effective option for treatment regardless of which genotype they have, and whether or not they have severe renal impairment or liver cirrhosis. However, patients who have been previously treated with an NS3/4A protease inhibitor or an NS5A inhibitor or both are less likely to have a sustained response. In Australia, the combination is not indicated for those with genotype 1 infection who have been previously treated with regimens containing both of these drug classes such as elbasvir/grazoprevir or paritaprevir/ombitasvir. Prescribers need to be aware that glecaprevir/pibrentasvir has the potential to cause numerous drug interactions.

T T manufacturer provided additional useful information

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NEW DRUGS

Table **Efficacy of glecaprevir/pibrentasvir for chronic hepatitis C**

Genotype	Study	Duration (weeks)	Patient history	Response rate*
Patients without cirrhosis				
1	Surveyor-I (phase 2, open label)[1]	8	treatment naïve or experienced	97% (33/34)
	Endurance-1 (phase 3, open label)[2]	8	treatment naïve or experienced	99.1% (332/335)
		12	treatment naïve or experienced	99.7% (331/332)
2	Surveyor-II (phase 2, open label)[1]	8	treatment naïve or experienced	98% (53/54)
		12	treatment naïve or experienced	96% (24/25)
	Endurance-2 (double-blind, placebo controlled)[3]	12	treatment naïve or experienced	99.5% (201/202)
3	Surveyor-II (phase 2, open label)[1]	8	treatment naïve	97% (28/29)
		12	treatment naïve or experienced	93% (28/30)
		12	treatment experienced	92% (22/24)
	Surveyor-II, part 3 (phase 3, open label)[4]	12	treatment experienced	91% (20/22)
		16	treatment experienced	95% (21/22)
	Endurance-3 (phase 3, open label)[2]	8	treatment naïve	95% (149/157)
		12	treatment naïve	95% (222/233)
		12 (sofosbuvir + daclatasvir)	treatment naïve	97% (111/115)
4, 5, 6	Surveyor-I (phase 2, open label)[1]	12	treatment naïve or experienced	100% (34/34)
	Surveyor-II, part 4 (open label)[3]	8	treatment naïve or experienced	93% (54/58)
	Endurance-4 (open label)[3]	12	treatment naïve or experienced	99% (120/121)
Patients with cirrhosis				
1, 2, 4, 5, 6	Expedition-1 (phase 3, open label)[5]	12	treatment naïve or experienced	99% (145/146)
3	Surveyor-II, part 3 (phase 3, open label)[4]	12	treatment naïve	98% (39/40)
		16	treatment experienced	96% (45/47)

* The primary efficacy outcome in the studies was the proportion of patients with a sustained virologic response 12 weeks after the end of the treatment course.

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

Trifluridine/tipiracil

Approved indication: colorectal cancer

Lonsurf (Servier)
film-coated tablets containing 15 mg/6.14 mg or 20 mg/8.19 mg
Australian Medicines Handbook Appendix A

This fixed-dose combination therapy is indicated for people with metastatic colorectal cancer who have previously been treated with (or not considered candidates for) fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, and drugs targeting vascular endothelial growth factor (VEGF) such as bevacizumab, and epidermal growth factor receptor (EGFR) such as cetuximab and panitumumab. Currently, only the tyrosine kinase inhibitor regorafenib is indicated for these patients.

Tablets contain trifluridine, a thymidine-based nucleoside analogue, and tipiracil, a thymidine phosphorylase inhibitor. Once trifluridine enters cells, it is phosphorylated to its active form and incorporated into DNA. This interferes with DNA synthesis and inhibits proliferation of rapidly dividing cells. Tipiracil boosts the effect of trifluridine by reducing its degradation.

Treatment is given in 28-day cycles. The recommended starting dose is trifluridine 35 mg/m^2 twice a day on days 1–5 and days 8–12. Tablets should be taken within one hour after eating in the morning and evening. After administration, peak plasma concentrations of trifluridine and tipiracil are reached in two and three hours. The majority of the trifluridine dose (55%) is eliminated in the urine.

Approval of this combination therapy is based on a randomised, placebo-controlled trial in 800 patients with previously treated metastatic colorectal cancer.[1] After enrolment, 534 patients were given the trifluridine combination and 265 were given placebo. All patients received supportive care. Median overall survival increased from 5.3 months with placebo to 7.1 months with the trifluridine combination. The corresponding median duration of progression-free survival was 1.7 months and 2 months.[1]

Serious adverse events were more common with the active treatment than with placebo. Over half of patients receiving the trifluridine combination delayed starting their next cycle of treatment because of toxicity. The most common serious adverse effects were neutropenia (38% of patients), leukopenia (21%) and anaemia (18%). Thrombocytopenia was also reported. Other common events with this combination included nausea, decreased appetite, fatigue, diarrhoea, vomiting and respiratory tract infections. Four per cent of patients had febrile neutropenia and there was one treatment-related death from septic shock.[1]

As myelosuppression is such a problem with this product, dose modification is common. Full blood counts are needed before treatment is started and to monitor for toxicity during treatment. Life-threatening infections are a risk and antimicrobials and granulocyte-colony stimulating factor may be required.

Higher exposure to trifluridine and tipiracil was observed in moderate renal impairment. This corresponded with more serious adverse events requiring dose reductions in these patients compared to those with normal or mild renal impairment. More frequent monitoring for haematological toxicities is therefore required. The drug is not recommended in severe renal impairment or end-stage renal disease as there are no data in these populations. There was a higher incidence of grade 3 or 4 hyperbilirubinaemia in moderate–severe hepatic impairment so the combination is not recommended for these patients.

Trifluridine is primarily metabolised by thymidine phosphorylase. In vitro studies have found that neither drug is metabolised by cytochrome P450 enzymes.

The combination of trifluridine and tipiracil prolonged overall survival of pre-treated patients with metastatic colorectal cancer by a median of seven weeks. However, treatment causes gastrointestinal toxicity and serious bone marrow suppression so close patient monitoring is paramount.

TT manufacturer provided additional useful information

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NEW DRUGS

Ribociclib

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Approved indication: breast cancer

Kisqali (Novartis)
200 mg tablets
Australian Medicines Handbook Appendix A

Like palbociclib, ribociclib is a small-molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6. It should be used in combination with an aromatase inhibitor such as letrozole and is indicated as an initial endocrine-based therapy for advanced or metastatic breast cancer that is hormone receptor-positive (oestrogen and/or progesterone) and human epidermal growth factor receptor 2 (HER2)-negative.

Inhibiting CDK4 and 6 kinases, which are increased in hormone receptor-positive breast cancers, aims to reduce cell proliferation. The recommended starting dose of ribociclib is 600 mg once daily for 21 days of a 28-day treatment cycle. This is followed by seven days off ribociclib treatment. An aromatase inhibitor should be taken every day of the 28-day cycle.

The approval of ribociclib in Australia is mainly based on a phase 3 randomised controlled trial in 668 postmenopausal women with previously untreated advanced or metastatic hormone receptor-positive and HER2-negative breast cancer.[1,2] Women were randomised 1:1 to ribociclib (600 mg) plus letrozole (2.5 mg) or placebo plus letrozole. After a median follow-up of 26.4 months, median progression-free survival was significantly longer in the ribociclib arm compared with the letrozole-only arm (25.3 vs 16 months).[2] The corresponding overall response rates were 42.5% versus 28.7%. Overall survival rates were not statistically significantly different between the groups. However, the survival data were not mature at this time point.

Adverse events are common with ribociclib – 44.6% of patients needed their dose reduced because of an event and 7.5% had to discontinue treatment permanently. The most common reasons for stopping were elevated liver enzymes and vomiting.

The most frequently reported adverse events with ribociclib are neutropenia (76.9%), nausea (53.3%), fatigue (41.3%), diarrhoea (38.3%), alopecia (34.4%), leucopenia (32.9%), vomiting (33.5%), constipation (27.8%), rash (22.2%) and back pain (24.3%).[2] Neutropenia is often severe (grade 3 or 4) with ribociclib and requires dose interruption. Hepatobiliary toxicity occurred in 24% of patients. In terms of cardiac effects, 7.5% of patients had a prolonged QT interval on at least one occasion and 0.9% had their ribociclib dose adjusted or interrupted because of prolonged QT or syncope.

ECG, complete blood counts, liver function and serum electrolytes should be assessed before treatment is started and in subsequent treatment cycles as dose reduction, interruption or discontinuation may be required.

Ribociclib is contraindicated in patients with corrected QT interval >450 milliseconds or who already have, or are at risk of developing, long QT syndrome. Ribociclib should not be co-administered with drugs that prolong the QT interval as it could have additive effects.

Ribociclib is extensively metabolised and is a substrate of cytochrome P450 (CYP) 3A4, so concurrent use of strong CYP3A4 inhibitors and inducers is not recommended as they may alter ribociclib plasma concentrations. If a strong CYP3A4 inhibitor cannot be avoided, the ribociclib dose should be reduced. Pomegranates and grapefruits (including juice) are not recommended as they inhibit CYP3A enzymes and may increase concentrations of ribociclib. Other foods are not expected to affect ribociclib exposure.

Peak plasma concentrations of ribociclib are reached within 1–4 hours and repeated dosing results in steady-state concentrations after eight days. Ribociclib is extensively metabolised, mainly by CYP3A4. Its half-life is 32 hours and most of the dose is eliminated in the faeces (69.1%) and urine (22.6%). Dose adjustment is not required in mild–moderate renal impairment and ribociclib has not been studied in severe impairment. The ribociclib dose should be adjusted in patients with moderate–severe hepatic impairment.

Ribociclib in combination with letrozole prolonged progression-free survival by 9.3 months compared to letrozole alone in postmenopausal women with advanced or metastatic breast cancer. However, there is not yet evidence that therapy improves overall survival. Myelosuppression and ribociclib's cardiac and hepatic effects can be serious and treatment limiting, and ribociclib has many potential drug interactions.

REFERENCES

1. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as first-line therapy for HR-positive advanced breast cancer. N Engl J Med 2016; 375:1738-48. https://doi.org/10.1056/NEJMoa1609709
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At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

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