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CONTENTS

ARTICLE

Herpes zoster vaccination in Australia: what's available and who benefits?

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SUMMARY

Acute herpes zoster and associated postherpetic neuralgia is caused by reactivation of latent varicella zoster virus. It can be debilitating for older adults and interfere with activities of daily living.

A live, attenuated single-dose vaccine, that protects against both acute herpes zoster and postherpetic neuralgia, is available for free to all Australians aged 70 years, and in a catch-up program for those aged 71–79 years.

The vaccine is contraindicated in people who are immunocompromised, but can be considered in those who are receiving low doses of selected disease-modifying antirheumatic drugs.

Records of the Australian Immunisation Register suggest that only a third of 70 year olds received the vaccine in the first year-and-a-half of the program. This is likely an underestimation, but emphasises the importance of ensuring the vaccine is offered to all eligible patients and that vaccination is recorded on the Register.

A non-live recombinant herpes zoster vaccine has recently been developed which is more efficacious than the live vaccine in clinical trials. It is registered in Australia but not currently available.

Introduction

Herpes zoster, commonly known as shingles, typically presents as a unilateral, painful vesicular rash with a distinctive dermatomal distribution. It is caused by reactivation of latent varicella zoster virus from dorsal nerve root ganglia following primary infection (chickenpox), often many decades earlier.[1,2]

The main trigger of virus reactivation is thought to be related to a decline in varicella zoster virus-specific cell-mediated immunity that occurs naturally with ageing (immunosenescence), or as a consequence of immunosuppression (from disease or medical therapy).[3,4] In the majority of cases, herpes zoster resolves on its own. However, it causes significant discomfort, particularly to older people who have the highest risk of developing postherpetic neuralgia. This is characterised by debilitating pain and dysaesthesia persisting for more than three months.[5]

In Australia around 120,000 new cases of herpes zoster occur each year and account for approximately one in 1000 of all GP visits.[6,7] Although it can occur at any age after primary infection, the risk of herpes zoster and postherpetic neuralgia increases substantially from 50 years of age onward.[6] People who live to age 85 years have approximately a 50% risk of developing herpes zoster.[5]

A recent large study from the USA suggests there is no impact of the childhood chickenpox vaccination program on the incidence of herpes zoster in adults.[8]

Why vaccinate against herpes zoster?

Almost all adults in Australia have been infected with the varicella zoster virus and are therefore at risk of developing herpes zoster.[9,10] Pain accompanies herpes zoster in about 80% of patients aged over 50 years, and varies from burning to lancinating pain, sometimes with paraesthesia, anaesthesia or allodynia.[3]

Antiviral therapy (valaciclovir or famciclovir) given within 72 hours of rash onset can help resolve acute pain and accelerate the healing of skin lesions. However, it is thought to have little or no effect on the likelihood of developing postherpetic neuralgia.[11]

Postherpetic neuralgia is problematic because it can be refractory to treatment with analgesics, neuroleptics and other drugs, and can last for months and even years.[12,13] In older adults it often interferes substantially with activities of daily living and can have a very negative impact on overall well-being.[14,15]

Vaccination protects individuals from herpes zoster and postherpetic neuralgia and reduces associated medical and psychosocial outcomes and costs for the patient.[3,13] The limited impact of current treatment for herpes zoster and postherpetic neuralgia makes vaccination a particularly important strategy to spare older Australians this debilitating disease.[16]

Recommendations for vaccination

A live attenuated vaccine against herpes zoster (Zostavax) was licensed in Australia in 2006. The vaccine contains approximately 14 times more attenuated varicella zoster virus (Oka strain) than the licensed chickenpox vaccines – this higher concentration is needed to produce a T-cell boosting response.

Since November 2016 the live vaccine has been offered through the National Immunisation Program to adults aged 70 years, and to those aged 71–79 years in a five-year catch-up program. It is contraindicated in individuals with significant immunosuppression due to disease or therapy.

Zoster vaccine is funded for people aged 70–79 years because they are expected to benefit the most. People in this age group have a higher risk of herpes zoster and postherpetic neuralgia compared to those aged 50–69 years.

Zostavax is registered for use from 50 years of age and is recommended in the Australian Immunisation Handbook for all immunocompetent adults aged 60 years and older.[17] Routine administration from 50–59 years is not recommended because of the relatively low disease incidence and because waning vaccine immunity in the 5–10 years after vaccination would result in insufficient protection when reaching an older age.

Age 70–79 years is considered the best time to target the one-dose vaccine so protection lasts until people reach their 80s, when disease risk is highest. The efficacy of the vaccine is low after 80 years of age, but individual benefit is still likely.

People aged 50–69 years and over 80 years who wish to receive the vaccine have to obtain a prescription and pay for it. Zoster vaccination is recommended for household contacts (aged ≥50 years) of anyone who is immunocompromised (currently or expected to be). This reduces the likelihood of exposure to shedding virus for the immunocompromised person.[17]

The vaccine can be given at the same visit as other inactivated or live vaccines, including pneumococcal vaccine.[17] It is also safe to give to someone who has had a previous episode of herpes zoster, to prevent recurrence. However, because herpes zoster itself provides an immune boost, vaccination is not recommended until at least 1–3 years after the initial herpes zoster episode.[17]

The lifetime risk of recurrent herpes zoster is 1–5%.[18,19] Repeat (booster) doses of Zostavax are not currently recommended or funded but a subsequent dose 10 years after a first dose is safe and results in an immune boost.[20] Checking for evidence of past chickenpox by serology is not required before vaccination, except in special circumstances such as HIV infection or before transplant.

How effective is the live vaccine?

In the Shingles Prevention Study (40,000 adults aged 60 years and over), vaccine efficacy against herpes zoster was 51% and against postherpetic neuralgia was 67%, in three years of follow-up (see Table).[21] When follow-up was extended to 4–7 years, vaccine protection against herpes zoster declined to approximately 40% but remained around 60% against postherpetic neuralgia.[22] After 7–11 years, efficacy declined further to 21% for herpes zoster and 35% for postherpetic neuralgia.[23] Protection against herpes zoster was less when the vaccine was given to adults over 70 years of age (the target National Immunisation Program age group) compared to when it was given to those aged 60–69 years. However, there appeared to be no difference in the protection against postherpetic neuralgia in the short term between these two age groups. Essentially, vaccination still modified the severity of the herpes zoster burden of illness.[21]

The impacts of vaccination have also been confirmed in post-licensure studies in the UK and USA.[24-27] In the UK, vaccine uptake by 70–79 year olds reached 58–72% and effectiveness in the first three years was 62% against herpes zoster and 70–88% against postherpetic neuralgia (see Table).[24] In the USA, where the vaccine was given to people aged 60 years and older, its effectiveness in the first year was higher for more severe herpes zoster outcomes (77% for hospitalised herpes zoster, 70% for postherpetic neuralgia) compared to herpes zoster in outpatients (38%). Protection against more severe herpes was also better preserved over the seven year observation period.[25]

Table **Efficacy of the live herpes zoster vaccine (Zostavax) in adults aged 60 years and over**

Study		Vaccine protection at follow-up period		
		3 years	4–7 years	7–11 years
Shingles Prevention Study (≥60 years)[21-23]	herpes zoster	51%	40%	21%
	postherpetic neuralgia	67%	60%	35%
Post-licensure study in UK (>70 years)[24]	herpes zoster	62%	–	–
	postherpetic neuralgia	70–88%	–	–

Safety of live vaccine

Post-licensure safety data from the USA and Australia have confirmed the good safety profile of the live vaccine.[28,29] In clinical trials the vaccine was well tolerated in adults aged 50 years and older, with only mild and transient (not lasting more than four days) injection-site reactions, such as pain, swelling, erythema or pruritus, reported by about 50% of vaccine recipients. However, two deaths associated with inappropriate administration of the vaccine to severely immunocompromised individuals have been reported.[30,31] It is therefore absolutely essential to check patients for immune suppression (medical history, medicines) before giving the vaccine.

Contraindications to live vaccine

Because the vaccine contains live attenuated virus, it is contraindicated in people who are currently or have been recently severely immunocompromised, due to primary or acquired medical conditions or from medical treatment.

Detailed guidelines regarding vaccination of individuals on immunosuppressive therapy are given in the Australian Immunisation Handbook.[17] However, it is not possible to provide prescriptive evidence-based advice on all individual circumstances, given the wide range of medical conditions and immune-modulating drug therapies. If there is uncertainty regarding a patient's level of immunosuppression, discussion with the treating or infectious disease specialist is recommended. For example, the live vaccine can be given to people taking low doses of some disease-modifying antirheumatic drugs (azathioprine, methotrexate and mercaptopurine) or denosumab, who are not otherwise severely immunocompromised.

The vaccine is also contraindicated in pregnant women, and those who have had anaphylaxis to the vaccine (either Zostavax or varicella vaccine) or its components (including gelatin or neomycin).[17]

Australian experience with live vaccine

The implementation, coverage and safety of the Australian live vaccine program has been evaluated in older adults.[29] Disappointingly, in the first 17 months of the program, vaccine uptake was only 34% in 70 year olds and 26% in 71–79 year olds according to the Australian Immunisation Register. Uptake was higher among indigenous Australians but varied across jurisdictions. These low estimates of coverage are likely, in part, due to under-reporting by GPs as the number of Zostavax doses distributed under the National Immunisation Program was almost double the number recorded in the Immunisation Register. This highlights the critical need for immunisation providers to ensure vaccination is documented and the data are transmitted to the Register for all vaccines.

Adverse events following immunisation should be reported to the Therapeutic Goods Administration Adverse Events Management System. Events are also captured by AusVaxSafety, which is an active participant-based system that has surveyed around 15,000 patients about their experiences after vaccination.[29,32] The vaccine safety profile is consistent with what was expected, when used as recommended. The majority of notifications to both systems were injection-site reactions and rash, which were mild and resolved spontaneously.

The impact of the zoster vaccination program on disease incidence in Australian has not yet been assessed.

Recombinant subunit zoster vaccine

There is a new herpes zoster recombinant subunit adjuvanted vaccine (HZ/su, Shingrix). It is not a live vaccine and requires a two-dose schedule with approximately 2–6 months between doses. The vaccine was registered in Australia in 2017 for people aged 50 years and above. However, it is not yet available for use. There is reportedly a limited global supply.

In 2018, an application by the manufacturer to include the HZ/su vaccine on the National Immunisation Program was unsuccessful due to uncertainty regarding cost-effectiveness. This vaccine is registered and used in some other countries, including the USA where the Centres for Disease Control and Prevention recommend it in preference to the live attenuated vaccine.[33]

The recombinant vaccine is more efficacious and more reactogenic than the live vaccine. In clinical trials, it provided 97% protection against herpes zoster for 50–59 year olds and 91% for those aged over 70 years.[34,35] Similar levels of protection were observed against postherpetic neuralgia over more than three years. Overall in those aged over 70 years, more people vaccinated with the recombinant vaccine than with placebo reported adverse events that prevented normal everyday activity in the week following vaccination (grade 3 injection-site reactions: 8.5% vs 0.2%, and grade 3 systemic reactions: 6% vs 2%).[34] Monitoring during the first eight months of its use in the USA has found the vaccine's safety profile to be consistent with pre-licensure trials.[36]

Importantly, the recombinant vaccine can potentially be used in immunocompromised people. To date, only a limited number of clinical trials in this population have been published with most reporting only

immunogenicity or safety. However, a recent study has found that two doses of the vaccine provide 68% protection against herpes zoster in people who have undergone autologous haemopoietic stem-cell transplant.[37] Several other trials in immunocompromised people have shown the vaccine has an acceptable safety profile.[38-40]

Conclusion

Immunisation against herpes zoster and postherpetic neuralgia using a live attenuated vaccine (Zostavax) is available under the National Immunisation Program for Australians who are 70–79 years of age. It provides modest protection against these severe and dreaded conditions that are common in older adults. Data from large post-licensure studies confirm the effectiveness and safety of this vaccine, when used according to recommendations. GPs should ensure they check patients for immunocompromising conditions before giving the live vaccine.

The uptake of Zostavax recorded on the Australian Immunisation Register is low and it is strongly recommended that GPs offer the vaccine to eligible patients and ensure administration is reported on the Australian Immunisation Register. A more efficacious non-live vaccine against herpes zoster has been registered but is not yet available in Australia. <

Conflict of interest: none declared

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ARTICLE

Managing the overlap of asthma and chronic obstructive pulmonary disease

SUMMARY

Approximately 20% of patients with obstructive lung disease have features of both asthma and chronic obstructive pulmonary disease.

These patients have a higher burden of disease and increased exacerbations compared to those with asthma or chronic obstructive pulmonary disease alone.

Management should address dominant clinical features in each individual patient, and comorbidities should be considered.

There are several interventions that are useful in the management of both asthma and chronic obstructive pulmonary disease.

As inhaled corticosteroids are key to the management of asthma, they are recommended in patients with overlapping chronic obstructive pulmonary disease.

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asthma, bronchodilators, COPD, corticosteroids, eosinophils, inhalers, obstructive lung disease

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are both common inflammatory diseases of the airways. They are usually distinct disorders but approximately 20% of patients with obstructive lung disease will have features of both conditions.[1,2] Asthma–COPD overlap is a term sometimes used to refer to this group of patients, but consensus on a precise definition is lacking.[2] Contributing to the controversy around a definition is the heterogeneity of clinical manifestations within this group and the relative importance of each disorder in an individual.[3]

COPD is characterised by persistent respiratory symptoms and airflow limitation, due to a combination of small airways disease and parenchymal destruction (i.e. emphysema). It is usually caused by exposure to noxious gases and particles, most commonly tobacco smoke.[4] Asthma is characterised by variable respiratory symptoms and airway narrowing from bronchoconstriction and airway inflammation.

Dual diagnoses of asthma and COPD have often been an exclusion criterion for clinical trials investigating the individual conditions. This has limited the availability of evidence to guide clinical management. A global survey on the diagnosis and management of asthma–COPD overlap highlighted uncertainty among GPs and specialists on the clinical approach to this group of patients.[5]

Diagnosis

The diagnosis of asthma–COPD overlap is based on symptoms and an assessment of lung function and airway inflammation.

Symptoms of asthma and COPD

Asthma commonly starts in childhood. The symptoms of breathlessness, chest tightness, cough and wheeze are variable from day to day but are worse in the night and early morning. Features of other allergic conditions such as rhinitis and eczema may be present and there may be a family history of asthma. Typical triggers of asthma may be identified, such as house dust, pollens and grasses.

Persistent dyspnoea that worsens with exercise and progresses over time is suggestive of COPD. Intermittent cough, with or without sputum production, and wheeze, may also be present. There may be a history of recurrent chest infections and flares (exacerbations) of respiratory symptoms. Onset is usually in midlife, and there is typically a history of cigarette smoking or exposure to other noxious agents associated with indoor or outdoor pollution.

The coexistence of asthma and chronic obstructive lung disease should be suspected in middle-aged or older patients with:

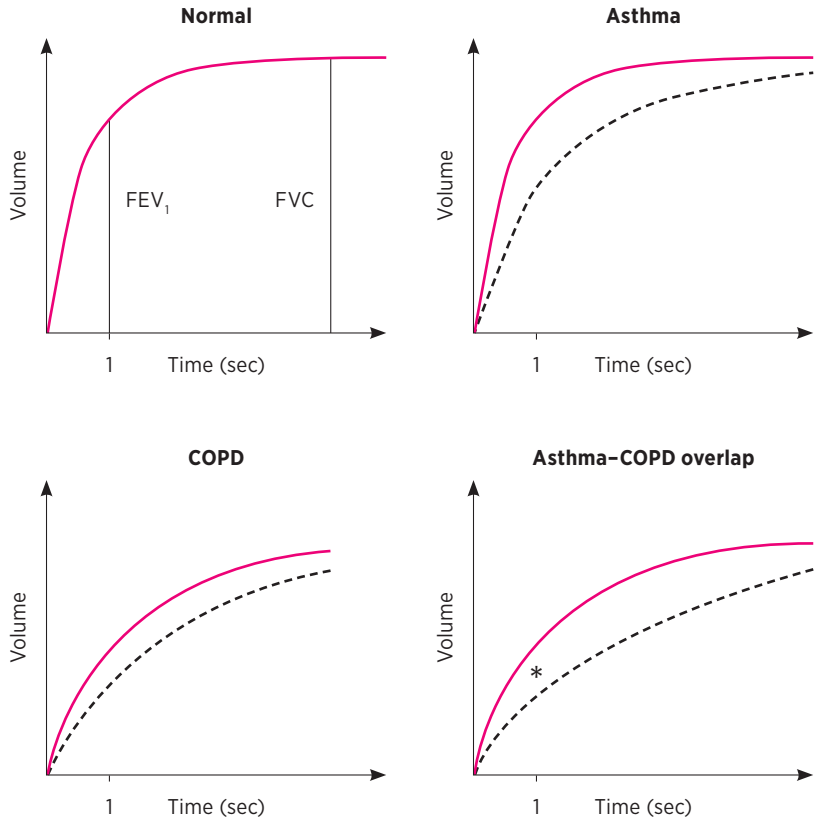
- a history of cigarette smoking
- a diagnosis of asthma before the age of 40 years
- clinical features of both diseases.

Spirometry

The diagnosis of obstructive lung disease relies on spirometry (see Fig). Pre- and post-bronchodilator spirometry should be performed. A ratio of post-bronchodilator forced expiratory volume in one second (FEV_1) to forced vital capacity (FEV_1/FVC) of less than 0.7 confirms persistent airflow limitation consistent with COPD.[4]

Reversibility can be defined as an FEV_1 increase of over 12% and more than 200 mL following bronchodilator use. While some reversibility of airflow limitation with bronchodilators may be found in patients with COPD alone, an FEV_1 increase of more than 400 mL suggests coexisting asthma.[6] However, there is also a subgroup of patients with long-standing asthma who have fixed airflow obstruction in whom reversibility cannot be demonstrated. These patients often have a long history of asthma that is difficult to control and are usually under the care of specialists.

Fig. **Examples of typical spirometry tracings in asthma, COPD and asthma–COPD overlap**



--- pre-bronchodilator — post-bronchodilator
* Difference between pre- and post-bronchodilator FEV_1 more than 400 mL.
FEV_1 forced expiratory volume in 1 second
FVC forced vital capacity
COPD chronic obstructive pulmonary disease

Airway inflammation

Asthma is characterised predominantly by eosinophilic and type 2 helper T lymphocyte-driven inflammation of the airways, whereas COPD typically involves neutrophilic inflammation.[7] In recent years the heterogeneity of airway inflammation in asthma, COPD and asthma–COPD overlap has been recognised, with eosinophilic, neutrophilic, mixed or paucigranulocytic inflammation occurring in all of these conditions.[1]

Eosinophilic airway inflammation may predict a favourable response to inhaled corticosteroids. Blood eosinophils have been suggested as a biomarker to support clinical decisions regarding the use of inhaled corticosteroids in patients with COPD. Patients with eosinophil blood counts of more than 300 cells/microlitre (0.3×10^9/L) are more likely to benefit.[4,8]

Systemic glucocorticoids will reduce the eosinophil count in blood, so the test should not be done while the patient is taking oral corticosteroids. Further prospective studies are required to elucidate the role of eosinophils in determining likelihood of response to inhaled corticosteroids in patients with asthma–COPD overlap.

Other measures of airway inflammation such as exhaled nitric oxide fraction and sputum eosinophilia are not readily available outside specialist centres.

Implications of overlapping asthma and COPD

Patients with coexisting asthma and COPD have an increased illness burden[1] compared to those with asthma or COPD alone. They have more frequent and severe exacerbations[9] and hospitalisations. This is despite having had fewer pack-years of smoking than those with COPD alone.[9] Mortality may also be increased.[1,10]

Asthma may also be a risk factor for developing COPD.[1,4,11] In severe asthma, structural changes such as airway remodelling can contribute to fixed airway obstruction and smaller airway size. Single nucleotide polymorphisms have been identified in biologically plausible genes associated with asthma–COPD overlap but their significance is unclear.[9]

Management

Consideration of the dominant features or traits in an individual patient can provide a useful framework for approaching the management of overlapping disease. There are several interventions that are useful in both COPD and asthma (see Box), and it is important that these are incorporated into the management of these patients.

Box **Interventions useful in both COPD and asthma**

- Bronchodilators for symptom control
- Inhaled corticosteroids for nearly all patients with asthma and selected patients with COPD
- Systemic glucocorticoids for severe exacerbations
- Smoking cessation
- Annual influenza vaccination
- Correction of inhaler technique
- Written action plan
- Management of comorbidities

COPD chronic obstructive pulmonary disease

Smoking cessation

Tobacco smoking is the most important risk factor for COPD, and the rate of decline in lung function can be slowed by stopping smoking. In patients with asthma, smoking is associated with progression to severe asthma and reduced glucocorticoid sensitivity.[12] It is therefore important to identify people with obstructive lung disease who continue to smoke and provide advice and support to help them stop. This involves both behavioural support and treatment of nicotine dependence, for example with nicotine replacement therapy, varenicline or bupropion.[6]

Vaccination

Annual influenza vaccination reduces exacerbations in patients with COPD, with only minor adverse effects. It is also recommended for patients with asthma.[13-15]

Pneumococcal vaccination can be given at the same time as inactivated influenza vaccine.[13] Polysaccharide pneumococcal vaccines provide protection against community-acquired pneumonia and exacerbations in patients with COPD.[16] There are also benefits for patients with asthma as those with severe disease have an increased risk of invasive pneumococcal disease.

The Australian Immunisation Handbook provides up-to-date clinical advice on the appropriate vaccines to use and timing of revaccination.[13]

Inhaler technique

Inhaled therapies are the foundation of pharmacotherapy for asthma, COPD and asthma–COPD overlap. Poor technique is common and associated with a worse prognosis in asthma and COPD.[17,18] There has been an increase in the number of different devices available in the past few years, which has increased the likelihood of handling errors. Currently available inhaler devices can be viewed in Lung Foundation Australia's Stepwise Management of Stable COPD brochure.

When inhaled therapies are started or changed, education by the prescriber should include instruction, visual demonstration and observation of patient technique. Metered-dose inhalers should be used with a valved spacer where possible. Technique should be reviewed and reinforced regularly.[6] Resources to assist with inhaler technique include 'How-to videos' available from the National Asthma Council Australia. Community pharmacists, respiratory and primary care nurses, and physiotherapists can also assist with patient education.

Bronchodilators

Short-acting beta$_2$ agonists (salbutamol or terbutaline) can be used for short-term symptom relief in asthma, COPD and asthma–COPD overlap. Recent guidelines recommend against treating asthma in adults with short-acting bronchodilators alone.[19] In patients with COPD, long-acting bronchodilators are added if short-acting drugs are not controlling symptoms. They reduce breathlessness, decrease the risk of exacerbations and improve quality of life.[6] However in patients with asthma, long-acting bronchodilators should not be used without inhaled corticosteroids. Using long-acting beta$_2$ agonists (LABAs) alone in asthma may increase the risk of asthma-related death. Similar caution is recommended in asthma–COPD overlap.[3]

LABAs are added to inhaled corticosteroids in patients with asthma if symptoms remain uncontrolled. Tiotropium, a long-acting muscarinic antagonist (LAMA), can be considered as an add-on to inhaled corticosteroid/LABA maintenance therapy in patients with moderate to severe asthma.[19] Several LABA/LAMA combination inhalers are available (indacaterol/glycopyrronium, olodaterol/tiotropium, vilanterol/umeclidium and formoterol/aclidinium) and can be useful in patients with COPD whose symptoms are not controlled with a single long-acting bronchodilator. However, these combination inhalers should not be used without a regular inhaled corticosteroid in patients in asthma–COPD overlap.[14]

Inhaled corticosteroids

Inhaled corticosteroids are the cornerstone of therapy for asthma. They decrease the risk of exacerbations, improve asthma control and decrease the loss of lung function over time. As inhaled corticosteroid monotherapy is not recommended for COPD, it is unclear if it is effective in asthma–COPD overlap.[3] Despite this, guidelines recommend that regular, long-term inhaled corticosteroids should be prescribed for patients with asthma–COPD overlap.[14] Inhaled corticosteroids increase the risk of pneumonia in patients with COPD,[20] so the lowest effective dose should be prescribed.[14]

In patients with COPD alone, inhaled corticosteroid/LABA combination inhalers may be considered when there is a history of repeated exacerbations and FEV_1 is less than 50% predicted.[6] As patients with asthma–COPD overlap have a higher symptom burden and more frequent exacerbations than those with COPD alone, it is likely that they will require a long-acting bronchodilator in addition to inhaled corticosteroids to control symptoms.

Patients using inhaled corticosteroids should be advised to rinse their mouth and spit after each dose. If they are using a manually actuated pressurised metered-dose inhaler, they should also be using a valved spacer.

Exacerbations

Flares of dyspnoea, wheeze, cough and sputum suggest an exacerbation of obstructive lung disease, and should be managed with increased doses of a short-acting bronchodilator and systemic glucocorticoids. For instance, salbutamol 4–8 puffs (400–800 microgram) via a spacer every 3–4 hours, and prednisolone 30–50 mg daily for five days (as a morning dose after the initial dose) can be given. If there are two out of three of fever, increased sputum volume or purulence, five days of doxycycline or amoxicillin are indicated.[6]

Written action plan

Guidelines recommend a written action plan as a component of self-management in COPD and asthma.[6,14] The plan should include the patient's usual treatment and instructions on how to respond to deterioration. In patients with asthma–COPD overlap, an asthma or COPD action plan template can be used, depending on the dominant clinical features.[14] A library of Asthma Action Plan templates is available from the National Asthma Council Australia. A COPD Action Plan Kit is available from Lung Foundation Australia. Some GP practice software also links to Asthma Management Plans.

Pulmonary rehabilitation, including supervised exercise training and self-management education, reduces re-admission rates and improves quality of life in patients with COPD. Referral to a local program is recommended for patients with asthma–COPD overlap.[6,14]

Comorbidities

COPD is chiefly a disease of older people so the prevalence of asthma–COPD overlap increases with age. Age-related physiological changes may contribute to airflow limitation.[21] Comorbidities are frequent in older people and present challenges for management. GPs are well placed to identify comorbidities and their relative importance to the older person's quality of life, and to manage multidisciplinary care.

Cognitive impairment can affect self-management skills. Older people are less likely to use inhalers effectively.[22] Dexterity may be affected by osteoarthritis and should be considered when choosing an inhaler device. A personalised self-management program for older patients with asthma, which targeted barriers to self-care such as poor inhaler technique, limited understanding of the role of medicines, and environmental triggers, was shown to reduce exacerbations and improve quality of life.[23]

People with asthma–COPD overlap have often smoked and so are also at risk of cardiovascular disease. This is a common cause of death in patients with COPD. Symptoms such as dyspnoea and chest tightness can occur in both cardiovascular disease and asthma–COPD overlap. Osteoporosis frequently coexists due to limited physical activity, smoking and corticosteroid use.[21]

Polypharmacy is an important consequence of ageing and comorbidity. In people with overlapping asthma and COPD, there is an increased likelihood of drug–disease interactions, for example beta blockers used for ischaemic heart disease may lead to bronchospasm. When there are compelling cardiovascular indications for beta-blocker use, a cardioselective drug such as metoprolol can be trialled at the lowest effective dose.

Future directions

Asthma, COPD and asthma–COPD overlap are all heterogeneous disorders. The impact of various clinical features and biomarkers on the response to particular therapies requires clarification. Newer treatments for asthma, such as monoclonal antibodies targeting IgE or interleukin-5, may have a role in asthma–COPD overlap, and further studies are needed.

Macrolides have been studied for their anti-inflammatory properties in asthma.[24] Forty-eight weeks of azithromycin 500 mg three times per week was shown to reduce exacerbations and improve quality of life in a randomised controlled trial of adults with severe persistent symptomatic asthma.[24] Long-term macrolide therapy has also been shown to decrease the rate of exacerbations in patients with COPD, but there are concerns about QTc prolongation and hearing loss.[25] However, their role in asthma–COPD overlap is yet to be determined, as are the implications for antimicrobial stewardship.

Conclusion

Evidence to guide the clinical management of asthma–COPD overlap is limited. Incorporating interventions that are useful in both COPD and asthma, as well as considering the dominant clinical features and comorbidities in an individual patient, can help tailor therapy.

Bronchodilators are used for symptom control in patients with asthma–COPD overlap. Inhaled corticosteroids also have a vital role as these patients have features of asthma, whereas they are only recommended for some patients with COPD alone.

Patients with asthma–COPD overlap have a high symptom burden and frequent exacerbations. They will benefit from improving their self-management skills, including correct inhaler technique and the use of action plans. <

Conflict of interest: none declared

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ARTICLE

Management of heart failure with preserved ejection fraction

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SUMMARY

Heart failure with preserved ejection fraction is a highly heterogenous disease. There is emerging evidence that treatment should be tailored to the individual's associated comorbidities.

No current algorithms exist for the management of heart failure with preserved ejection fraction. Conventional therapies used in heart failure with reduced ejection fraction are yet to show a mortality benefit.

Key treatment objectives include control of hypertension and fluid balance.

Common comorbidities include coronary artery disease, atrial fibrillation, obesity, diabetes, renal impairment and pulmonary hypertension. These comorbidities should be considered in all patients and treatment optimised.

Introduction

Heart failure usually presents as exercise intolerance due to exertional dyspnoea. It is categorised according to left ventricular ejection fraction:

- heart failure with preserved ejection fraction (HFpEF, also known as diastolic dysfunction)
- heart failure with reduced ejection fraction (HFrEF).

Heart failure affects over half a million Australians and accounts for 1.6% of all hospitalisations. Approximately half of these cases are due to HFpEF. Despite sharing the same clinical symptoms, patients with a preserved ejection fraction tend to be older, more frequently female and obese, and have higher rates of comorbidities compared to those with a reduced ejection fraction.[1-3]

Although there have been significant advances in the management of HFrEF with several pharmacologic and device-based therapies recommended by guidelines, the current therapeutic options in HFpEF may alleviate symptoms but do not significantly reduce mortality.

Pathophysiology

Despite the marked differences in systolic function, patients with preserved ejection fraction and reduced ejection fraction can share the same level of functional impairment. Echocardiography is therefore vital to differentiate between them. Myocardial stiffening, reduced left ventricular compliance and impaired relaxation in diastole are characteristic,[4] although peripheral mechanisms have also been implicated, such as impaired oxygen uptake and remodelling of skeletal muscle. Myocardial stiffening results in elevated left ventricular pressures during filling, with further transmission to the left atrium and consequent pulmonary hypertension. This in part leads to the sensation of breathlessness. Left atrial myopathy is associated with worse haemodynamic features, likely due to a greater transmission of pressure.[5]

When considering HFpEF, it is important to exclude infiltrative cardiomyopathies. Approximately 13% of patients with HFpEF have cardiac amyloidosis. Patients with significantly increased wall thickness, low Doppler velocities, early-onset bilateral carpal tunnel syndrome, and other systemic manifestations of amyloidosis should undergo more detailed evaluation. Both cardiac MRI and nuclear imaging studies provide non-invasive methods of diagnosis.

Diagnosis

The diagnosis of HFpEF is challenging, in part due to clinical heterogeneity and the primary manifestation of symptoms and abnormalities, often with exertion. The condition is defined by a left ventricular ejection fraction of at least 50%, in combination with elevated biomarkers (either BNP or NT-proBNP) and echocardiographic features of structural or functional impairment.[1,6] Up to 15% of patients can have normal natriuretic peptide measures at rest, and the sensitivity of resting echocardiography is limited. Although multiple echocardiography criteria exist, including an elevated E/e' and left ventricular mass index, the presence of an enlarged left atrium, with a preserved ejection fraction and normal mitral valvular function, should prompt consideration of HFpEF.

The H_2FPEF score, which combines clinical and echocardiographic characteristics, is a useful and clinically validated screening tool for patients

presenting with dyspnoea (Table).[7] It can help guide clinicians to refer patients on for exercise-based evaluation, either with invasive haemodynamics or diastolic stress testing with echocardiography.

Given the diverse spectrum of comorbidities associated with HFpEF, it is suggested that management be tailored to these comorbidities.[8-10] Distinct comorbidity phenotypes have been identified with differing long-term outcomes across groups.[8] Hypertension, fluid retention, obesity and metabolic syndrome, pulmonary hypertension, cardiac fibrosis and ischaemia, and renal impairment have been identified as treatment targets (and the key determinants of phenotype) in patients with HFpEF.[11]

Management

General principles for the management of HFpEF are outlined in the Box.[12] Structured weight-loss programs and exercise-based rehabilitation are recommended, as well as adequate control of comorbidities such as hypertension, and particularly atrial fibrillation and diabetes.

Non-drug interventions

Salt and fluid restriction are advised in HFpEF, although evidence for benefit is lacking.[4,13] Cessation of smoking, limiting alcohol intake and a high-fibre diet are advised.[14] Exercise training appears to improve exercise capacity and quality of life.[15] There is a dose-dependent decrease in the risk of HFpEF with a lower BMI and increasing exercise. However, the amount of exercise needed to be beneficial may be greater than standard recommendations. Further studies are in progress.[16]

Pharmacotherapy

In contrast to HFrEF, ACE inhibitors, angiotensin receptor antagonists (sartans), aldosterone antagonists, beta blockers and digoxin have not shown a mortality benefit in HFpEF.[17-22] However, study populations in the trials were variable because of varying definitions of the disease and difficulty in confidently diagnosing HFpEF. This clouded interpretation of the results.[23] In the absence of conclusive data, pharmacotherapy for HFpEF varies widely.

Neurohormonal antagonists

Hypertension is a major risk factor for HFpEF.[1] Blood pressure management is paramount, and an ACE inhibitor or angiotensin receptor antagonist is appropriate.[6] Despite not having a significant mortality benefit, perindopril, candesartan and spironolactone may have value in reducing the risk of hospitalisations from heart failure through inhibition of the renin–angiotensin–aldosterone system.[17-19]

Table **Screening tool for heart failure with preserved ejection fraction in patients with dyspnoea**

	Clinical variable	Values	Points
H_2	Heavy	Body mass index >30 kg/m^2	2
	Hypertensive	≥2 antihypertensive drugs	1
F	Atrial fibrillation	Paroxysmal or persistent	3
P	Pulmonary hypertension	Echocardiographic estimated pulmonary artery systolic pressure >35 mmHg	1
E	Elderly	Age >60	1
F	Filling pressure	Echo derived E/e' >9	1

H_2FPEF score and point allocation: a diagnosis of HFpEF is likely with a total score ≥6, intermediate with a score of 2–5, and unlikely with a score of ≤1.
Source: Adapted from reference 7

Box **Principles of management in patients with heart failure with preserved ejection fraction**

Avoid tachycardia	For patients with atrial fibrillation, use digoxin or beta blockers
Blood pressure control	ACE inhibitors, angiotensin receptor antagonists (sartans) or mineralocorticoid receptor antagonists may be of the greatest benefit
Comorbidities	Optimise cardiac and noncardiac conditions, particularly atrial fibrillation, obesity and diabetes mellitus
Diuretics	Use loop diuretics to relieve congestion, with close monitoring of renal function
Exercise training	Improves exercise capacity and quality of life

Source: Adapted from reference 12

The TOPCAT trial assessed 3445 patients with HFpEF (with an ejection fraction over 45%). Despite an overall negative outcome, later investigation found significant geographical heterogeneity in outcomes. Patients from Russia and Georgia appeared not to have the structural and functional features of a preserved ejection fraction. When they were removed from the analysis, spironolactone reduced hospitalisations. The PEP-CHF trial assessed the role of perindopril, with a weak signal of reduction in hospitalisation.[17]

Care must be taken to monitor for renal dysfunction and hyperkalaemia when starting spironolactone, particularly as renal dysfunction is prevalent in people with HFpEF. A combination of multiple antihypertensives may be needed to adequately control blood pressure, with ambulatory blood pressure monitoring providing the most accurate measure of control.

Diuretics

Diuresis helps lower left ventricular pressures, reducing pulmonary congestion and improving symptoms.[24] Furosemide (frusemide), a loop diuretic, is most commonly used. Patients with preserved ejection fraction are often more sensitive to diuresis than those with reduced ejection fraction and are at greater risk of developing renal dysfunction and hypotension.

Statins

Aside from their cholesterol-lowering benefits, statins also target systemic inflammation.[25] This is an important contributor to the pathogenesis of HFpEF. Their use has been associated with lower mortality in these patients,[26] even in those without coronary artery disease.[27] However, further trials are needed to confirm these results and elucidate the mechanism of action.

Sacubitril with valsartan

Sacubitril with valsartan inhibits both neprilysin and the angiotensin AT_1 receptor. In addition, neprilysin inhibition increases natriuretic and vasoactive peptides, leading to natriuresis, diuresis and vasodilation.[28] Although a significant reduction in mortality was seen with the combination in HFrEF, the recent PARAGON-HF trial[29] found it did not significantly reduce hospitalisations and mortality in patients with HFpEF.[30,31]

Managing comorbidities

Patients with HFpEF frequently display cardiac and non-cardiac comorbidities including coronary artery disease, hypertension, obesity and diabetes.[1-3] Some experts believe these extra-cardiac comorbidities lead to systemic inflammation, a key driver in the development of HFpEF.[32] These comorbidities must be considered as part of the initial evaluation, and aggressively managed.

Obesity

Obesity is associated with diastolic dysfunction and worse left ventricular remodelling.[33,34] Patients with obesity have increased epicardial fat, limited cardiac reserve, worse pulmonary vascular disease and greater biventricular remodelling.[35] Observational studies support the benefit of weight loss and exercise in improving quality of life and survival.[36] Caloric restriction is well tolerated and significantly improves heart failure symptoms and exercise capacity.[37]

Type 2 diabetes

Tight glycaemic control is important and metformin is the first-line oral hypoglycaemic drug.[6] Sodium-glucose co-transporter 2 inhibitors have shown significant benefits in HFrEF, reducing mortality in patients with and without diabetes.[38,39] These drugs may be beneficial in HFpEF by inducing osmotic diuresis, natriuresis and weight loss, and reducing heart failure hospitalisations and all-cause mortality.[40] Several trials are currently assessing outcomes in HFpEF.[41]

Renal impairment

HFpEF commonly co-exists with renal dysfunction, in part due to shared comorbid risk factors such as aging, hypertension and diabetes, and to the adverse haemodynamics promoting cardiorenal syndrome.[42] In patients with a comorbid chronic kidney disease phenotype, cardiorenal syndrome appears to result from renal venous congestion due to pulmonary hypertension and right ventricular dysfunction.[8] In these cases, careful diuresis may be required, and haemodynamic monitoring may be helpful to titrate therapy.[43]

Atrial fibrillation and rate control

Atrial fibrillation co-exists in approximately one-third of patients with HFpEF,[44] and may precede or follow the development of heart failure.[45] Patients with atrial fibrillation display elevated filling pressures and reduced cardiac output. The loss of atrial contraction in late diastole compounds the impaired left ventricular filling. As a result, the atrial myopathy promotes atrial fibrosis and higher transmission of left ventricular pressures onto the pulmonary circulation.[46] In suitable candidates, rhythm control should be considered in view of the potential benefits, although trial data are lacking. If this fails, traditional management principles apply, with long-term rate control and anticoagulation. Catheter ablation appears safe, with similar functional improvements and rates of recurrence as in patients with HFrEF.[47] Further studies are in progress.[48]

Rate control has also been suggested as a treatment target for patients in sinus rhythm to maximise diastolic filling. An increased heart rate is associated with cardiovascular death and hospitalisation in HFpEF,[49] although pharmacological rate control has yet to show a mortality benefit.[50,51] It may even be detrimental to the patient's exercise capacity[52] as it exacerbates their inability to compensate for exercise demands by inducing chronotropic incompetence.[53] For this reason, adaptive atrial pacing has been suggested as an alternative to pharmacological rate control.[54]

Coronary artery disease

Coronary artery disease affects over half of patients with HFpEF and is associated with increased mortality.[55] The symptom of exertional dyspnoea may indicate angina, and current recommendations advise exclusion of coronary disease. The decision for revascularisation is independent of the HFpEF diagnosis, and should be considered where appropriate.[55]

Right ventricular dysfunction

Chronic pulmonary hypertension, driven by persistent elevations in left-sided pressures, can lead to right ventricular failure in HFpEF.[56,57] These changes are typically seen later in the course of the disease and indicate a worse prognosis. Preliminary results with milrinone are promising, but further trials of these therapies are required.[58]

Drugs to avoid

Avoiding or minimising the use of non-steroidal anti-inflammatory drugs is recommended in heart failure, due to their association with sodium and fluid retention and increased risk of renal impairment and hospitalisations due to heart failure.[59]

Glitazones are not recommended due to the risk of worsening heart failure related to salt and water retention.[60] Despite being associated with worse outcomes in HFrEF, non-dihydropyridine calcium channel blockers appear safe to use in patients with preserved ejection fraction, although they are not necessarily beneficial.[61]

The combination of ACE inhibitors and neprilysin inhibitors can lead to angioedema, and they should not be used within 36 hours of each other.[6,62] A randomised controlled trial of isosorbide mononitrate demonstrated a worsening of exercise capacity, and is not recommended for HFpEF. Sildenafil has also been rigorously tested in several randomised trials and has not shown harm or benefit.[63]

Devices

The lack of benefit from drug therapies is likely due to the myriad of pathways activated in HFpEF, with the only definite uniting pathology being elevated left ventricular filling pressures. Consequently, devices targeting this pathway have been tested in trials over the past few years.

Interatrial septal device

A transcatheter interatrial left to right shunt has been shown to offset the high left atrium pressure that develops in HFpEF.[64-66] One-year observational outcomes have shown the safety of this device, with increased exercise tolerance, quality of life, and a trend toward decreased hospitalisations and heart failure symptoms.[67,68] A trial is under way.[69]

Implantable pulmonary arterial pressure monitoring

Continuous monitoring of haemodynamics through an implanted device allows for assessment of diastolic left ventricular pressures, and early appropriate administration of diuretics. The CHAMPION trial demonstrated reduced hospitalisations with this device by alerting physicians to high pulmonary pressures and directing subsequent changes to medicines.[70,71] This device is available for clinical use, however it is currently limited by availability and cost.

Future directions

In HFrEF, there is substantial evidence of improved outcomes with multidisciplinary care (including GPs, cardiologists, specialist nurses and allied health).[13] This approach should also be considered in patients with HFpEF. Clinics specialising only in HFpEF have shown benefits overseas, particularly in identifying 'treatable' forms of the condition such as amyloidosis, and in referring patients on to relevant clinical trials.[72]

Conclusion

HFpEF is a diagnostic and therapeutic challenge. Early identification of the disease along with aggressive control of comorbidities are key to management. Determining a patient's associated comorbidities will allow targeted use of available therapies. ≺

Harry Gibbs has received fees for presentations and advisory board attendance from Bayer and Bristol-Myers Squibb.

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ARTICLE

Drug interaction resources: mind the gaps

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SUMMARY

Drug interactions can lead to significant toxicity or loss of clinical effect. The risks increase with the number of drugs the patient takes.

General and specialised drug interaction resources are available. Access to up-to-date electronic resources is encouraged.

There are gaps in the information on interactions for new drugs, those with complicated metabolism and drugs with limited use. It may be necessary to use multiple resources to find the information.

When assessing information about interactions, clinicians should evaluate the relevance for each patient. In high-risk situations, expert advice can be valuable.

Clinicians should report new or unusual drug interactions to the Therapeutic Goods Administration.

Introduction

Treatment regimens are becoming increasingly complex, with a greater risk of drug interactions. Drug–drug interactions can cause significant patient harm. This is either due to drug toxicity or loss of efficacy. For example, voriconazole[1] and clarithromycin increase simvastatin concentrations risking rhabdomyolysis, while rifampicin decreases the anticoagulant effect of warfarin. Sometimes interacting drugs are intentionally co-prescribed, for example diltiazem can be used to increase ciclosporin concentrations. Drug–drug interactions can also occur with complementary medicines.

Clinicians should use the available drug–drug interaction resources, but be aware that, although advice may be similar from each resource, discrepancies also occur. It is important that potential drug–drug interactions are evaluated for their clinical significance and relevance to each patient. To identify interactions it is first necessary to have an accurate list of the patient's prescription, complementary and over-the-counter medicines. Drugs given by other routes, such as topical and inhaled, should also be considered.

Mechanisms

The mechanisms of drug–drug interactions vary.[2,3] Clinicians need to understand the drug's pharmacology including metabolic pathways to determine both pharmacodynamic (altered effect) and pharmacokinetic (altered concentration) interactions. It can be particularly complex to assess the clinical significance of interactions from multiple drugs which each have a potentially additive effect on a shared action, such as QT prolongation,[4] increasing serotonin, or lowering of the seizure threshold. Patient factors, such as organ dysfunction, age, concurrent medical conditions, electrolyte disturbances and genetic factors, may influence the risk or severity of the interaction.

Toxicity from drug–drug interactions can occur not only when starting or changing doses, but also when ceasing treatment, for example the strong induction effect of carbamazepine on cytochrome enzymes takes at least two weeks to reverse. Some drugs take a long time to be completely cleared such as amiodarone.[5] Patients should be monitored accordingly.[6]

Drug interaction resources

General and specialised resources are available to help assess the clinical impact of drug interactions. These include dedicated drug–drug interaction resources for antiretroviral drugs, hepatitis C therapies, antifungals, anticancer drugs and complementary medicines (Table 1). A subscription may be needed.

The Australian Medicines Handbook (AMH) provides practical information on drug interactions considered likely to be clinically important. When appropriate it gives specific information on drug metabolism, but does not include primary references.

MIMS and the Australian Drug Information (AusDI) interaction checkers, Stockley's Drug Interactions and Lexicomp assign their own 'severity/risk rating' or 'importance' for interactions. They give the probable mechanism of interaction, advise on actions to be taken and include clinical evidence and supporting, or in some cases disputing, references.

Some of the information used to develop drug–drug interaction resources includes:

- Australian and international product information
- primary literature (case reports and clinical papers)
- guidance from international regulatory bodies, such as the Therapeutic Goods Administration (TGA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA).

Gaps

Depending on the information used and their editorial criteria, resources may give different advice about interactions especially when assigning clinical significance. In some cases, interaction advice may be lacking entirely. These gaps can occur due to variations in product information, or when the metabolism of a drug is not well defined. A particularly challenging area for advice about drug–drug interactions is with new drugs, such as enzalutamide (Table 2), and older re-purposed drugs, such as pristinamycin. Clinical experience of these drugs in combination with other drugs is limited. Sometimes interaction information is extrapolated from other drugs in the same class or those with similar metabolism. Interactions may not be included in the resources until they have been reported to the TGA or published as case reports.

The available resources usually provide information about interactions between two drugs, however patients may be taking multiple drugs with many potential interactions. There is no resource currently available that can provide information about the overall risk of interactions with different combinations of drugs. Medicines information pharmacists may be able to provide advice in these cases.

Drug interactions – search strategy

When looking for information, clinicians are strongly encouraged to have access to the online interaction checking tool in the AMH. Similar tools in MIMS or AusDI are also valuable. For newer drugs, those with complex metabolism or for unusual drug–drug combinations, there may be a need to refer to multiple resources.

In order to predict the potential for a drug–drug interaction, cytochrome tables, such as in the AMH or Flockhart, are useful, along with the mechanism of action given in the product information. For specific drug classes, free access to specialised resources is available (Table 1). Electronic resources should be used to improve the currency of information. However, clinicans are reminded that not even electronic resources can be considered completely up to date, due to the speed of publication of medical literature.

Hospital and medicines information pharmacists have access to specialised resources, such as Stockley's or Lexicomp, along with locally researched drug–drug interaction resources. However, access to medicines information services and clinical pharmacologists varies by state. Pharmacists working in general practice are also a valuable resource, but are not widely available.[7]

Electronic decision support

Drug interaction alerts are included as decision support at the point of care in electronic prescribing and dispensing systems. For example, some interaction alerts in general practice software are referenced to the MIMS interaction checker.

There are concerns that systems generate so many warnings that there is a risk of alert fatigue. This has led to calls in the USA, particularly in the hospital environment, to standardise the information in electronic systems, with the development of methods to filter out unimportant drug–drug interaction alerts.[8] However, an international or local consensus on standardisation has not yet been reached.[8,9]

Real-world data

For new drugs there may be few clinical trials or case reports of drug–drug interactions in 'real-world' conditions involving patients with multiple comorbidities taking many drugs. For example, many resources about antiretroviral drug–drug interactions are based on theoretical information, so the clinical relevance in everyday practice is unknown. A Spanish group has therefore established a website that allows clinicians to submit cases of antiretroviral drug–drug interactions.[10]

Clinicians are encouraged to publish case reports of new or unusual drug–drug interactions, as these are valuable in informing clinical practice. Reporting suspected drug and vaccine interactions to the Therapeutic Goods Administration is also encouraged via the TGA Adverse Event Management System.

Conclusion

Clinicians should consult drug–drug interaction information, evaluate it and consider its relevance for their patient. For new drugs or when information is inconsistent or absent, it may be necessary to refer to multiple interaction resources or seek expert advice, for example from a medicines information pharmacist. <

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Table 1 **Online drug interaction resources**

Area	Resource and web link	Interaction checker*	Comment	Origin	Availability
General	Individual product information	No	Not exhaustive and not routinely updated with new clinically important drug–drug interactions	Australia	Free via TGA website – lists most current product information Also on MIMs/AusDI (check currency)
	Australian Medicines Handbook	Yes – capacity to search interactions between: • 2 individual drugs • 2 drug classes • 1 individual drug and entire drug class	Provides practical information on clinically important interactions Information on drug metabolism including quick reference tables for drugs and CYP enzymes and P-glycoprotein No primary references provided	Australia	Subscription required
	MIMS Drug Interaction Database AusDI Drug Interaction Database	Yes	Backbone for some GP prescribing software The content of these interactions databases can differ from each other	Australia	Subscription required
Specialised	Stockley's Drug Interactions	Yes	Authorative resource preferred by most medicines information pharmacists	UK	Subscription required
	Lexicomp Drug Interactions	Yes	Although a useful resource, it tends to extrapolate interaction advice from other drugs in the same class or other drugs with the same metabolism. It is sometimes overcautious and includes drug–drug interactions, even when evidence or even plausibility is lacking	USA	Subscription required Also available with full UpToDate subscription Most hospitals have access
	Flockhart Table	No	Provides tables of cytochrome substrates, inhibitors and inducers	USA – Indiana University School of Medicine	Free
	YouScript	Yes	Considers individual patient genetic phenotypes and drug interaction risk, quick guide to pharmacokinetic data for drug exposure changes	USA	Subscription

Continued over page

Table 1 **Online drug interaction resources (continued)**

Area	Resource and web link	Interaction checker*	Comment	Origin	Availability
Specific drug classes	**Antiretroviral** HIV Drug Interactions	Yes	Easy to use – can print a personalised drug–drug interaction report	UK - University of Liverpool	Free
	Antiretroviral HIV Clinical Cases Drug–Drug Interactions - 'real-world cases'	Yes	Search outcomes from real-world clinical cases	Spain – FLS Science, plus international collaboration	Free – but need to register Available since May 2019
	Antiretroviral and hepatitis C direct-acting antivirals HIV/HCV Drug Therapy Guide	Yes	Easy to use – can print a personalised drug–drug interaction report	Canada - Toronto General Hospital	Free
	Hepatitis C direct-acting antivirals HEP Drug Interactions	Yes	Easy to use – can print a personalised drug–drug interaction report	UK - University of Liverpool	Free
	Antifungal Fungal Pharmacology	Yes	Easy to use – can print a personalised drug–drug interaction report	Netherlands - Radboud University Medical Centre	Free
	Oncology Cancer Drug Interactions database	Yes	Easy to use – can print a personalised drug–drug interaction report	UK and Netherlands – University of Liverpool and Radboud University	Free
Complementary medicines	Natural Medicines	Yes	Includes published drug–drug interaction case reports and theoretical interactions based on CYP metabolism Can print patient handouts, multiple languages	USA	Subscription required
	Various other resources include interactions with complementary medicines: AusDI, Stockley's Herbal Medicines Interactions				

* Interaction checkers generate interactions between all possible pairs of drugs but cannot provide information about the overall combination of multiple drugs

TGA Therapeutic Goods Administration

AusDI Australian Drug Information

CYP cytochrome P450

Table 2 **Comparison of online drug interaction resources for enzalutamide***

Enzalutamide with / Resource	Oxycodone (metabolised by CYP3A4 (major), CYP2D6 (minor))	Mirtazapine (metabolised by CYP3A4)	Rivaroxaban (metabolised by CYP3A4, substrate of P-glycoprotein)
Enzalutamide product information (Revised 2019 Sep 4)	No direct recommendation. In interaction section – 'analgesics' listed but not specifically oxycodone	No direct recommendation	No direct recommendation. In interaction section – anticoagulants, only warfarin listed
Australian Medicines Handbook (AMH)	Although no interaction found, need to consider pharmacokinetic and background information provided, which suggests ↓oxycodone. Consider an alternative or monitor pain relief and adjust oxycodone dose	Although no interaction found, need to consider pharmacokinetic and background information provided, which suggests ↓mirtazapine. Possible additive seizure risk	Although no interaction found, need to consider pharmacokinetic and background information provided and extrapolate from other potent CYP3A4 inducers. ↓rivaroxaban
MIMS Interaction Database	No interaction listed	No interaction listed	No interaction listed
Stockley's Drug Interactions	Theoretical evidence predicts ↓oxycodone	Theoretical evidence predicts ↓mirtazapine	Theoretical evidence predicts ↓rivaroxaban, but confusing as no information to suggest enzalutamide's effect on P-glycoprotein#
Lexicomp Drug Interactions	Risk Rating D: need to consider dose modification as ↓oxycodone	Risk Rating D: need to consider dose modification as ↓mirtazapine	Risk Rating X: avoid – see comments
Micromedex Drug Interactions	Major interaction. ↓oxycodone	No interaction listed	No interaction listed
Cancer Drug Interactions	Do not co-administer# If co-administration clinically necessary, close monitoring required	Do not co-administer# If co-administration clinically necessary, may need to increase mirtazapine dose as enzalutamide ↓mirtazapine	Do not co-administer# If co-administration clinically necessary, close monitoring of anti-Xa recommended

* Resources in this table reviewed online 2019 Aug 23.

Notes

Enzalutamide, an anti-androgen for metastatic castration-resistant prostate cancer, will be increasingly seen in the community. It is an unrecognised, yet major contributor to drug interactions and has a particularly complex metabolism.

It is a potent CYP3A4 inducer, moderate CYP2C9 and CYP2C19 inducer, but its effect on P-glycoprotein is conflicting in the manufacturer's information. This, combined with the limited published reports of clinical outcomes from drug interactions to date, has resulted in variation or, in some cases, an absence of reporting of drug–drug interactions. In addition, the extended half-life (approximate mean 6 days) makes drug–drug interactions difficult to predict, with maximum induction potential occurring up to one month from starting enzalutamide, and effects on enzymes continuing for at least one month after cessation. Management of anticoagulation in patients taking enzalutamide is particularly challenging and input from a haematologist is recommended.

Enzalutamide has complex metabolism:

- substrate CYP2C8 (major), CYP3A4 (minor)
- induces CYP3A4 (potent), CYP2C9 and CYP2C19 (moderate)
- product information says in vitro enzalutamide inhibits P-glycoprotein but it also says it may act as an inducer
- induces CYP2B6, OAT, UGT

Resource comments that these combinations have not actually been clinically studied

CYP cytochrome P450

↓ reduces drug concentration

An A3 single-page version of this table is available online.

Apixaban (metabolised by CYP3A4, substrate of P-glycoprotein)	Dabigatran (substrate of P-glycoprotein)	Comments
No direct recommendation. In interaction section – anticoagulants, only warfarin listed	Use with caution as dabigatran is a P-glycoprotein substrate and a drug with narrow therapeutic window	Difficult to quickly determine drug–drug interactions if you do not know how the other drug is metabolised
Although no interaction found, need to consider pharmacokinetic and background information provided. However AMH does not suggest enzalutamide has any effect on P-glycoprotein, *so would assume no interaction*	Although no interaction found, need to consider pharmacokinetic and background information provided. However AMH does not suggest enzalutamide has any effect on P-glycoprotein, so *would assume no interaction*	Enzalutamide is not listed in specific P-glycoprotein substrate/inhibitor/inducer table which makes interaction interpretation difficult
No interaction listed	No interaction listed	Personal communication with MIMS editorial team (August 2019) that this content is under review
Theoretical evidence predicts ↓apixaban, but confusing as no information to suggest enzalutamide's effect on P-glycoprotein#	Use with caution as may increase dabigatran	Enzalutamide not listed in specific P-glycoprotein substrate/inhibitor/inducer table, although role of P-glycoprotein is mentioned in dabigatran/enzalutamide interaction
Risk Rating X: avoid	No interactions identified	For rivaroxaban, there is a statement that in Canada these combinations would say 'use with caution' rather than 'avoid'
No interaction listed	No interaction listed	Micromedex, a US database, less commonly referred to for drug–drug interaction advice
Do not co-administer# If co-administration clinically necessary, close monitoring for anti-Xa recommended	Potential Interaction# If co-administration clinically necessary, close monitoring for dabigatran toxicity recommended	

ARTICLE

National Medicines Policy 2.0: a vision for the future

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Keywords
drug regulation, National Medicines Policy, polypharmacy

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SUMMARY

Australia's National Medicines Policy was launched 20 years ago with the aim of improving health outcomes for all Australians. It was developed in partnership with healthcare professionals, consumers and the pharmaceutical industry.

The key parts of the Policy focus on timely access to high-quality and affordable medicines and their safe and judicious use. It also supports a viable and responsible pharmaceutical industry.

Since the Policy was first launched, Australia has seen significant changes in healthcare systems, medicines subsidies, health services remuneration, digital technologies and the pharmaceutical industry.

Medicines themselves have also changed, as have consumers' expectations. To respond to these changes, the National Medicines Policy needs to be updated with a greater focus on implementing and measuring outcomes.

Introduction

In October 2019, the health minister, Greg Hunt, announced there would be a review of Australia's National Medicines Policy.

The policy was one of the first of its kind when it was implemented in 1999.[1] It provides overarching policy direction focusing on four interconnected pillars:

- timely access to medicines that are affordable to individuals and the community
- high-quality medicines that are safe and effective
- the quality use of medicines
- maintenance of a viable and responsible medicines industry.

These objectives remain as important and relevant to the nation now as they did in the 1990s.

Why do we need an update of the National Medicines Policy?

The overall goal of the National Medicines Policy is to optimise health outcomes for Australians through a collaborative partnership with key stakeholders. This remains fundamental to the health of the individual at all levels of the health system. However, the last two decades have seen substantial changes in people's expectations, as well as changes in healthcare and information systems, medicines themselves (e.g. biologicals and biosimilars, and precision medicine), medicines subsidies and health services remuneration, digital technologies, and the pharmaceutical industry.[2,3] These changes have challenged the very foundations of the National Medicines Policy.

There were calls for a review of the National Medicines Policy five years ago,[2] and more recently this has gathered pace.[3] There are some critical issues that need to be comprehensively addressed when updating the National Medicines Policy (see Box).

Consumers and healthcare professionals

Consumers seeking and receiving health care have evolved over the last two decades.[4] They have better access to information (and advertising) via the internet and online networking groups, and rightly expect to be more informed and involved in their own health. People expect to receive high-quality, safe and effective health care that is tailored to their needs while reducing their out-of-pocket costs.[5]

People are living longer. They have more chronic health conditions and so are taking multiple concurrent medicines. The use of complementary and alternative therapies continues to be high.[6] In addition to polypharmacy, other challenges that have escalated over the past 20 years include poor outcomes for people living with mental illness[7] (especially indigenous Australians),[8] antimicrobial resistance, and the continuing burden of medication-related harms. These place a considerable strain on healthcare systems, policies and budgets with effects rippling towards the community through social and welfare services.

Healthcare professionals now see a wider spectrum of people[4] and are more cognisant of the gap in the health and well-being of vulnerable members of the community. This includes indigenous Australians, frail older people, people living with mental illness as well as migrants and refugees.

Healthcare professionals are more aware of people's literacy and health literacy levels, their social determinants of health and their beliefs and opinions about treatments. There is also now a wider range of health professionals involved in prescribing, with an important need for consistent and rigorous training and credentialling to ensure the quality use of medicines. The healthcare provider has also changed with expanding scopes of practice, which in some cases may be seen as blurring of the traditional boundaries of practice.

The healthcare environment

The healthcare environment has changed since the National Medicines Policy was first put in place. Care is increasingly being delivered in people's homes, and in community health centres and outreach centres. Hospital stays have been reduced, and continuity of care from hospitals to primary care settings and to people's homes or residential care is becoming increasingly important. However, there remain noticeable gaps in care which can lead to preventable harm. With the ageing population, older people are often accompanied by family members and carers, who have an increasingly important role in their care and advocacy. Family members, including young children, remain the primary translators for migrants and refugees due to limited interpreter services within the health system.

Equitable access and medicine remuneration

Advances in technology and pharmaceutical products, personalised (precision) medicine, and tailored and targeted delivery of health care are a double-edged sword. On the one hand, these developments provide the promise of significantly improved health care, but on the other hand, there is increased complexity, cost and expectations for the delivery of effective and high-quality health care. This is matched with increasing demands on ever tighter health budgets. Together this poses a substantial challenge for maintaining a viable and responsible medicines industry.

Further complexity includes the need to restrict the use of some medicines to address challenges like antimicrobial resistance and misuse of prescription opioids. The increasing co-dependency of medicines, devices and diagnostics means we need to rethink how we remunerate and incentivise industry to develop new antimicrobials. Providing remuneration and incentives based on sales of medicines, as determined by their unit price multiplied by volume of sales, is no longer a rational approach when medicines need to be used judiciously.

Jurisdictional differences in affordable access to expensive and off-label medicines remain inequitable. National leadership and disruption of our current medicines funding mechanisms are needed to address this.

Health services

Increasing preventive care and self-care, as well as self-management are considerations in the management of chronic medical conditions. Non-pharmacological therapy for chronic medical conditions is delivered by medical and allied health professionals. Such health services and their appropriate remuneration should be considered alongside drug treatment options when providing tailored services to people.

Box Key considerations in upgrading to National Medicines Policy 2.0

Patient-centred focus

- Vulnerable people matter – older frail people, indigenous Australians, migrants and refugees and those living with mental illness, disability, or with chronic ill health.

Medication safety

- Medication safety and the systems to monitor medicines harms are priorities.
- Alignment with WHO Global Patient Safety Challenge: Medication without harm which focuses on high-risk situations and transitions of care, polypharmacy and high-risk medicines.

Medicines cost and access

- Affordable medicines for governments and consumers. Out-of-pocket consumer costs can be a barrier to medicines access and health care.
- Equitable access to expensive and off-label medicines between jurisdictions.
- Medicines supply – shortages pose a major challenge. Supply chains are vulnerable because of the global consolidation of the medicines industry.

Digital health

- Digital health initiatives e.g. My Health Record, electronic medication management and real-time prescription monitoring.
- Connected data repositories and management systems to improve collation, storage and analysis of health data, and inform health policy and health-related decisions.

Stakeholder partnerships and collaboration

- Closer partnerships between National Medicines Policy stakeholders to support policy implementation.

Legislation

- Up-to-date legislation and regulatory frameworks to support the increasing complexity of therapeutic interventions and devices are essential to protect the public.

Digital health

Digital health initiatives provide some of the most significant opportunities to improve the quality and coordination of health care. They could potentially have a major impact on quality use of medicines and implementation of the National Medicines Policy.

Strategies such as a national digital health record system, electronic medication management and real-time prescription monitoring provide a platform to reduce preventable harms and improve the quality use of medicines. However, they need to be fully implemented across the health sector to realise these benefits.

Connected information systems can assist in the development of data repositories and management systems to optimise collation, storage and analysis of real-world data and data collected through research. These can be used to inform health policy and other health-related decisions.

Future directions

The National Medicines Policy and the web of systems, policies, guidelines and legislation within it need a reboot. This shake-up needs to account for advances in digital technology, knowledge, and understanding of how people currently access and expect to access healthcare in the future, before it is constrained by such practicalities as cost and resource issues. An essential element of this reboot will be a clear plan and commitment to implementation strategies so that the impact and benefits of the Policy are realised.

Planning a reboot should not only consider the evolution of the National Medicines Policy to better reflect the current environment, but also how it can be reviewed at more timely intervals. This is important as new therapies emerge that create new challenges and opportunities to improve health care, or indeed cause harm.

A greater focus is needed in the next iteration of the National Medicines Policy on measuring health outcomes that are valued and relevant to patients. These outcome data are important to support health funding decisions. Improved access to real-world data in medicines use and patient-relevant outcomes (including safety) must be a priority.

Australians need to be empowered to seek health care in a dynamic and progressive world. In the quest for a healthy and long life, we need to aim for an agile and dynamic national health and medicines policy that continues to foster shared partnerships to deliver optimal health outcomes for the nation. <

Conflicts of interest: none declared

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BOOK REVIEW

Doctor's Bag Companion

Ellerton K, Craig S
Melbourne: Kirrily Ellerton and Simon Craig; 2019. 106 pages

This small volume is designed to be a rapid reference for GPs confronting a patient with an urgent medical issue or emergency. The book is a convenient A5 size and is ring bound, enabling it to be opened flat on a working surface. The pages are thick and fluid resistant, making it ideal for use in an acute clinical setting. Colour-coded text boxes allow the reader to access specific topics rapidly. The pages also have strips of colour on the margins, but these do not relate consistently to specific parts of the book and do not facilitate navigating the book's content. It may be a publication glitch.

The material is didactic and is drawn from recognised medical authorities in Australia and New Zealand. However, it is not a replacement for proper training and knowledge. Doctors experienced in managing emergencies may benefit from quick access to the information in this book, especially in a rapidly changing clinical situation.

The book is nominally divided into paediatric and adult sections, and addresses the most common and significant emergencies in the different age groups. For adults, topics include cardiac arrest, chest pain, anaphylaxis, asthma and chronic obstructive pulmonary disorder, dystonia, hypoglycaemia, seizures, migraine and alcohol withdrawal. Paediatric topics include cardiac arrest, seizures, anaphylaxis, asthma and acute pain. In all age groups there is also a summary of appropriate antibiotic use in important acute infections. Additional sections include the management of sexually transmitted diseases, palliative care and nursing home patients. There are picture guides for wound and burns management. There is a useful quick reference chart for vital signs on the back cover. Perhaps consideration could be given to including an aid for estimating a child's weight in kilograms (e.g. weight = (2 x age) + 8). It would also be useful to include a couple of blank pages for a doctor to add their own notes.

The paediatric section is organised so that each opened double page corresponds to a body weight in kilograms. The resuscitation data and drug doses are provided specific to these weights. However, there are major problems with this approach. Definitions of 'paediatric' vary, although it is usually defined as being from birth to puberty. Indeed, most clinicians would treat patients over 50 kg as adults. Yet in this book, weight ranges in the paediatric section continue up to 70 kg. This leads to anomalies, particularly in recommendations in cardiac arrest resuscitation that are at odds with those of the Australian and New Zealand Committee on Resuscitation (ANZCOR).[1] In cardiac resuscitation, ANZCOR states that adult algorithms should be followed for patients over the age of eight years (which corresponds to a weight of approximately 25 kg). ANZCOR guidelines also state that for single rescuers the initial ratio of compressions to breaths in CPR should be 30:2 in all age groups, and 15:2 in paediatrics (≤ 9 years) only if there are two or more rescuers. This book's recommendation of a compression:ventilation ratio of 15:2 up to a body weight of 70 kg is not in line with ANZCOR.

Weight-related doses and fluid volumes in the paediatric section are very useful but unfortunately they are taken to extremes with unnecessary precision. For example, the dose for buccal midazolam in a child weighing 17 kg is given as 1.02 mL of a 5 g/mL ampoule – this degree of precision is clearly unnecessary. Doses should be rounded off to be more appropriate to actual clinical practice.

This book is potentially an excellent resource that could be very useful for medical practitioners who may deal with emergencies on an occasional basis. It provides a ready reference to facilitate rapid and safe clinical assessment and management. However, there are some flaws that should be addressed before the book can be unreservedly recommended. If these could be addressed then this would be a very valuable addition to every doctor's bag.

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NEW DRUGS

New drugs

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First published 17 December 2019

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.

Patiromer sorbitex calcium

Approved indication: hyperkalaemia

Veltassa (Vifor)
sachets containing 8.4 g powder for oral suspension

High concentrations of potassium can induce fatal cardiac arrhythmias. Hyperkalaemia can be an adverse effect of drugs which inhibit the renin–angiotensin–aldosterone system, such as the ACE inhibitors and the angiotensin receptor antagonists. This can be a particular problem in patients with chronic kidney disease. One approach to the problem is to use potassium-binding substances. While binders, such as sodium resonium, have been available for many years, they are poorly tolerated so better alternatives are needed.

Patiromer is an ion exchange polymer made up of beads of patiromer sorbitex calcium. It is mixed in water, apple or cranberry juice to form a suspension. This should be taken with food. In the gut, patiromer exchanges potassium for calcium. By binding potassium, the free concentration of potassium for absorption is reduced and faecal excretion of potassium increases. This lowers serum potassium. No patiromer is absorbed, but it could affect the absorption of other drugs including metformin, thyroxine and ciprofloxacin. The daily dose of patiromer should therefore be separated from other oral drugs by at least three hours.

The OPAL-HK trial enrolled 243 patients who had chronic kidney disease (estimated glomerular filtration rate 15–60 mL/min/1.73m^2) and serum potassium concentrations of 5.1–6.5 mmol/L. They were all taking inhibitors of the renin–angiotensin–aldosterone system, mainly ACE inhibitors. According to the severity of their hyperkalaemia, the patients started on either 4.2 g or 8.4 g of patiromer twice daily. The dose could be adjusted in response to the concentration of serum potassium. After four weeks the mean change in potassium was a decline of 1 mmol/L. The concentration fell into the target range in 76% of the patients.[1]

In the second phase of the trial, patients who had a potassium concentration within the target range were randomised to continue patiromer or switch to a placebo. After four weeks there was no change in the 55 patients who continued treatment, but the potassium concentration climbed by a median of 0.72 mmol/L in the 52 patients who switched to placebo. A potassium concentration of 5.5 mmol/L or above was reported in 60% of the placebo group compared with 15% in the patiromer group.[1]

A phase II trial investigated the doses needed to treat hyperkalaemia in patients with chronic kidney disease and type 2 diabetes.[2] All patients were treated with inhibitors of the renin–angiotensin–aldosterone system. Depending on the potassium concentration, the 306 participants were randomised to receive different doses of patiromer. After an eight-week treatment period there was a maintenance phase of 44 weeks during which the dose of patiromer was adjusted to control the concentration of potassium. All doses of patiromer reduced the mean potassium concentration within the first four weeks of the trial. For example, a dose of 12.6 g twice daily resulted in a mean reduction of 0.55 mEq/L (0.55 mmol/L) in patients with mild hyperkalaemia and 0.97 mEq/L (0.97 mmol/L) in those with moderate hyperkalaemia. During the maintenance phase approximately 77–95% of all patients had potassium concentrations in the target range at each monthly visit. Concentrations rose after treatment ceased.[2]

Patiromer has also been studied in patients with heart failure. The 120 patients in the trial either had chronic kidney disease or a history of hyperkalaemia that had required discontinuation of treatment with, for example, an ACE inhibitor. Patients took 15 g patiromer or a placebo twice a day, plus spironolactone. After four weeks of treatment potassium concentrations had increased in the placebo group and decreased with patiromer. The difference between the groups was 0.45 mEq/L (0.45 mmol/L). Hyperkalaemia occurred in 7% of the patients taking patiromer and 25% of the placebo group.[3]

During the clinical trials, most adverse effects were related to the gut. In the OPAL-HK trial 11% of patients experienced constipation, but diarrhoea also occurred in some patients (3%).[1] The action of patiromer will cause hypokalaemia in some patients. As well as reducing potassium concentrations, patiromer can cause a fall in magnesium. Serum concentrations of magnesium therefore need to be monitored for at least the first month of treatment. As patiromer releases calcium in exchange for potassium, some patients may be at risk of hypercalcaemia.

Patiromer could enable patients who have had to cease taking drugs that inhibit the renin–angiotensin–aldosterone system because of hyperkalaemia to continue treatment. While patiromer reduces serum

potassium, it is unknown if this will eventually improve clinical outcomes. Most of the trials were short term, but treatment may need to be long term as the potassium rises once patiromer is stopped. The main trials used twice-daily doses, but the product information recommends a once-daily dose. Longer term safety also needs to be confirmed. Other ion exchange substances have been associated with intestinal necrosis and patients with a history of bowel surgery or obstruction were excluded from the trials of patiromer. As there is a delayed onset of effect, patiromer should not be used alone in the emergency management of hyperkalaemia.

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, the European Medicines Agency and the Therapeutic Goods Administration.

NEW DRUGS

Aust Prescr 2020;43:30–31
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Tisagenlecleucel

Approved indication: B-cell cancers

Kymriah (Novartis)
infusion bag containing modified autologous T cells

Tisagenlecleucel is a genetically modified cell therapy developed for relapsed and refractory B-cell cancers. It is specifically approved for children and young adults (≤25 years old) with B-cell precursor acute lymphoblastic leukaemia, and for adults with diffuse large B-cell lymphoma (the most common form of non-Hodgkin lymphoma).

This product is prepared using the patient's own T cells. These are harvested from blood, then, in the laboratory, a transgene is introduced which encodes a protein called chimeric antigen receptor (CAR). This receptor is expressed on the surface of the T cells and allows them to bind to the CD19 antigen on B cells and precursor B cells. This binding activates inflammatory cytokines and destroys the CD19-positive cells.

Before the modified T cells are administered, the patient is given a short course of chemotherapy (2–4 days) to deplete their lymphocytes. To reduce the risk of an infusion reaction to tisagenlecleucel, patients are given paracetamol and an antihistamine 30–60 minutes beforehand.

The approval of tisagenlecleucel is based on two open-label, phase II trials – one in B-cell precursor acute lymphoblastic leukaemia[1] and the other in diffuse large B-cell lymphoma.[2] Both trials were single-arm studies.

One of the trials enrolled 75 patients with B-cell lymphoblastic leukaemia.[1] They were aged 3–23 years at baseline and had at least 5% lymphoblasts in their bone marrow at screening. Participants had received a median of three previous therapies and 46 of them had had an allogeneic stem cell transplant (using cells from another person).

Following lymphodepleting chemotherapy, participants were given a single infusion of tisagenlecleucel (median dose of 3.1×10^6 T cells/kg). The primary end point of the trial was an overall remission rate of more than 20%. This was defined as complete remission or complete remission with incomplete blood count recovery that lasted for at least 28 days.

In patients with at least three months follow-up, the remission rate was 81%. The event-free survival rate was 73% at six months and 50% at 12 months. The overall survival rate was 90% at six months and 76% at 12 months.[1]

In the other trial, tisagenlecleucel was assessed in 93 adults with relapsed or refractory diffuse large B-cell lymphoma.[2] The participants had previously received at least two lines of therapy.

After lymphodepleting therapy, patients were given a median of 3.0×10^8 cells by infusion. The best overall response was 52% (40% had a complete response and 12% had a partial response). The estimated probability of overall survival at 12 months was 49%. In those who had a complete response, this was 90%.[2]

Tisagenlecleucel has several serious and sometimes fatal adverse effects. Patients need to be closely monitored in the first week after infusion and need to stay within two hours of the facility where they received the infusion for the first month.

Cytokine release syndrome is very common with tisagenlecleucel. This is an inflammatory reaction that can cause hypotension, pulmonary oedema and coagulopathy and result in multiorgan failure. In the leukaemia trial, 81% of patients in the safety cohort developed cytokine release syndrome – 44% of these cases were severe. In the lymphoma trial, 58% of patients were affected including 22% who were severely affected. The median onset of these reactions was three days and their duration was 7–8 days. The anti-interleukin-6 antibody, tocilizumab, can be used to treat moderate to severe cases. A minimum of four doses of the drug should be kept on hand before the infusion is started. Corticosteroids may be used in life-threatening cases. Emergency equipment should also be available. Risk factors for severe cytokine release syndrome in leukaemia patients include high tumour burden, progressive disease following lymphodepleting therapy, infection and fever.

Febrile neutropenia was very common, as were infections (67% of the leukaemia cohort and 54% of the lymphoma cohort). These were fatal in some cases.

Encephalopathy and confusion or delirium were frequently reported – 38% in the leukaemia trial and 21% in the lymphoma trial. Headache was also very common in both trials (35% and 23%), as were nausea, diarrhoea, hypotension, tachycardia, acute kidney injury and hypokalaemia. A third of children and young adults with leukaemia had elevated liver enzymes.

In the leukaemia study, there were seven deaths that were not related to disease progression. Two of them occurred within 30 days of the infusion. Causes included embolic stroke related to mycosis, cerebral haemorrhage (in the context of coagulopathy and resolving cytokine release syndrome), encephalitis after prolonged neutropenia and lymphopenia, and mycosis.

There were eight deaths in the lymphoma trial that were not related to disease progression. They all occurred at least 30 days after the infusion. Causes included multiple organ failure, cerebral haemorrhage,

haemorrhage of a duodenal ulcer, pulmonary haemorrhage, chronic kidney disease, neuroendocrine carcinoma and sepsis.

Treatment with tisagenlecleucel should be delayed if someone has unresolved adverse effects from chemotherapy, uncontrolled infection, graft versus host disease, or rapidly progressing leukaemia or lymphoma. There is limited experience with this drug in patients who have active leukaemia or lymphoma in the CNS.

Treatment is not recommended in people with HIV or hepatitis B or C. Live vaccines should not be given for at least six weeks before tisagenlecleucel therapy and until the patient's immune system has recovered following treatment.

After administration of tisagenlecleucel, the modified T cells undergo clonal expansion followed by a slow decline. The tisagenlecleucel transgene has been shown to persist in blood and bone marrow for up to two years after the infusion in some patients.

Tisagenlecleucel is the first chimeric antigen receptor therapy to be approved in Australia. Although response rates seemed high (81% in acute lymphoblastic leukaemia and 52% in lymphoma), it is hard to quantify efficacy as there were no comparators in the trials. Doctors and their patients also need to consider the serious and life-threatening toxicities that can occur with this therapy.

T T manufacturer provided additional useful information

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1. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 2018;378:439-48. https://doi.org/10.1056/NEJMoa1709866
2. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med 2019;380:45-56. https://doi.org/10.1056/NEJMoa1804980

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 website of the European Medicines Agency.

LETTERS

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.

Letter to the Editor

Bruce Shepherd Medal for independent medicine

Aust Prescr 2020;43:32
https://doi.org/10.18773/austprescr.2020.009

I would like to congratulate the Editor, Dr John S Dowden, on the award of the Bruce Shepherd Medal by the Australian Doctors Federation. He is one of 19 recipients who received the 2019 medal, which is awarded to those who have made an outstanding contribution to independent medicine. The Australian Doctors Federation is dedicated to protecting independent professional practice and recognises that independence is also crucial when providing information about medicines. For many years Dr Dowden has maintained the independence of *Australian Prescriber* from external influences and this has enabled the journal to evolve into a trusted source of information for Australian health professionals.

Dr Aniello Iannuzzi
Chairman, Australian Doctors Federation, Sydney

Correction

Blood pressure: at what level is treatment worthwhile? [Correction]

Aust Prescr 2020;43:33
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First published 19 December 2019

The article on blood pressure treatment (Aust Prescr 2019;42:127-30) has been corrected. View corrected article.

The Table comparing international guidelines for the treatment of hypertension (p.128) misquoted the US starting point for the general population as ≥140/80 mmHg. It should have read ≥140/90.

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