Australian Prescriber

AN INDEPENDENT REVIEW

nps.org.au/australian-prescriber

August 2020
Volume 43 Number 4

NPS MEDICINEWISE

CONTENTS

EDITORIAL

Immunosuppression for COVID-19: repurposing medicines in a pandemic

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Keywords
COVID-19, immunosuppression, interleukin-1, interleukin-6, pandemic, tocilizumab

First published 17 June 2020
Aust Prescr 2020;43:106–7
https://doi.org/10.18773/austprescr.2020.037

It might seem paradoxical to suggest immunosuppression could play a role in managing COVID-19. The seemingly logical therapeutic option for this disease would be an antiviral. Unfortunately, repurposing antiviral therapies has proven disappointing so far, and evidence to support their routine use in COVID-19 is currently lacking.[1-4]

While the current standard of care for most people with COVID-19 is supportive, a subset of patients become severely unwell with a potentially life-threatening hyperinflammatory state called cytokine release syndrome.[5] This clinical state is difficult to predict in advance. When it occurs it is characterised by rapidly worsening multiorgan dysfunction including respiratory failure and a clinically distinctive coagulopathy involving immunothrombosis of the pulmonary vasculature.[6] Antigens presented by infected cells activate both the innate and adaptive immune systems. The uncontrolled upregulation of immune cells leads to a surge of proinflammatory cytokines including interleukin-6 and interleukin-1. This in turn increases vascular permeability and inflammatory cell recruitment into lung parenchyma causing acute lung injury and subsequent respiratory failure. As a myriad of proinflammatory molecules and inflammatory markers are involved in both the typical immune response to infection and this hyperinflammatory and hypercoagulable state, the key drivers of inflammation and mortality in severe COVID-19 are contentious. As such, the benefit of treating this hyperinflammatory state has not yet been completely established in COVID-19.

In patients with severe COVID-19, there is significant mortality in the second week of disease,[7,8] despite many studies describing a progressive fall in viral count.[9,10] This may partially explain the lack of success with antivirals. In this situation, immune-driven damage, such as cytokine release syndrome, may be what is driving mortality. Therefore early recognition and prompt initiation of immunosuppression may benefit these patients.

Cytokine release syndrome is a known phenomenon, and pathophysiologically similar syndromes exist in autoimmune diseases such as systemic juvenile idiopathic arthritis and adult onset Still's disease. It is also encountered as a complication of chimeric antigen receptor T-cell (CAR T-cell) therapy used for haematological malignancies.

Interleukin-6 and interleukin-1 driven pathways have a central role in cytokine release syndrome associated with COVID-19 and in other previously recognised cytokine release syndromes. Therapies targeting these pathways include tocilizumab (an interleukin-6 receptor antagonist) and anakinra (an interleukin-1 receptor antagonist). These are both registered by the Therapeutic Goods Administration (TGA) for cytokine release syndrome-like autoimmune conditions such as systemic juvenile idiopathic arthritis. Anakinra has previously been used in the treatment of macrophage activation syndrome, a cytokine release syndrome associated with autoimmune conditions.[11] Tocilizumab is registered for the management of cytokine release syndrome secondary to CAR T-cell therapy. The possibility of adopting these immunosuppressive therapies in COVID-19 is supported by early evidence from observational studies.[12] However, these drugs need the same caution as any off-label and experimental prescribing in COVID-19 until they are validated in clinical trials.[13-15]

Not all immunosuppressive drugs hold the same promise. While systemic corticosteroids are effective immunosuppressants, previous and current outbreaks suggest that their broader physiological effects lead to uncertain benefit and potential harm.[16-18] Accordingly, they are avoided in routine care unless for a recognised indication. Colchicine has also generated interest due to its effect on the inflammasome-mediated interleukin-1 beta pathway which is part of the innate immune response. However, its use in COVID-19 remains unproven.[19] Baricitinib, a Janus kinase inhibitor used for rheumatoid arthritis, was identified through a machine-learning exercise as potentially reducing viral entry into cells in COVID-19, but currently has no established use in cytokine release syndrome.[20]

Some important distinctions exist between the rational repurposing of immunosuppression in COVID-19 and other widely discussed experimental therapies.[21] Tocilizumab is already part of the evidence-based management of CAR T-cell-induced cytokine release syndrome,[6,22] a condition that shares pathological similarities. In contrast, proposed antiviral strategies that include chloroquine, hydroxychloroquine, and ivermectin are reliant on novel mechanisms of action and low-quality evidence, while raising significant safety concerns.[23,24]

COVID-19 poses a multifaceted threat requiring a multimodal and stratified treatment approach, possibly transitioning from virus-targeted approaches in the early state of disease to immunomodulation in late-onset immune-mediated disease. The example of interleukin-6 and interleukin-1 inhibition demonstrates that a cohesive and considered approach towards off-label prescribing in COVID-19 is needed. This should be used in consultation with relevant subspecialties and drug and therapeutic committees.[21] Decision making should also include patients and their families.[25] As it is not yet standard of care, reporting safety and efficacy outcomes as part of clinical trials is highly desirable. With such measures, repurposed medicines can be appropriately recruited into the pandemic fight without defying sensible prescribing.[21,25] <

Conflict of interest: none declared

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EDITORIAL

What is hypertension?

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antihypertensive drugs, blood pressure, cardiovascular risk, hypertension

Aust Prescr 2020;43:108–9
https://doi.org/10.18773/austprescr.2020.025

Hypertension is both a disease and a major risk factor for other diseases. Population studies show an increasing rate of cardiovascular events such as stroke, myocardial infarction, heart failure, atrial fibrillation and premature mortality, with increasing blood pressure (from systolic blood pressures ≥115 mmHg). This relationship is exponential, and stronger for systolic pressure than for diastolic pressure.

Untreated very high (>180/110 mmHg) or rapidly rising blood pressure (such as in eclampsia) can overcome normal microvascular autoregulation. This leads to acute damage in the microcirculation and results in a multisystem clinical syndrome of accelerated or malignant hypertension, or cerebral haemorrhage, which are immediate threats to life.[1] Accelerated or malignant hypertension is now fortunately uncommon. The main consideration in the majority of individuals is the relationship between their blood pressure and subsequent risk of cardiovascular disease. Given the continuous relationship of blood pressure to risk, any level of blood pressure used to define 'hypertension' will always be arbitrary. The critical issue is, how do we define hypertension, and does it matter?

International guidelines for the management of hypertension have been published for more than 40 years. The most recent updates are from Australia (2016),[2] the USA (2017),[3] Canada (2018),[4] Europe (2018)[5] and the UK (2019).[6] In defining hypertension, these guidelines have taken two approaches, either basing their definition on a threshold for treatment, or alternatively on the blood pressure above which the risk of events is increased.

The Australian, Canadian, European and UK guidelines have chosen a cut-off level of blood pressure above which the benefits of treatment, demonstrated by interventional clinical trials of blood pressure lowering therapy, are considered to outweigh the harms of treatment. Using this approach, the cut-off point which defines hypertension is 140/90 mmHg using standard clinic methods of measurement. These guidelines also emphasise the range of severity of hypertension by stratifying blood pressure above the cut-off point. Hypertension, using this grading scheme, is defined as:

- grade 1 – 140–159 mmHg systolic or 90–99 mmHg diastolic
- grade 2 – 160–179 mmHg systolic or 100–109 mmHg diastolic
- grade 3 – 180 mmHg systolic or 110 mmHg diastolic and above.[2]

The benefit of lowering blood pressure to prevent hypertension-related disease and reduce cardiovascular events and mortality is unequivocal in patients with very substantial elevations in blood pressure. This was reported in 1967 with publication of the first randomised controlled interventional study of antihypertensive therapy in patients with diastolic blood pressures averaging 115–129 mmHg.[7] Subsequent studies, which have mostly used measures of clinic blood pressure, have shown the benefit of blood pressure lowering when the systolic pressure is above 140 mmHg in all patients up to age 80 years[8,9] and above 160 mmHg in those over 80 years.[10] The relative risk reduction is similar across the range of baseline cardiovascular risk. Patients with the highest baseline risk have the greatest absolute benefit (lowest numbers needed to treat to prevent an event).[11]

In contrast, the US guideline has redefined hypertension, for both clinical and public health decision making, on the degree of blood pressure elevation associated with increased cardiovascular risk (hazard ratio 1.5–2.0). The US categories for stage 1 hypertension are systolic blood pressures of 130–139 mmHg or diastolic blood pressures of 80–89 mmHg and stage 2 is systolic blood pressures of 140 mmHg and above. These categories are substantially lower than in the threshold-based guidelines, and do not distinguish risks at levels above 140 mmHg, despite the known exponential increased risk with increasing blood pressure.

A consideration with the US definition is that current evidence from interventional studies does not show a benefit from starting blood pressure lowering therapy if the untreated systolic blood pressure is below 140 mmHg in individuals without cardiovascular disease.[5] There may possibly be benefit from blood pressure lowering at a lower baseline blood pressure only in those with the highest cardiovascular risk and established cardiovascular disease.[5] The majority view at present is therefore that the definition of hypertension is best based operationally on an evidence-based treatment threshold.[2,4,5,6]

Blood pressure is highly variable within an individual, and is not well characterised from a single or very few measurements. Historically, a diagnosis of hypertension in the majority of interventional trials has been based on repeated clinic measures taken on multiple occasions. There are now additional approaches for measuring the blood pressure

profile over 24 hours (non-invasive ambulatory blood pressure) or over a longer time (home blood pressure monitoring) that are more closely linked to cardiovascular outcomes.[1,2] These methods result in readings that are lower than clinic measurements which must be considered when making a diagnosis of hypertension. A daytime ambulatory or home blood pressure of 135/85 mmHg is approximately equivalent to a clinic blood pressure of 140/90 mmHg.[1,2] An alternative approach initially promoted in Canada is that of using automated measurements of blood pressure in the clinic. This approach results in readings that are lower than usual clinic blood pressures, but very similar to the average daytime reading from a 24-hour ambulatory monitor. However, this approach has not yet been widely adopted internationally and importantly is not the method of blood pressure measurement recommended for use in current cardiovascular risk calculators.[2]

Why bother with a definition of hypertension, given the continuous nature of the relationship between blood pressure and risk, and the difficulties with measurement? Arbitrarily defining hypertension as being an average sustained clinic blood pressure of 140/90 mmHg or above is clinically useful as it clearly identifies a level of blood pressure where individuals, if untreated and without established vascular disease, could benefit from blood pressure lowering therapy and should be offered it. Clinicians can be confident this definition is supported with clinical trial evidence. Grade 2 hypertension above this clearly identifies increasing risk with increasing blood pressure, reflecting the known exponential relationship between blood pressure and vascular outcomes and an even stronger imperative for treatment. Individual treatment decisions are, however, more complex than a definition. Fortunately, there is a range of excellent guidelines on hypertension to support these.[2-6] <

Genevieve Gabb is a member of the Executive Committee, High Blood Pressure Research Council of Australia, and a member of the Clinical Committee, Heart Foundation of Australia.

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LETTERS

Letters to the Editor

QUM and COVID-19 in young adults

Aust Prescr 2020;43:110
https://doi.org/10.18773/austprescr.2020.038

I read the editorial on COVID-19 and the quality use of medicines[1] with great interest and found it very balanced and rational. I liked the approach of the editorial.

I have a question – can COVID-19 treatment be left to antipyretic and other symptomatic treatment for young adults with no comorbidities and taking other precautions such as isolation? Are there any studies reported? Is experimental prescribing with hydroxychloroquine, antivirals and antibiotics absolutely necessary? In the early phase of the pandemic, many patients with mild disease might have self-treated or were medically treated as if they had flu and came out of it in 4–5 days without knowing that it was COVID. Their immune system must have worked well.

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REFERENCE

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Darren Roberts and Alexandra Bennett, the authors of the editorial, comment:

These questions are important, but the harms and benefits of these treatments for COVID-19 in this age group are poorly defined.

It is increasingly clear that the natural history of COVID-19 reflects risk factors whereby younger age and fewer comorbidities are favourable.[1-3] For example, despite a high number of cases of adults under 50 years of age in Australia, only 7% were hospitalised and 0.03% died.[4] In India, mortality has been reported as 0.4% in those under 40 years of age.[5]

Randomised controlled trials are needed to quantify the efficacy of antiviral treatments for reducing COVID-19 disease progression.[6] To our knowledge there are no trials in young adults with mild disease. However, death and other adverse effects to antivirals in COVID-19 have been reported, but mostly in patients with severe disease so the observation may be confounded by indication.[7] Therefore, more data are required to confirm the safety and efficacy of antivirals in lower severity COVID-19. In Australia, the use of antiviral treatments outside a clinical trial is not recommended[8] and we support this.

It seems reasonable to assume that general health advice for other mild infections, as described by Manjiri Gharat, also apply in COVID-19. We are not aware of data supporting a benefit of antipyretics in COVID-19. However, some authors have questioned their safety in COVID-19 including paracetamol-associated acute hepatitis[9] and non-steroidal anti-inflammatory drug-associated systemic infection.[10] These risks appear theoretical so are insufficient to advise against the use of antipyretics, but more data are required.

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

Managing dental pain in general practice

Aust Prescr 2020;43:111
https://doi.org/10.18773/austprescr.2020.039

Regarding the article about managing dental pain in primary care,[1] I am disappointed that COX-2 inhibitors were not discussed, as they may be substituted when ibuprofen is not possible. I was also disappointed to see oxycodone so liberally advocated for pain. It is little surprise patients seeking potent opioids attend GP surgeries in out-of-hours settings for oxycodone scripts citing dental pain. Furthermore, atypical opioids (i.e. buprenorphine, tramadol, tapentadol) may be a better option. A recent article discusses their use in chronic pain to limit long-term abuse.[2]

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Aovana Timmerman and Peter Parashos, the authors of the article, comment:

COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs) such as celecoxib can be considered as an alternative analgesic for patients with gastrointestinal, renal or cardiovascular problems, or for patients who cannot tolerate traditional NSAIDs.[1] However, ibuprofen is preferred over celecoxib as it has been shown to be more effective for dental pain. Also, COX-2 inhibitors have been associated with an increase in cardiotoxicity.

In regard to 'oxycodone so liberally advocated for pain', we presume this refers to the questionnaire survey findings cited by Dr Teoh[2] that '16–27% of dentists would preferentially use an opioid or paracetamol instead of NSAIDs for pain relief'. To clarify, this comment did not specifically identify oxycodone. The original paper[3] indicated that 'Only 4–9% of dentists would routinely prescribe inappropriate analgesics, including diclofenac, tramadol, mefenamic acid, ketoprofen, codeine, oxycodone, dexamethasone and diazepam' from a sample of only 382 responses. Hence, oxycodone was only one of eight inappropriate drugs prescribed by a relatively small sample of dentists surveyed.

Because the effectiveness of opioids for patients with dental pain is modest, they are only used in combination with NSAIDs or paracetamol, and only for severe pain.[1]

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LETTERS

Dental pain and antibiotics

Aust Prescr 2020;43:112
https://doi.org/10.18773/austprescr.2020.040

Editor – As a dental surgeon, I was so pleased to read this informative article[1] aimed at GPs. I have had too many patients over the years who have been prescribed antibiotics by their GP when this was contraindicated. Patients presenting to a general practice with dental pain should be immediately referred to a dental surgeon. GPs should be reminded that oral and maxillofacial surgeons are available to treat severe cases.

Patients might refrain from seeking appropriate dental treatment once they have been prescribed antibiotics by their GP. This delay in seeing a dentist often leads to greater damage and loss of dentition. Ultimately this can have a big impact on the patient later in life because of reduced dental function and often reduced socialisation.

Gerard Little
Dental surgeon, Toowoomba, Qld

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Editor – I listened to the podcast reviewing the latest Therapeutic Guidelines: Oral and dental. I was particularly interested in the patient with dull toothache with no trigger stimulus, provisionally diagnosed as a suspected infected root canal in the absence of both systemic features and facial swelling but unable to see a dentist within 24 hours. The guidelines advise that it is reasonable to prescribe antibiotics in these circumstances along with urgent referral to a dentist. I would comment that this is possibly not within the dental guidelines of antimicrobial stewardship. Your article on the management of dental pain in primary care[1] clearly states the contrary and recommends analgesics would be more appropriate. It states that 'antibiotics are only indicated as an adjunct to dental treatment when there are signs of systemic involvement, progressive and rapid spread of infection, or when the patient is immunocompromised'.

Beng Lee
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Aovana Timmerman and Peter Parashos, the authors of the article, comment:

We completely agree with Dr Little's comments. In a medical setting, if the antibiotic prescription is perceived as necessary to help resolve the dental problem (usually due to a spreading infection), then patients should be clearly advised that they need to urgently attend their dentist for definitive treatment. In these circumstances, patients should not wait until they have completed the course of antibiotics before going to their dentist.

In regards to Dr Lee's comments, if a patient presents with dental pain and the cause is suspected to be root canal infection in the absence of systemic involvement and facial swelling, we would recommend the GP only prescribe analgesics appropriate to the level of pain being experienced,[1] and refer the patient promptly to a dentist for diagnosis and management.

As mentioned in our article, antibiotics may be recommended as an adjunct to dental treatment, but only in specific situations. Although the Therapeutic Guidelines specify that antibiotics may be considered in some circumstances if the patient cannot see a dentist within 24 hours, there is no evidence to support this timeframe. Also, there is a risk that the patient will rely on the antibiotic prescription rather than seeking urgent dental care.

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Fosfomycin and breastfeeding

Aust Prescr 2020;43:113
https://doi.org/10.18773/austprescr.2020.042

A recent article on the treatment of resistant urinary tract infections stated that small amounts of fosfomycin are excreted in breast milk so it is not recommended in breastfeeding.[1] Fosfomycin absorption is largely dependent on the salt form – trometamol salts are modestly absorbed (34–58%) and calcium salts are poorly absorbed (<12%). Fosfomycin secreted into human milk would likely be in the calcium form and is unlikely to be absorbed.

Foods and the acidic milieu of the stomach both significantly reduce oral absorption. Concentrations secreted into human milk have been reported to be about 10% of what is present in maternal plasma.[2-6] It is not likely that the amount present in breast milk would produce untoward effects in a breastfeeding infant. On balance fosfomycin may be used with caution.

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ARTICLE

Deprescribing in older people

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Keywords
aged, deprescribing, drug withdrawal symptoms, falls, polypharmacy

Aust Prescr 2020;43:114–20
https://doi.org/10.18773/austprescr.2020.033

SUMMARY

Deprescribing is the process of discontinuing drugs that are either potentially harmful or no longer required.

It can be achieved in older people and may be associated with improved health outcomes without long-term adverse effects.

The risk of drug withdrawal effects can often be mitigated by carefully monitoring and gradually tapering the dose.

Deprescribing should ideally be a shared decision-making process between the patient and the prescriber.

Introduction

Why deprescribe? Older people living with multiple chronic diseases often have a high risk of adverse health events which can be modified by medicines. For these people, the quality use of medicines includes starting new drugs, adjusting doses and discontinuing those that are no longer beneficial. Despite the great potential benefit they can derive from medicines, these patients are at high risk of experiencing medicine-related harm. Using more drugs than is clinically indicated can increase this risk.

Polypharmacy, defined as the concomitant use of five or more medicines,[1] is associated with an increased risk of adverse outcomes such as hospital admissions, falls and premature mortality.[1,2] It is also expensive for patients. The number of older Australians affected has increased by over 50% since 2006 to nearly one million.[3] This rising prevalence and the associated concerns about poorer health outcomes have led to increasing attention on inappropriate polypharmacy.

Deprescribing addresses the harms associated with inappropriate polypharmacy. It is a patient-centred process involving the discontinuation of one or more drugs that are potentially harmful or no longer required.[4]

Is deprescribing safe?

Many drugs are indicated to delay mortality so prescribers may be reluctant to discontinue them. Despite this concern, a systematic review of deprescribing found no change in mortality overall in randomised studies (odds ratio (OR) 0.82, 95% confidence interval (CI) 0.61–1.11).[5] However, mortality was significantly decreased in non-randomised studies (OR 0.32, 95% CI 0.17–0.60).[5] The review also found that patient-specific interventions significantly reduced mortality in randomised studies, but generalised educational interventions aimed at upskilling practitioners to alter prescribing behaviour did not change mortality. This evidence indicates that reducing polypharmacy may be achieved without perceivable adverse impacts on mortality and with clinically important benefits for some patients. Other reviews have investigated the impact of deprescribing in specific drug classes and specific settings (such as aged-care facilities and hospitals). This research generally suggested that deprescribing is safe (Table 1).[5-11]

What are some prompts to consider deprescribing?

Medicines should be reviewed regularly to ensure that each drug is effective for that individual and therapy remains consistent with their care goals. Treatment should also be underpinned by a current and valid diagnosis.[12] A significant event like a fall, or an admission to hospital or a residential care facility, should prompt a thorough medicine review.[12] A review should also be triggered by increasing frailty or a decline in either their cognitive function or ability to manage activities of daily living.[12]

Falls

Older people are at a significantly increased risk of falls. This is exacerbated by both polypharmacy and certain drugs such as psychotropics, cardiovascular drugs and anticholinergics.[1,13] A New Zealand study found that deprescribing sedative and anticholinergic drugs significantly reduced the number of falls each person experienced.[14] Providing older people with written information supporting discontinuation has been shown to be an effective strategy to improve sedative discontinuation.[15] Although our systematic review suggested that deprescribing does not alter the risk of having a first fall, it reduces the number of

subsequent falls for an older person who has already fallen.[5] Another review found that deprescribing interventions based on a medicine review resulted in a relative risk reduction of 24% (OR 0.76, 95% CI 0.62–0.93)[7] in the number of people who fell.

Adverse effects

Older people are more susceptible to adverse effects due to increased frailty, poor homeostatic reserve and age-related changes in pharmacokinetics and pharmacodynamics.[16] It can be a challenge to detect adverse effects in older people, particularly in those with cognitive impairment who may not be able to articulate their concerns. It is not uncommon for an adverse effect to be identified as a new symptom or condition, which can lead to a prescribing cascade (see an example in the Box). In this example, the prescribers did not consider the possibility of an adverse effect when evaluating the new symptoms. The cascade has been described in a study that found that older people who are prescribed cholinesterase inhibitors are at increased risk of subsequently being prescribed an anticholinergic drug (adjusted hazard ratio 1.55, 95% CI 1.39-1.72).[17] The cascade could also occur in the alternate order – a new anticholinergic drug could contribute to confusion or delirium. If this is misdiagnosed as dementia, it could result in the prescription of a cholinesterase inhibitor.

The prevalence of polypharmacy in older people increases the likelihood that more than one drug contributes to the same adverse effect (e.g. oxycodone and oxybutynin both resulting in constipation and dry mouth).

End-stage diseases

In older people with a severe life-limiting condition, such as advanced dementia or end-stage organ failure, the potential benefit of preventive medicines may not be realised due to the person's short life expectancy and may not be the goal of their treatment. For example, 2–5 years of statin use is generally required to reduce the risk of stroke or myocardial infarction.[18]

Box **Example of a prescribing cascade**

An 85-year-old female was admitted to hospital with a hip fracture. She had fallen at home while changing her bedsheets after an episode of urinary incontinence, which she reported had worsened over the last few weeks. She had recently commenced donepezil for the management of Alzheimer's disease. In hospital, she was prescribed oxybutynin to treat the incontinence.

Prescribing oxybutynin to manage the adverse effects of the donepezil is an example of a prescribing cascade.

Managing preventive medicines can be challenging in the context of life-limiting illness or frailty. For example, although at least 15% of older Australians live with diabetes,[19] little evidence is available on the effects of discontinuing drugs for diabetes. A recent review identified only two low-quality controlled studies of deprescribing these drugs.[11] Tight glycaemic control (glycated haemoglobin (HbA1c) <7%) may be appropriate in those who have sufficient life expectancy to benefit from the reduced risk of microvascular complications. However, for frail older people, intensive therapy increases the risk of hypoglycaemia without a mortality benefit. De-intensification of therapy is therefore often appropriate.[20] In both studies, there was no significant difference in HbA1c between the group that discontinued diabetes drugs and those that continued.[11]

Approaches to safe deprescribing

Drugs may sometimes be discontinued in older people with limited or no adverse effects.[5] In other cases, the symptoms of the underlying condition may reappear or withdrawal effects may occur. A review did not find significant harms when antihypertensives, benzodiazepines and psychotropics were discontinued in older people.[21]

The risk of harm can be mitigated by gradually tapering medicines and carefully monitoring for withdrawal effects. It is often not possible to tell if a condition is a current problem while symptom-relieving drugs are used (e.g. proton pump inhibitors to manage reflux, or analgesics to manage pain). For these drugs, discontinuation should be trialled rather than considered definitive. If symptoms recur, restarting the medicine at a lower dose may be sufficient to manage this.[21]

Reappearance of the original disease or symptoms

Many older people are prescribed antihypertensives to reduce their risk of cardiovascular events. This needs to be carefully balanced with the potential for harms (e.g. dizziness, falls).[22] A study of frail older people found that deprescribing antihypertensives resulted in an immediate increase in blood pressure, although this reverted to baseline within nine months.[23] Another study found that systolic blood pressure increased by 7 mmHg (95% CI 3–12) after discontinuing antihypertensives.[24] Blood pressure should be routinely monitored during the first year after deprescribing to identify increases that may occur.[22]

For symptom management, proton pump inhibitors are recommended for 2–8 weeks, yet they are

Table 1 **Summary of systematic reviews of deprescribing** *Continued over page*

Study	Participants				Setting	Deprescribing intervention
	Number	Age (years)*	Female (%)	Inclusion criteria		
Shrestha et al 2019[6]	1375	Mean age 74.1–86.1	57.6	Life-limiting illness and limited life expectancy	Hospital or RACF	Deprescribing medicine(s) or deprescribing as part of medicine optimisation
Kua et al 2019[7]	18,408	83% of studies had mean age 80–89	69.4	Terminally ill or palliative care residents not included	RACF	Deprescribing polypharmacy and deprescribing individual targets
Thillainadesan et al 2018[8]	2522	Mean or median age 74.5–86.7	Not reported	Hospitalised older people	Hospital	Deprescribing to reduce potentially inappropriate medicines
Page et al 2016[5]	34,143	73.8 ± 5.4	48.2	One or more medicines	Hospital, RACF, community	Deprescribing polypharmacy and deprescribing individual targets
Johansson et al 2016[9]	10,980	Mean age 69.7–87.7	0 to 80%	Polypharmacy (≥4 medicines)	Hospital, RACF, community	Strategies to reduce polypharmacy
Boghossian et al 2017[10]	1758	48–57, except one trial with mean age 73	Not reported	PPI use for at least 1 month	Community	Deprescribing PPIs
Black et al 2017[11]	6352	Mean age 77–84	0.5 to 58%	Glyburide, serum creatinine ≥176 micromol/L HbA1c ≤6%, on any diabetes medicine	RACF, community	Deprescribing antihyperglycaemics

* Reported as mean ± SD unless otherwise stated # Higher scores represent increased quality of life

CI confidence interval
EQ-5D EuroQol-5D
HbA1C glycated haemoglobin
N/A not applicable
OR odds ratio
PPI proton pump inhibitor
QOL quality of life
RACF residential aged-care facility
RCT randomised controlled trial
RR risk ratio
SD standard deviation

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

commonly continued for prolonged periods.[10] Stopping them may result in rebound hyperacidity, or lack of symptom control,[10] especially during the first two weeks. A study that deprescribed proton pump inhibitors during hospital admissions found that 57% were still discontinued after three months.[25] Tapering the dose may reduce the risk of rebound symptoms, particularly if the initial dose is high. Proton pump inhibitors, H_2 antagonists or antacids (e.g. Mylanta) can be used as needed to relieve rebound symptoms.

The fracture risk in people with osteoporosis may be reduced using denosumab or bisphosphonates. Bisphosphonates can be discontinued after 3–6 years in many people without altering fracture risk.[5,26] For example, a six-year study of zoledronic acid suggested treatment could be stopped after six annual infusions, with treatment effects maintained for at least three years.[26] Unlike bisphosphonates, denosumab is not incorporated into the bone matrix so the effect on bone resorption is not maintained after treatment is discontinued. Discontinuing denosumab therefore results in rapid bone loss and the fracture risk reverts to baseline levels.[27,28] Periodic monitoring may identify changes in bone mineral density after a bisphosphonate has been discontinued.

Withdrawal symptoms

Discontinuing drugs can result in withdrawal symptoms. People taking long-term benzodiazepines are likely to be physiologically dependent. A withdrawal syndrome can include anxiety,

Table 1 **Summary of systematic reviews of deprescribing (continued)**

Analysis type	Impact on health outcomes		
	Mortality	**Quality of life#**	**Falls**
Narrative summary	60 days: 23.8% intervention vs 20.3% control (p=0.36) 12 months: 26% intervention vs 40% control (p=0.16)	One RCT: 7.1 intervention vs 6.9 control (p=0.04) One RCT: –1.0 intervention vs –1.0 control (p=0.94)	Rate of falls over 12 months: fell from 1.3 to 0.8 (p=0.006) in intervention group vs 1.4 to 1.3 (p=0.66) in control group Proportion of people falling at least once: 0.6 intervention vs 0.7 control (p=0.40)
Meta-analysis	OR 0.90 (95% CI 0.82–0.99) Medication review-directed deprescribing: OR 0.74 (95% CI 0.65–0.84)	N/A	No significant change in the number of residents who had a fall Medication review-directed deprescribing reduced number of people who fell (OR 0.76, 95% CI 0.62–0.93)
Narrative summary	No significant change in mortality reported (values not stated)	No significant difference at 6 months in self-reported QOL QOL using EQ-5D: 0.358 intervention vs 0.294 control (p=0.008)	Rate of falls per 1000 person years: 1.5 ± 8.3 intervention vs 10.6 ± 25.4 control group (p<0.004)
Meta-analysis	Randomised trials: OR 0.82 (95% CI 0.61–1.11) Patient-specific interventions: OR 0.62 (95% CI 0.43–0.88)	No significant changes in QOL reported	Risk of experiencing at least one fall: OR 0.65 (95% CI 0.40–1.05) Rate of falls in participants who did fall: mean difference 0.11 (95% CI –0.21–0.02)
Meta-analysis	OR 1.02 (95% CI 0.84–1.23)	N/A	N/A
Meta-analysis	N/A	N/A	N/A
Narrative summary	RR 0.73 (95% CI 0.29–1.87)	N/A	N/A

* Reported as mean ± SD unless otherwise stated # Higher scores represent increased quality of life

CI	confidence interval	OR	odds ratio	RCT	randomised controlled trial
EQ-5D	Euro-Qol-5D	PPI	proton pump inhibitor	RR	risk ratio
HbA1C	glycated haemoglobin	QOL	quality of life	SD	standard deviation
N/A	not applicable	RACF	residential aged-care facility		

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

irritability, insomnia and myoclonic jerks. One study demonstrated that 38% of people reported withdrawal symptoms when discontinuing benzodiazepines and Z-drugs (zopiclone and zolpidem).[29] This highlights the importance of slowly tapering medicines to minimise withdrawal symptoms.[30] This also increases the likelihood of the medicine being successfully deprescribed.

Enablers and barriers to deprescribing for patients

It is important to involve patients and their carers in the decision to discontinue medicines when possible.[4] Most older people are willing to stop one or more drugs if their doctor says they can.[31] A person may be reluctant to do this if they believe a drug is still necessary or that they may derive future benefit from it.[32] Patients may be concerned about relapse or withdrawal symptoms,[32] but are more willing to have a medicine deprescribed if they know they can restart it if required.[33] Inadequate time with the prescriber to discuss discontinuation, and lack of guidance on how to stop a medicine (e.g. is tapering needed, what monitoring and follow-up will occur), is another barrier.[32] This highlights the importance of providing additional information about the risks and benefits of medicine use to facilitate an older person's willingness to deprescribe. For example, those who received a brochure that described harms from Z-drugs and suggested alternative options were significantly more likely to discontinue the medicine than those who received usual care.[15]

Tools to support deprescribing decisions

There are many tools to assist clinicians to deprescribe medicines in older people.[34] Implicit tools such as the deprescribing algorithm (Table 2)[35-38] outline approaches for reviewing an older person's medicine list to identify targets for deprescribing. These tools require application by a health professional. Explicit tools provide criteria-based guidance on how to approach the deprescribing of specific drugs – an example of medicine-specific guidelines is shown in Table 3.

Referring an older person for a Home Medicines Review or a Residential Medication Management Review by a pharmacist can assist the process. The pharmacist can help to identify targets for deprescribing and develop a plan for tapering doses. Deprescribing advice from pharmacists has been shown to reduce inappropriate prescribing in older people.[39] It is important to ensure that medicine changes are communicated with the older person's community pharmacist so they can assist in implementing the change. This is particularly important if the pharmacist prepares a dose administration aid for the older person.

After identifying deprescribing targets, it is necessary to consider the order in which to deprescribe medicines. Often it is useful to deprescribe medicines with limited noticeable withdrawal effects first to reassure the person that the process is tolerable (Table 4).[35,37,40-45] It is usually advisable to limit deprescribing to just 1–3 medicines at a time. However, it is important to make sure they do not have overlapping indications so it is clear which medicine is responsible if withdrawal effects occur.[35]

Table 2 **Examples of medicine decisions using the deprescribing algorithm**

Criteria	Examples
1. Is the medicine inappropriately prescribed?	Empagliflozin in renal impairment Laxatives in patients with diarrhoea Mineral supplements in patients with no documented deficiency
2. Is the medicine having any adverse effects or interactions?	Symptomatic postural hypotension in a patient taking multiple antihypertensives – discontinuing antihypertensive drugs in older people with orthostatic hypotension increases the probability of recovery.[36]
3. Is the medicine intended for symptom relief and symptoms are stable or resolved?	Inhaled corticosteroid in a patient with stable chronic obstructive pulmonary disease – a 'real-life' study observed that withdrawal of inhaled corticosteroids is possible with no increased risk of exacerbations in patients with stable chronic obstructive pulmonary disease.[37]
4. Is the medicine intended to prevent future events?	Prolonged dual antiplatelet therapy after percutaneous coronary intervention – continuing clopidogrel-based dual antiplatelet therapy beyond six months after percutaneous coronary intervention in older people increases bleeding risk without significantly preventing ischaemic events.[38]

Source: reference 35

Table 3 **Tools to support deprescribing decisions**

Link	Organisation	Description
www.primaryhealthtas.com.au/resources/deprescribing-resources	Primary Health Tasmania	Deprescribing guidelines for commonly used medicines (e.g. benzodiazepines, aspirin, statins)
http://www.match-d.com.au	WA Centre for Health and Ageing, University of Western Australia	Medication appropriateness tool for comorbid health conditions in dementia
http://www.nswtag.org.au/deprescribing-tools	NSW Therapeutic Advisory Group	Deprescribing guidelines for commonly used medicines in older adults (e.g. proton pump inhibitors, long-term opioid analgesics) Deprescribing consumer information leaflets
https://deprescribing.org/resources	Bruyère Research Institute	Deprescribing guidelines and algorithms for commonly used medicines (e.g. antihyperglycaemics) Deprescribing information pamphlets for consumers

Table 4 **Risk of adverse drug withdrawal events for common target medicines in older people**

Reason for considering discontinuation of the drug			Risk of withdrawal event or symptom recurrence
Inappropriate medicines	**No symptomatic benefit from continued therapy**	**Possible symptomatic benefit from continued therapy**	
Benzodiazepines, antipsychotics, tricyclic antidepressants, long-acting sulfonylureas, non-steroidal anti-inflammatory drugs, stimulant laxatives	Antihypertensives	Analgesics, inhaled, topical or oral corticosteroids, diuretics, antiemetics, oral and topical oestrogens, anti-reflux drugs, anxiolytics, hypnotics, levodopa, nasal decongestants, nitrates	Likely – taper dose before stopping
Antispasmodics, anticholinergic antihistamines, short-acting calcium channel blockers, muscle relaxants, dipyridamole, nitrofurantoin, oxybutinin, amiodarone	Statins, potassium supplements, mineral supplements, vitamins, bisphosphonates, other antidiabetic drugs, strontium	Iron supplements, herbal remedies, cough suppressants, digoxin, prophylactic antibiotics, antiglaucoma drugs	Less likely – stop drug without dose tapering

Source: references 38-45

Conclusion

In the deprescribing process, the potential benefits and risks of continuing and discontinuing medicines are considered for the individual. Deprescribing to reduce polypharmacy can be achieved with potential benefits for mortality, quality of life and cognition. While some medicines can be deprescribed without noticeable effects, others are associated with predictable drug withdrawal symptoms. These medicines require more careful deliberation, tapering and monitoring if they are to be discontinued. Deprescribing medicines that are no longer indicated reduces the risk of drug-related harm and is an essential part of the quality use of medicines. ◀

Conflict of interest: none declared

Acknowledgement: Kathleen Potter drafted Table 4 in collaboration with Christopher Etherton-Beer.

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Australian Prescriber
VOLUME 43 : NUMBER 4 : AUGUST 2020

ARTICLE

Management of proteinuria: blockade of the renin–angiotensin–aldosterone system

SUMMARY

Proteinuria, in particular albuminuria, is a potentially significant modifiable risk factor for cardiovascular disease and the progression of kidney disease.

Current treatment guidelines for albuminuria recommend a single renin–angiotensin–aldosterone inhibitor. This can be an ACE inhibitor or an angiotensin receptor antagonist.

The routine use of combined renin–angiotensin–aldosterone inhibition for albuminuria is not supported by current evidence. Combination therapy is associated with higher rates of adverse events such as hyperkalaemia and progressive renal impairment.

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Keywords
ACE inhibitors, albuminuria, angiotensin receptor antagonists

Aust Prescr 2020;43:121–5
https://doi.org/10.18773/austprescr.2020.021

Introduction

Proteinuria, defined as all urinary proteins including albumin, is associated with an increased risk of coronary heart disease and cerebrovascular disease.[1-3] Moderately increased albuminuria (microalbuminuria) increases the risk of coronary heart disease by 50% and stroke by 70%. Severely increased albuminuria (macroalbuminuria) more than doubles the risk of both coronary heart disease or stroke.[2,4] Table 1 shows the degrees of albuminuria.

Albuminuria has also been associated with an increased risk of gastrointestinal haemorrhage[5] and progression of kidney disease.[6] Increased urinary albumin over time has been associated with a greater risk of major renal events, including dialysis, transplantation and death.[7]

Albuminuria is an important target for intervention. In addition to treating the specific cause of albuminuria, other management approaches are frequently used to reduce the degree of albuminuria. These therapies include inhibitors of the renin–angiotensin–aldosterone system. However, their optimum use has been a source of discussion and controversy.

Guidelines for treating proteinuria

The current Kidney Disease Improving Global Outcomes (KDIGO) guideline, published in 2013, recommends the use of either an ACE inhibitor or an angiotensin receptor antagonist (sartan) in all adults with albuminuria over 300 mg/day.[8] It also suggests one of these drugs is used in patients with diabetes and moderately increased albuminuria.[8] There was insufficient evidence for the guideline to recommend combining an ACE inhibitor with an angiotensin receptor antagonist for preventing the progression of chronic kidney disease, regardless of albuminuria.

In 2015 the Kidney Health Australia publication Chronic Kidney Disease Management in General Practice recommended a 50% reduction in albuminuria as a target of treatment. It advised against combination ACE inhibitor and angiotensin receptor antagonist therapy,[9] as did the NICE guidelines in the UK.[10]

Efficacy

Multiple trials have reported that ACE inhibitors are effective at reducing proteinuria in both diabetic and non-diabetic populations.[11-13] ACE inhibitors also reduce the rate of progression of kidney disease, and the risk of dialysis or transplantation by up to 50% in patients with proteinuria.[11-13]

The angiotensin receptor antagonists are effective for reducing proteinuria in diabetic and non-diabetic populations.[14] Major trials have also reported that they slow the progression of kidney disease.[15-17] During the first 6–12 months of treatment, a 50% reduction in proteinuria is associated with a 40–50% reduction in the risk for progression of kidney disease.[18]

Table 1 **Albuminuria excretion rates**

Diagnostic test	Normal	Moderately increased albuminuria (microalbuminuria)	Severely increased albuminuria (macroalbuminuria)
24-hour urine albumin collection (mg/24 hours)	<30	30–300	>300
Urine albumin:creatinine ratio (mg/mmol)	<3	3–30	>30

Rationale behind combination therapy

Combined inhibition of the renin–angiotensin–aldosterone system was first evaluated on the basis of three pathophysiological considerations.[19] First, any renin–angiotensin–aldosterone inhibition with an ACE inhibitor or angiotensin receptor antagonist is incomplete due to substantial redundancy built into human physiological systems. Second, studies have shown that chronic treatment with ACE inhibitors or angiotensin receptor antagonists results in aldosterone escape with plasma concentrations reaching pre-treatment levels within 6–12 months in up to 40% of patients.[20] Third, given that treatment with an ACE inhibitor or angiotensin receptor antagonist alone does not completely eliminate proteinuria, adding a second renin–angiotensin–aldosterone inhibitor may provide further reduction.[20]

Combination with angiotensin receptor antagonists

There have been numerous studies of treatment with an ACE inhibitor and an angiotensin receptor antagonist (Table 2). The ONTARGET trial evaluated combination treatment with telmisartan and ramipril against either drug alone.[21] Combination treatment was associated with increased harms including hyperkalaemia, renal impairment, hypotension and syncope.[21] However, interpretation of these data in the clinical management of patients with albuminuria is potentially complicated for multiple reasons.

First, most participants in the ONTARGET trial did not have chronic kidney disease or albuminuria, therefore any clinical benefits for patients with albuminuric chronic kidney disease were unlikely to be detected.[22] Second, the doses of both drugs were doubled following a short run-in period, resulting in an increased likelihood of overtreatment and adverse effects.[22] In practice, it is likely that doses would be adjusted according to clinical need and response, rather than doubled. During the trial, albuminuria increased during the follow-up period. The increase in albuminuria over time was statistically lower in the telmisartan alone and combination groups, than with ramipril alone. There was no significant difference in albuminuria between telmisartan alone and combination treatment.[23] In addition, the rates of cardiovascular events were not statistically different between the three groups.[21]

The VA NEPHRON-D trial evaluated losartan alone and in combination with lisinopril. This trial was stopped early due to an increased incidence of acute kidney injury and hyperkalaemia with combination therapy.[24]

In 2018, the LIRICO and VALID trials failed to demonstrate any significant cardiovascular or renal benefits with combination treatment. Neither trial found increased harms such as those seen in the ONTARGET or VA NEPHRON-D trials, however it is important to note that both the LIRICO and VALID trials were limited by a lack of statistical power and small sample sizes.[25,26]

Combination with direct renin inhibitors

The ALTITUDE trial studied aliskirin, a direct renin inhibitor, added to an ACE inhibitor or an angiotensin receptor antagonist for reducing cardiovascular and renal events. This trial was terminated early due to an increased incidence of hyperkalaemia and renal impairment.[27] A similar trial in patients with heart failure also showed increased harm with the addition of aliskirin to an ACE inhibitor.[28] Direct renin inhibitors are no longer marketed in Australia.

Combination with aldosterone antagonists

Aldosterone antagonists have known antiproteinuric effects. A systematic review found that adding an aldosterone antagonist to an ACE inhibitor or angiotensin receptor antagonist reduced proteinuria in patients with chronic kidney disease. Currently, it is unknown whether this combination reduces the risk of end-stage kidney disease or major cardiovascular events in patients with proteinuric chronic kidney disease. Treatment with an aldosterone antagonist increased the risk of gynaecomastia and doubled the risk of hyperkalaemia.[29]

The RALES trial studied spironolactone, an aldosterone antagonist, added to an ACE inhibitor in patients with heart failure. The trial ended early due to the overwhelming mortality benefit associated with adding spironolactone.[30] Importantly however, this combination was associated with increased rates of hyperkalaemia and hyperkalaemia-associated morbidity and mortality.[31,32]

The ASPIRANT trial reported that in patients with resistant hypertension, adding an aldosterone antagonist such as spironolactone to standard therapy may be beneficial in reducing systolic blood pressure.[33]

Implications for clinical practice

Proteinuria, in particular albuminuria, is a strong predictor of adverse renal and cardiovascular events. Screening for albuminuria is recommended in all adults with one or more risk factors for chronic kidney disease such as diabetes, hypertension, obesity, current smoking, cardiovascular disease, family history of chronic kidney disease and Aboriginal or Torres Strait Islander people.[34]

Appropriate recognition and treatment of albuminuria, even in patients who are normotensive, can reduce patient morbidity and mortality. Treatment of

Table 2 **Summary of randomised controlled trials of combination ACE inhibitor and angiotensin receptor antagonist treatment**

Study	Patients	Entry criteria	Treatment arms	Outcomes	Follow-up period (median)	Results
ONTARGET[21]	25,620	Vascular disease or high-risk diabetes	1. Telmisartan 2. Ramipril 3. Telmisartan + ramipril	Composite cardiovascular outcome (death, myocardial infarction, stroke and hospitalisation)	56 months	No statistically significant difference in cardiovascular events between groups Higher incidence of hyperkalaemia, renal impairment, hypotension and syncope with combination treatment
VA NEPHRON-D[24]	1448	Type 2 diabetes and random urine ACR >33 mg/mmol	1. Losartan + placebo 2. Losartan + lisinopril	First change in eGFR or decline of ≥50% in eGFR, or end-stage kidney disease or death	26 months	Terminated early due to higher incidence of hyperkalaemia and acute kidney injury with combination treatment
LIRICO[25]	1243	Diabetes, ≥1 cardiovascular risk factor and a urine ACR >3.4 mg/mmol	1. ACE inhibitor* 2. Angiotensin receptor antagonist* 3. ACE inhibitor + angiotensin receptor antagonist	Composite cardiovascular outcome (death, myocardial infarction, stroke and hospitalisation) Doubling of serum creatinine or progression to end-stage kidney disease	32 months	No statistically significant differences in cardiovascular or renal outcomes between groups No statistically significant differences in adverse outcomes between groups
VALID[26]	103	Type 2 diabetes, serum creatinine 159–309 micromol/L and urine ACR >56 mg/mmol	1. Benazepril 2. Valsartan 3. Benazepril + valsartan	Progression to end-stage kidney disease	41 months	Reduced progression to end-stage kidney disease in valsartan alone group No statistically significant differences in adverse outcomes between groups

ACR albumin:creatinine ratio
eGFR estimated glomerular filtration rate
* any commercially available drug

comorbidities and cardiovascular risk factors should always accompany treatment of albuminuria. Gradually increasing to the maximum tolerated dose of an ACE inhibitor or angiotensin receptor antagonist is likely to yield the greatest benefit. This dose titration will depend on the patient's tolerance and may be limited by adverse events such as hypotension, dizziness, cough or hyperkalaemia.

Although data supporting a combination renin–angiotensin–aldosterone inhibitor are lacking for the treatment of albuminuria, there may be specific circumstances such as heart failure or refractory hypertension when it may be appropriate. However, this should only occur with close monitoring due to the higher rate of adverse events such as hyperkalaemia, acute kidney injury, progressive chronic kidney disease, hospitalisation and death.[31,32]

ACE inhibitors, angiotensin receptor antagonists and cancer risk

A recently published large population-based cohort study suggested that treatment with an ACE inhibitor was associated with a small but significant increase in the risk of lung cancer compared with angiotensin receptor antagonists. It further found that the risk of lung cancer was higher with longer durations of treatment.[35] However, a meta-analysis of randomised controlled trials also found an increased risk of lung cancer with angiotensin receptor antagonists.[36]

At present, given the conflicting data and lack of long-term prospective evidence, it is not possible to claim that an ACE inhibitor is safer than an angiotensin receptor antagonist or vice versa. Instead, the choice of drug should be based on patient factors, tolerability and clinician experience.

Conclusion

Combining renin–angiotensin–aldosterone drugs to increase blockade of the system reduces proteinuria, but has been consistently associated with a higher incidence of adverse events including hyperkalaemia and acute kidney injury without clear benefits. Combination therapy should not be routinely prescribed to patients with proteinuria. The recommended treatment is monotherapy with either an ACE inhibitor or an angiotensin receptor antagonist. ≺

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ARTICLE

Chronic leukaemias in the community

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Keywords
chronic lymphocytic leukaemia, chronic myeloid leukaemia, drug interactions, patient adherence, targeted therapy, tyrosine kinase inhibitors

Aust Prescr 2020;43:126–30
https://doi.org/10.18773/austprescr.2020.034

SUMMARY

Patients with chronic myeloid leukaemia and chronic lymphocytic leukaemia are now predominantly managed in an outpatient setting, with infrequent need for hospital-based therapy.

New targeted oral treatments have transformed survival outcomes. An increasing number of patients now have a life expectancy approaching that of the general population.

Suboptimal drug adherence is common and a key reason for therapy failure and poor clinical outcomes.

The pharmacokinetics of new oral targeted drugs are significantly impacted by drug–drug interactions and an altered gastric pH.

Long-term use of some of the new oral drugs is associated with complications, including cardiovascular events and infections, which can be fatal if not recognised.

Introduction

The management of haematological malignancies has changed dramatically in the last couple of decades with a better understanding of molecular pathobiology. These changes are seen most dramatically in chronic myeloid leukaemia and chronic lymphocytic leukaemia where cytotoxic chemotherapy is increasingly being replaced by oral targeted therapy such as tyrosine kinase inhibitors (see Table). Consequently, patients require fewer hospital-based treatments and are transitioning to outpatient and community care.

New treatment options have transformed survival outcomes. Before the availability of tyrosine kinase inhibitors, the median survival in chronic myeloid leukaemia was 4–7 years. Now most patients have a life expectancy comparable to the general population.[1] Similarly, median survival in chronic lymphocytic leukaemia is improving.

With increasing prevalence as a result of increased survival rates, it is now common for GPs and pharmacists to be involved in the management of patients receiving oral therapies for chronic leukaemias. It is therefore important to be aware of these new treatments and their potential complications, including significant adverse effects and drug interactions (see Table).

Chronic myeloid leukaemia

Patients with chronic myeloid leukaemia are commonly asymptomatic and diagnosed during a routine examination or investigation. If symptoms do occur, they are usually related to anaemia, splenomegaly and constitutional symptoms. These symptoms include malaise, lethargy, early satiety, weight loss and abdominal fullness or pain in the left upper quadrant. In peripheral blood, suggestive findings include a persistent neutrophilia often seen with myelocytes, metamyelocytes or occasional blasts (features known as 'left shift'). Basophilia, eosinophilia and thrombocytosis can also be seen.

Diagnosis

The diagnosis of chronic myeloid leukaemia is established by the detection of the BCR-ABL1 fusion gene (also known as the Philadelphia chromosome) formed by a reciprocal translocation of chromosomes 9 and 22. The protein produced from this fusion gene is a constitutively active, oncogenic tyrosine kinase which drives malignant proliferation.

The most sensitive method for detecting the BCR-ABL1 fusion gene is using a reverse transcriptase-polymerase chain reaction (RT-PCR) test of blood or bone marrow samples. The same test is used to quantify residual disease and monitor treatment response.

Treatment and monitoring

Chronic myeloid leukaemia presents in three phases – chronic, accelerated and blast phase. If left untreated, the chronic phase progresses to blast phase, which is usually fatal. About 90–95% of patients are diagnosed in the chronic phase. The mainstay of treatment is tyrosine kinase inhibitors, which block the activity of the oncogenic BCR-ABL1 tyrosine kinase. Blast-phase disease, which is much less common, may still require high-dose chemotherapy and allogeneic stem cell transplantation.

Tyrosine kinase inhibitors are started at diagnosis and for many patients will be continued for life

Table **Targeted oral therapy for chronic leukaemias – key management points**

Indication	Drug	Dosing advice	Complications
Chronic myeloid leukaemia	Imatinib	Dose is usually 400–600 mg daily. Tablets should be taken with food to minimise gastrointestinal adverse effects.	• Compared to other tyrosine kinase inhibitors, imatinib has a higher incidence of nausea, vomiting, diarrhoea and fluid retention (peripheral oedema, eyelid and periorbital oedema).
	Dasatinib	Initial dose is 100 mg daily. May be taken with or without food.	• May prolong QT interval, and concomitant drugs that also prolong QT interval should be avoided. • Significant interaction with antacids taken within 2 hours of administration. H_2 antagonists and proton pump inhibitors decrease absorption so their combined use with dasatinib is not recommended. • Risk of pleural and pericardial effusions which may require dose adjustment and occasionally percutaneous drainage. • Pulmonary hypertension is a rare complication which can be fatal if undetected and requires immediate cessation of the drug. It may manifest as unexplained dyspnoea or signs of right heart failure. A transthoracic echocardiogram may find signs of right heart pressures and a right heart catheterisation is required for a definitive diagnosis.
	Nilotinib	Standard dose is 300 mg (2 tablets) twice daily. Must be taken on an empty stomach (2 hours before, or 1 hour after food) as drug absorption increases with a high-fat meal.	• May prolong QT interval, and concomitant drugs that also prolong QT interval should be avoided. • Increased risk of vaso-occlusive vascular events such as ischaemic heart disease, ischaemic cerebrovascular events and peripheral artery occlusive disease. This warrants proactive management of cardiovascular risk factors. • Elevation of blood lipids and glucose has been observed and close monitoring is recommended. • Increased incidence of pancreatitis.
Chronic lymphocytic leukaemia	Ibrutinib	Starting dose is 420 mg daily. May be taken with or without food.	• Use of cytochrome P450 3A4 inhibitors such as azole antifungals and macrolide antibiotics should be avoided. Dose reduction of ibrutinib may be required (in consultation with the haematologist). • Significant haemorrhagic complications have been reported and are related to ibrutinib's effect on platelet activation. Thoroughly assess risk and benefit before concomitant use with anticoagulants or antiplatelets. • In patients having surgery with a high risk of bleeding, withhold ibrutinib for 3–7 days before and after the procedure. • Ibrutinib use is associated with increased cardiac arrhythmias particularly atrial fibrillation. Management can be challenging given that concurrent anticoagulation should be avoided.
	Venetoclax (initially used in combination with rituximab)	Starting dose is 20 mg titrated weekly to 400 mg with monitoring. Should be taken with food at the same time each day to ensure consistent bioavailability as meals increase bioavailability of venetoclax 3–5-fold depending on fat content.[2]	• Specialist monitoring required during titration because of the risk of severe tumour lysis syndrome. • Venetoclax is associated with cytopenias, particularly severe neutropenia, which occasionally require dose modifications.

unless there are unacceptable adverse effects or drug resistance. Treatment response is monitored by quantitative RT-PCR of BCR-ABL1. The median population value of this test is set at 100% at diagnosis, down to 0.001% in response to treatment. Some patients who achieve durable and deep molecular remission over years may successfully cease their drug without relapse of disease. This is known as treatment-free remission. However, they must meet stringent criteria and undergo frequent monitoring by their haematologist as rapid relapses can occur.

The choice of tyrosine kinase inhibitor is dependent on disease risk, patient comorbidities and patient preference. There are currently drugs approved for first-line use in Australia – imatinib which is a first-generation tyrosine kinase inhibitor, and dasatinib and nilotinib which are both second generation. The rate of disease progression is slightly higher with imatinib, although this drug may be less likely to cause life-threatening adverse events. Dasatinib and nilotinib can induce faster responses. A third-generation tyrosine kinase inhibitor, ponatinib, is reserved for patients resistant to other tyrosine kinase inhibitors. However, it has a higher rate of vascular toxicity including myocardial infarction, cerebrovascular accidents and peripheral vascular disease.

Chronic lymphocytic leukaemia

Most patients with chronic lymphocytic leukaemia are asymptomatic at diagnosis. There may be constitutional symptoms (night sweats, weight loss and fever), lymphadenopathy, splenomegaly or both. Occasionally, the disease can be associated with autoimmune haemolytic anaemia, immune thrombocytopenia and recurrent infections. Unexplained and persistent lymphocytosis along with typical blood film findings, such as smudge cells, can suggest chronic lymphocytic leukaemia but do not exclude other lymphoproliferative neoplasms.

Diagnosis

Diagnosis is based on the presence of a clonal population of lymphocytes (≥ 5 x 10^9/L for ≥3 months) with an immunophenotype typical of chronic lymphocytic leukaemia (by flow cytometry). A clonal population of less than 5 x 10^9/L is termed monoclonal B-lymphocytosis, which may progress to chronic lymphocytic leukaemia at a rate of 1–2% per year.

Treatment and monitoring

In the early stages, patients without active or symptomatic disease such as progressive cytopenias or constitutional symptoms (unexplained fever, night sweats, weight loss and disabling lethargy) can be monitored without treatment, as there is no survival benefit for early intervention.[3] In fit patients chemotherapy remains the standard of care (fludarabine, cyclophosphamide and rituximab) with over 80% of patients having a partial or complete response.[4]

In relapsed or resistant disease, oral targeted therapies commonly used include ibrutinib and venetoclax. Both have high efficacy, particularly in disease carrying high-risk genetic abnormalities such as a *TP53* mutation. Ibrutinib is an inhibitor of Bruton's tyrosine kinase, which B-cells rely on for survival and proliferation. In contrast, venetoclax blocks the function of the Bcl-2 protein which protects tumour cells from cell death.[4,5]

Adherence to treatment

Adherence is critical in ensuring the effectiveness of therapy and GPs can play an important role in checking that patients have been taking their medicines as directed.[6] In chronic myeloid leukaemia, patients taking imatinib are over 17 times more likely to lose control of the disease when adherence rates are less than 85%.[7] Similarly, studies of ibrutinib for chronic lymphocytic leukaemia have found that dose reduction or significant dose interruptions are associated with worse rates of progression-free survival.[8]

In general, adherence to oral cancer therapy varies markedly (46–100%) and tends to deteriorate over time. Adherence rates can be influenced by patient, disease, healthcare provider and treatment-related factors.[9] In chronic myeloid leukaemia, a systematic review noted that drug-related adverse events were the most common reason for intentional non-adherence. Forgetfulness was the most common unintentional reason.[10]

Avoiding drug interactions

The absorption of these oral targeted drugs is variably affected by alterations in the gastric environment, therefore strict dietary precautions and avoidance of concomitant drugs that increase gastric pH are important. All drugs mentioned in the Table are major substrates of cytochrome P450 (CYP) 3A4 (in addition to other CYP and non-CYP pathways). Drugs that inhibit or induce CYP3A4 can therefore significantly increase toxicity or reduce efficacy.[11] Prescribers and pharmacists should be vigilant in monitoring and checking for drug interactions (see Table).

Cardiovascular implications

GPs play an important role in cardiovascular risk management. They can assist in monitoring and managing risk factors such as smoking, hypertension, dyslipidaemia and obesity.

As the life expectancy of patients with chronic myeloid leukaemia has increased, it is important to address other causes of morbidity. In particular, dasatinib and nilotinib increase the risk of cardiovascular events, such as ischaemic heart disease and cerebrovascular disease.

Hypertension can occur or worsen during treatment with ibrutinib, and antihypertensives should be started or adjusted accordingly.[12]

Infection and vaccination

Chronic lymphocytic leukaemia can be associated with impaired immunity and an increased risk of infections, particularly in advanced disease and following treatment with immunosuppressive therapy.[13] International guidelines recommend inactivated influenza vaccine (annually) and pneumococcal vaccine before treatment with B-cell-depleting drugs such as rituximab and ibrutinib.[13,14] Vaccination with live vaccines such as varicella zoster is contraindicated in patients with chronic lymphocytic leukaemia as deaths have occurred.[12] Selected patients with secondary hypogammaglobulinaemia and recurrent severe infections despite antibiotics may be considered for intravenous immunoglobulin therapy.

Currently, there is no recognised link between chronic myeloid leukaemia and an increased risk of infections, aside from hepatitis B reactivation in those with chronic infection. Antiviral prophylaxis may therefore be appropriate, especially in those with positive hepatitis B serology.[15] There are limited data on the effectiveness of vaccinations in chronic myeloid leukaemia, although influenza and pneumococcal vaccines should be considered.[13] Due to limited data, recent international guidelines advise against live attenuated vaccines in patients with chronic myeloid leukaemia who are taking tyrosine kinase inhibitors.[14]

Pregnancy

Men and women with chronic leukaemia planning to have children should discuss their intentions with their treating haematologist to assess the risks and benefits of ongoing therapy. After careful discussions, treatment may be paused during pregnancy planning through to postpartum. All drugs listed in the Table have caused or are suspected of causing fetal harm (pregnancy category C or D), and their effects on male fertility are uncertain. Outside of specialist advice, effective contraception is generally recommended.

Future directions

In chronic myeloid leukaemia, current research is focused on deepening the molecular response and management of resistant disease, which includes novel treatments such as asciminib which targets an alternative site on the BCR-ABL1 oncoprotein. Research is also focused on a better understanding of drug pharmacokinetics for personalised dosing.

In chronic lymphocytic leukaemia, treatment options are continuing to evolve as long-term remission is now a distinct possibility. Recent trials have found that ibrutinib and venetoclax alone, or in combination, are highly effective in the front-line setting. Newer generation Bruton's tyrosine kinase inhibitors such as acalabrutinib, and therapeutics targeting other signalling pathways such as phosphatidylinositol 3-kinase, have proven to be effective.[16]

Conclusion

As patients with common chronic leukaemias benefit from rapidly advancing therapies, management priorities are shifting from inducing remission to ensuring a sustained response and managing the complications of treatment. As these patients are increasingly managed in the community, a combined effort between community health professionals and treating specialists is required for optimal outcomes. ◀

David Yeung receives research support from Bristol Myers Squibb and Novartis, and honoraria from Bristol Myers Squibb, Novartis, Pfizer and Amgen. None of these companies has had a role in the preparation of this manuscript.

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FURTHER READING

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New drugs

Brigatinib

Approved indication: non-small cell lung cancer

Alunbrig (Takeda)

30 mg, 90 mg and 180 mg film-coated tablets

Some non-small cell lung cancers are driven by particular mutations or genetic rearrangements of the genes coding for tyrosine kinases. Examples include the anaplastic lymphoma receptor kinase (ALK) and the ROS1 tyrosine kinase. About 3–5% of non-small cell lung cancers are ALK-positive. If one of these driver mutations is present, the patient can be treated with a tyrosine kinase inhibitor, such as crizotinib. A problem with crizotinib is that the cancer eventually becomes resistant to treatment. This has led to the development of so-called 'second-generation' tyrosine kinase inhibitors, such as alectinib, ceritinib and now brigatinib.

For patients with ALK-positive non-small cell lung cancer, brigatinib treatment begins with a daily dose of 90 mg. If this is tolerated for a week, the dose is increased to 180 mg once a day. The peak concentration is reached within four hours, but the absolute bioavailability of the tablets is unknown. Brigatinib is partly metabolised and partly excreted unchanged with an elimination half-life of 25 hours. Liver disease may increase concentrations of brigatinib, but it has not been studied in patients with moderate or severe hepatic impairment. Similarly, patients with severe renal impairment were not included in the trials.

As the metabolism of brigatinib includes cytochrome P450 (CYP) 2C8 and 3A4, there is a potential for interactions with inducers or inhibitors of these enzymes. Strong inhibitors of CYP3A, such as antifungals and macrolide antibiotics, should be avoided. Grapefruit juice should also be avoided. Inducers to avoid include carbamazepine, phenytoin and St John's wort. As brigatinib can induce CYP3A, it could reduce the effectiveness of substrates such as hormonal contraceptives. Although pregnancy is very rare in women with lung cancer, there is probably an increased risk of fetal abnormalities with brigatinib.

An open-label phase II trial studied daily doses of 90 mg or 180 mg in 222 patients with locally advanced or metastatic ALK-positive non-small cell lung cancer. The cancers had progressed during previous treatment with crizotinib with 69% of the patients having brain metastases. During a median follow-up of eight months, the investigators considered that there was an objective response in 45% of the patients given brigatinib 90 mg and 54% of those given brigatinib 180 mg. At the higher dose, progression-free survival was 12.9 months, with an 80% probability of the patients being alive at one year. An independent assessment considered that the size of the intracranial lesions had decreased in 67% (12/18) of the patients, with measurable brain metastases at baseline, who received brigatinib 180 mg.[1]

An open-label phase III trial compared crizotinib with brigatinib 180 mg in 275 patients who had not previously been treated with an ALK inhibitor. Brain metastases were present in 29% of the patients. The median duration of treatment was 7.4 months with crizotinib and 9.2 months with brigatinib. There was an objective response in 71% of the 137 patients randomised to receive brigatinib, compared with 60% in the crizotinib group. The estimated 12-month progression-free survival was 67% with brigatinib and 43% with crizotinib. In patients with measurable brain metastases, there was a response in 78% (14/18) of the brigatinib group and 29% (6/21) of the crizotinib group.[2]

The most common adverse reactions to brigatinib are gastrointestinal effects. While nausea, vomiting and diarrhoea were common in the phase III trial, they were less frequent than with crizotinib. Adverse events that were more frequent with brigatinib included cough, hypertension and rash. There were also more frequent increases in creatine kinase, lipase and amylase.[2] Serious adverse reactions include interstitial lung disease, bradycardia, hyperglycaemia and visual disturbances. It may be necessary to withhold or stop treatment with brigatinib. In the phase III trial, 29% of patients had a dose reduction and 12% had to discontinue.[2]

The Australian approved indication for brigatinib is for the treatment of ALK-positive advanced non-small cell lung cancer in patients who have previously been treated with crizotinib. However, the evidence from the phase III trial suggests that brigatinib could be a better first-line option. While 85–86% of the patients treated with brigatinib and crizotinib were still alive after a year, there was a significant difference in progression-free survival, particularly in patients with brain metastases.[2] Obviously, any difference in overall survival will emerge with longer term data. This will help to guide what sequence to use the

Aust Prescr 2020;43:131–2
https://doi.org/10.18773/austprescr.2020.043
First published 25 June 2020

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.

NEW DRUGS

drugs in. An indirect comparison of alectinib, brigatinib and ceritinib evaluated patients who had cancer that was refractory to crizotinib. It calculated that median overall survival was similar with brigatinib and alectinib (27.6 vs 22.7–26 months) but significantly longer than with ceritinib (27.6 vs 14.9 months).[3]

manufacturer did not supply data

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

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

Brolucizumab

Aust Prescr 2020;43:133–4
https://doi.org/10.18773/austprescr.2020.045
First published 25 June 2020

Approved indication: macular degeneration

Beovu (Novartis)
pre-filled syringes and vials containing 120 mg/mL solution

Age-related macular degeneration is a common cause of visual loss. It may be due to atrophy (dry) or choroidal neovascularisation (wet).[1] As the development of blood vessels involves vascular endothelial growth factor A (VEGF-A), this protein is a target for drug therapy. Anti-VEGF treatments for wet age-related macular degeneration include aflibercept and ranibizumab. These drugs are injected into the vitreous humor.

Brolucizumab is a monoclonal antibody which binds to VEGF-A. By preventing VEGF-A from binding to its receptor, brolucizumab should reduce neovascularisation. Only a small volume (0.05 mL) of solution is injected into the vitreous. Very little enters the systemic circulation. Brolucizumab has a systemic half-life of 4.4 days and is eliminated like other proteins. Its pharmacokinetics are unlikely to be affected by liver or kidney disease, or other drugs.

The trials of brolucizumab assessed its effect on the best corrected visual acuity. They enrolled patients who could read between 78 and 23 letters on a retinopathy scale. This vision is approximately equivalent to 20/32 and 20/400 on a Snellen chart.

A phase II trial enrolled patients over the age of 50 years with previously untreated neovascular macular degeneration. The average numbers of letters they could read on the retinopathy scale was 54.8. Participants were given an intravitreal injection of aflibercept (45 patients) or brolucizumab (44 patients) each month for three months followed by an injection every eight weeks. Although the trial continued for 56 weeks, efficacy was assessed at weeks 12 and 16. After 12 weeks visual acuity had improved by 6.89 letters with aflibercept and by 5.75 with brolucizumab. The corresponding mean changes at 16 weeks were 6.62 and 6.04 letters. This met the study criteria for showing that brolucizumab was statistically non-inferior to aflibercept.[2]

Two phase III trials, HAWK and HARRIER, also used aflibercept as an active control in 1082 untreated patients.[3] Like the phase II trial, there was a loading phase of three intravitreal injections, but then brolucizumab was injected every 12 weeks while aflibercept 2 mg was given every eight weeks. Both trials used the recommended dose of brolucizumab 6 mg, but HAWK also tested 3 mg. From a mean baseline visual acuity of 61.2 letters in the HARRIER trial, patients treated with brolucizumab gained an average of 6.9 letters after 48 weeks. This was non-inferior to the gain of 7.6 letters with aflibercept. In the HAWK trial the average best-corrected visual acuity was 60.6 letters. After 48 weeks this improved by 6.1 letters with brolucizumab 3 mg and by 6.6 letters with 6 mg. Again, this was non-inferior to the increase of 6.8 letters with aflibercept. In both trials, when assessed at 16 weeks, there was statistically significantly less disease activity in patients treated with brolucizumab 6 mg (22.7% and 24%) compared with aflibercept (32.2% and 34.5%).[3]

There are risks with injecting an antibody into the eye. In the phase III trials the common adverse effects included conjunctival haemorrhage and pain. There is a risk of uveitis, endophthalmitis and retinal haemorrhage and detachment.[3] Approximately 5% of patients had a reduction in vision of at least 15 letters in the phase III trials, but this outcome was similar with aflibercept. There was an imbalance in cases of uveitis. In one trial it affected 2.2% of the patients given brolucizumab compared with 0.3% of the aflibercept group. Other ocular adverse events include cataract, vitreous detachment and raised intraocular pressure.[3] As treatment involves injecting a protein, some patients will develop hypersensitivity.

There may be benefits if patients only need an intravitreal injection every 12 weeks. However, in the phase III trials many patients had to switch to injections every eight weeks. The proportions who were able to continue brolucizumab 6 mg at 12-week intervals for 48 weeks were 51% and 55.6%.[3] Patients who have no disease activity when assessed after four months of treatment are more likely to be able to remain on a 12-week regimen. Like other intravitreal injections, brolucizumab should not be used concurrently in both eyes.

T manufacturer provided the AusPAR and the product information

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NEW DRUGS

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

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

Galcanezumab

Aust Prescr 2020;43:135–6
https://doi.org/10.18773/austprescr.2020.044
First published 25 June 2020

Approved indication: migraine

Emgality (Eli Lilly)
prefilled pen, prefilled syringe containing 120 mg/mL

Several drugs can be considered for prophylaxis in patients who have frequent migraines. The range of options was recently increased by the approval of erenumab, an injectable monoclonal antibody. Galcanezumab is another monoclonal antibody that acts on calcitonin gene-related peptide (CGRP).

Concentrations of CGRP increase during a migraine attack resulting in vasodilation. By binding to CGRP galcanezumab blocks this effect. The long half-life of galcanezumab (27 days) results in its action being sustained for several weeks.

A loading dose is recommended followed by monthly subcutaneous injections. As galcanezumab is an antibody it is catabolised, so hepatic and renal impairment are unlikely to affect its pharmacokinetics.

There have been two trials (EVOLVE 1 and EVOLVE 2) of galcanezumab in episodic migraine.[1,2] The patients in these trials were experiencing 4–14 days of migraine headaches each month. After other prophylactic drugs were stopped, the patients were randomised to monthly injections of galcanezumab 120 mg or 240 mg, or placebo. Efficacy was assessed after six months.

In EVOLVE 1 (862 patients) the reduction in days of headache compared to placebo averaged 1.9 days with galcanezumab 120 mg and 1.8 days with galcanezumab 240 mg.[1] The corresponding reductions in EVOLVE 2 (915 patients) were two days and 1.9 days (see Table).[2]

The REGAIN trial studied patients with chronic migraine who had at least 15 days of headache every month. A group of 278 patients injected galcanezumab 120 mg, 277 injected 240 mg and 558 injected a placebo monthly. After three months, the number of days with migraine headache per month had reduced by a mean of 4.8 days with 120 mg and 4.6 days with 240 mg. These outcomes were statistically better than the reduction of 2.7 days seen in the placebo group. There was a reduction of at least 50% in the number of days with headache in 27.6% and 27.5% of the galcanezumab groups compared with 15.4% of the placebo group.[3]

A longer term open-label trial studied 270 patients with episodic or chronic migraine. Half the patients injected galcanezumab 120 mg and the other half injected 240 mg for up to a year. The mean number of days of migraine headache per month dropped by 5.6 days, from a baseline of 9.7, with 120 mg and by 6.5 days, from a baseline of 11.4, with 240 mg.[4]

In the long-term study 60 of the 270 patients stopped treatment. Eighteen discontinued because of lack of efficacy and 13 (4.8%) because of adverse events. Common adverse effects include reactions and pain at the injection sites, arthralgia, myalgia and dizziness. Injecting an immunoglobulin can cause immune reactions. After 12 months, 12.4% of the patients injecting the recommended monthly dose of 120 mg had developed antidrug antibodies.[4] Anaphylaxis is rare. While there were few reports of cardiovascular effects in the trials, patients with a history of cardiovascular events were excluded. The safety of galcanezumab in pregnancy and lactation is also unknown. There are no paediatric data.

The place of drugs aimed at CGRP is currently being established. Galcanezumab is also being studied in cluster headache. While galcanezumab can reduce the number of days of migraine, it is uncertain whether it will work when other prophylaxis has failed. Patients

Table **Efficacy of galcanezumab prophylaxis in episodic migraine**

Treatment (monthly subcutaneous injection)	Trial					
	Evolve 1[1]			Evolve 2[2]		
	Placebo	Galcanezumab 120 mg	Galcanezumab 240 mg	Placebo	Galcanezumab 120 mg	Galcanezumab 240 mg
Patients randomised	433	213	212	461	231	223
Mean number of migraine headache days per month at baseline	9.1	9.2	9.1	9.2	9.1	9.1
Mean reduction in migraine headache days per month after 6 months	2.8	4.7	4.6	2.3	4.3	4.2
Proportion of patients having at least a 50% reduction in migraine headache days per month at 6 months	38.6%	62.3%	60.9%	36%	59.3%	56.5%

whose migraine had not responded to three or more other drugs were excluded from the trials. If a patient tries galcanezumab, the response should be assessed after 8–12 weeks to see if it is worthwhile continuing to use it for prophylaxis.

T manufacturer provided the product information

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

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

Semaglutide

Aust Prescr 2020;43:137–9
https://doi.org/10.18773/austprescr.2020.046
First published 16 July 2020

Approved indication: type 2 diabetes

Ozempic (Novo Nordisk)
pre-filled pens containing 1.34 mg/mL solution

When type 2 diabetes is no longer controlled by diet, exercise and metformin there are many options for additional treatment. These options include the glucagon-like peptide-1 (GLP-1) analogues such as dulaglutide and exenatide. When there is hyperglycaemia, these agonists act on GLP-1 receptors in the pancreas to increase insulin secretion.[1]

Semaglutide is another genetically engineered GLP-1 receptor agonist. As a peptide, it has to be given by subcutaneous injection. The half-life of semaglutide is approximately one week, so it only needs to be injected once a week. A steady state is reached after 4–5 weeks of weekly injections. It is cleared like other peptides, so excretion should not be affected by renal or hepatic impairment.

Semaglutide has been studied in a series of trials titled the Semaglutide Unabated Sustainability in Treatment of type 2 diabetes (SUSTAIN). These phase III trials assessed the effect of weekly injections on concentrations of glycated haemoglobin (HbA1c) (see Table).[2-9]

Monotherapy

Although semaglutide will probably be a second-line treatment, it has been approved as monotherapy when metformin is contraindicated or cannot be tolerated. In the SUSTAIN 1 trial, 388 previously untreated patients were randomised to receive semaglutide (0.5 mg or 1 mg) or a placebo. At the start of the study the mean HbA1c was 64.54 mmol/mol (8.05%). In the 259 patients randomised to semaglutide the HbA1c fell by 15.9–16.96 mmol/mol (1.45–1.55%) after 30 weeks. There was minimal change in the placebo group. Patients treated with semaglutide lost 3.7–4.5 kg in weight.[2]

Added to metformin monotherapy

SUSTAIN 8 studied 788 patients with diabetes that was not controlled by metformin. They were randomised to receive either semaglutide 1 mg or canagliflozin 300 mg. The average baseline HbA1c concentration was 66.7 mmol/mol (8.3%). After one year this had declined by 16 mmol/mol (1.5%) with semaglutide and 10.7 mmol/mol (1%) with canagliflozin. There was a weight loss of 5.3 kg with semaglutide and 4.2 kg with canagliflozin.[9]

Added to metformin (with or without sulfonylureas)

SUSTAIN 4 was an open-label trial that compared adding weekly semaglutide (0.5 mg or 1 mg) or once-daily insulin glargine to the treatment of 1082 patients with inadequately controlled diabetes (mean HbA1c 65.8 mmol/mol (8.2%)). Metformin monotherapy was being used by 523 patients while 559 were also taking a sulfonylurea. At week 30 the mean HbA1c concentration had declined by 13.22–17.93 mmol/mol (1.21–1.64%) with semaglutide, while adding insulin reduced it by 9.06 mmol/mol (0.83%). Patients injecting semaglutide lost weight while those injecting insulin gained weight.[5]

Added to metformin (with or without a thiazolidinedione)

SUSTAIN 2 enrolled 1231 patients who had insufficient glycaemic control despite treatment with metformin, a thiazolidinedione or both. They were randomised to add semaglutide (0.5 mg or 1 mg) or daily sitagliptin (100 mg), an inhibitor of dipeptidyl peptidase-4. After 56 weeks, from a baseline of 64.8 mmol/mol (8.1%), the HbA1c concentration had fallen by 14.4–17.6 mmol/mol (1.3–1.6%) with semaglutide. The reduction with sitagliptin was 6 mmol/mol (0.5%). Patients injected with semaglutide lost 2.4–4.2 kg more weight than the sitagliptin group.[3]

Added to insulin

SUSTAIN 5 studied the effect of adding semaglutide to the treatment of 397 patients with diabetes that was being managed with basal insulin. Most of these patients (83%) were also taking metformin, but still had an average HbA1c concentration of 67.9 mmol/mol (8.4%). The patients were randomised to take semaglutide (0.5 mg or 1 mg) or a placebo for 30 weeks. At the end of the trial HbA1c had been reduced by 15.8–20.2 mmol/mol (1.4–1.8%) with semaglutide compared with a reduction of 1 mmol/mol (0.1%) in the placebo group. Compared to the reduction in weight in the placebo group (1.4 kg), patients injecting semaglutide lost an extra 2.3–5.1 kg.[6]

Comparison with other GLP-1 agonists

SUSTAIN 3 compared semaglutide 1 mg to weekly injections of exenatide 2 mg. The 813 patients in this open-label trial had an average HbA1c of 67.7 mmol/mol (8.3%) despite taking one or two oral antidiabetic drugs. After 56 weeks this concentration had declined by 16.8 mmol/mol (1.5%) with semaglutide and by 10 mmol/mol (0.9%) with exenatide. Body weight reduced by 5.6 kg with semaglutide and by 1.9 kg with exenatide.[4]

NEW DRUGS

Table **Efficacy of semaglutide weekly injections in type 2 diabetes**

Trial (design)	Duration (weeks)	Baseline drug therapy	Patient allocations			Mean baseline HbA1c mmol/mol (%)	Mean decrease in HbAlc mmol/mol (%) at end of trial
SUSTAIN 1[2] (double-blind)	30	None	Semaglutide	0.5 mg	129	64.88 (8.09%)	15.9 (1.45%)
				1 mg	130	65.29 (8.88%)	16.96 (1.55%)
			Placebo		129	63.43 (7.95%)	0.27 (0.02%)
SUSTAIN 2[3] (double-blind)	56	Metformin with or without thiazolidinediones	Semaglutide	0.5 mg	409	64.1 (8.0%)	14.4 (1.3%)
				1 mg	409	64.4 (8.0%)	17.6 (1.6%)
			Sitagliptan	100 mg	407	65.8 (8.2%)	6.0 (0.5%)
SUSTAIN 3[4] (open-label)	56	One or two of: metformin, sulfonylureas, thiazolidinediones	Semaglutide	1 mg	404	67.9 (8.4%)	16.8 (1.5%)
			Exenatide	2 mg	405	67.6 (8.3%)	10.0 (0.9%)
SUSTAIN 4[5] (open-label)	30	Metformin with or without sulfonylureas	Semaglutide	0.5 mg	362	65.4 (8.1%)	13.22 (1.21%)
				1 mg	360	66.6 (8.3%)	17.93 (1.64%)
			Insulin glargine	360	360	65.4 (8.1%)	9.06 (0.83%)
SUSTAIN 5[6] (double-blind)	30	Insulin (basal) with or without metformin	Semaglutide	0.5 mg	132	67.9 (8.4%)	15.8 (1.4%)
				1 mg	131	67.3 (8.3%)	20.2 (1.8%)
			Placebo		133	68.6 (8.4%)	1.0 (0.1%)
SUSTAIN 6[7] (double-blind)	104	Up to two oral drugs with or without insulin	Semaglutide	0.5 mg	826	72 (8.7%)	12.1 (1.1%)
				1 mg	822	72 (8.7%)	15.8 (1.4%)
			Placebo		1649	72 (8.7%)	5.0 (0.4%)
SUSTAIN 7[8] (open-label)	40	Metformin	Semaglutide	0.5mg	301	67.5 (8.3%)	16.5 (1.5%)
				1 mg	300	66.2 (8.2%)	19.4 (1.8%)
			Dulaglutide	0.75 mg	299	65.7 (8.2%)	12.1 (1.1%)
				1.5 mg	299	66.1 (8.2%)	14.9 (1.4%)
SUSTAIN 8[9] (double-blind)	52	Metformin	Semaglutide	1 mg	394	67.1 (8.3%)	16.0 (1.5%)
			Canagliflozin	300 mg	394	66.3 (8.2%)	10.7 (1%)

HbA1c glycated haemoglobin

Semaglutide (0.5 mg or 1 mg) was compared to weekly injections of dulaglutide (0.75 mg or 1.5 mg) in the open-label SUSTAIN 7 trial. This randomised 1201 patients who had an average HbA1c concentration of approximately 66.4 mmol/mol (8.2%) despite taking metformin. After 40 weeks the reductions in HbA1c were 16.5 mmol/mol (1.5%) with semaglutide 0.5 mg and 12.1 mmol/mol (1.1%) with dulaglutide 0.75 mg. The corresponding reductions for semaglutide 1 mg and dulaglutide 1.5 mg were 19.4 mmol/mol (1.8%) and 14.9 mmol/mol (1.4%). Depending on the dose, weight loss with semaglutide was 4.6–6.5 kg and 2.3–3 kg with dulaglutide.[8]

Safety

Some of the adverse effects of semaglutide can be predicted from its mechanism of action.[1] For example, there is a risk of hypoglycaemia when semaglutide is given with insulin or a sulfonylurea. Treatment with semaglutide should begin at a low dose and be increased after four weeks. As GLP-1 receptors are found in the brain, heart and kidneys, as well as in the pancreas, semaglutide may have effects on these organs. For example, semaglutide has been associated with an increase in heart rate. It delays gastric emptying. Gastrointestinal events such as nausea, vomiting and diarrhoea are the most frequent

adverse reactions. Withdrawals due to adverse events varied across trials. In SUSTAIN 1 approximately 6% of patients taking semaglutide withdrew because of adverse events compared with approximately 2% of the placebo group.[2] Less frequent adverse effects include acute pancreatitis, cholethiasis and complications of diabetic retinopathy. Injecting a peptide can cause an immune response. In addition to injection site reactions, anaphylaxis has been reported rarely. Laboratory tests show that semaglutide may increase concentrations of lipase and amylase.

In animal studies semaglutide has been toxic during pregnancy. It should not be used by pregnant or breastfeeding women.

Place in therapy

Semaglutide is an option when the use of a GLP-1 analogue is considered. This will usually be if drug therapy with metformin is insufficient to control type 2 diabetes. In the open-label trials the absolute differences between semaglutide and exenatide[4] and dulaglutide[8] were small, but they met the criteria for statistical superiority for the reductions in HbA1c and body weight. While increasing the dose of semaglutide to 1 mg will cause a slightly greater reduction of HbA1c it will also increase adverse effects.

Changes in the concentrations of HbA1c are a surrogate outcome in type 2 diabetes. It is too early to assess all the long-term clinical outcomes, however semaglutide might have some benefit in patients with a high risk of cardiovascular events. SUSTAIN 6 enrolled 3297 patients with cardiovascular disease, chronic heart failure or chronic kidney disease. These patients had an average HbA1c concentration of 72 mmol/mol (8.7%). They were randomised to semaglutide (0.5 mg or 1 mg) or a placebo. After a median follow-up of 2.1 years there had been a cardiovascular event in 6.6% of the semaglutide group and 8.9% of the placebo group. However, deaths from cardiovascular causes were similar (2.7% vs 2.8%) in both groups. The patients injecting semaglutide also had more complications from diabetic retinopathy (3.0 vs 1.8%).[7]

An oral formulation of semaglutide has been developed. If this is approved for use in Australia, it may give semaglutide an advantage over the other GLP-1 analogues.

T T manufacturer provided additional useful information

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

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

NEW DRUGS

Correction

Lithium therapy and its interactions [Correction]

Aust Prescr 2020;43:141
First published 12 June 2020
https://doi.org/10.18773/austprescr.2020.041

There was a sub-editing error in the article on lithium interactions (Aust Prescr 2020;43:91-3), which has now been corrected. View corrected article.

In the last sentence of the 'Diuretics' section, the word 'increase' should have read 'alter': Other diuretics such as the osmotic methylxanthine (e.g. theophylline) and loop (e.g. furosemide (frusemide)) and potassium-sparing (e.g. spironolactone) diuretics may also alter lithium concentrations.

Update

Antipsychotic switching tool [Update 2]

Aust Prescr 2020;43:141
https://doi.org/10.18773/austprescr.2020.036

The online tool by Nicholas Keks et al has been updated. View updated tool (v3).

The olanzapine oral switches to amisulpride, lurasidone, paliperidone, risperidone and ziprasidone have been updated to include the risk of cholinergic rebound when olanzapine is withdrawn.

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