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EDITORIAL

Principles of ethical prescribing for self and others: hydroxychloroquine in the COVID-19 pandemic

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Prescribing medicines with putative benefit for COVID-19 disease appears very attractive to consumers, clinicians and some senior politicians.[1] However, there are no medicines with any robust evidence of clinical benefit, including the antimalarial hydroxychloroquine, the antibiotic azithromycin and the antiretroviral combination of lopinavir with ritonavir. Indeed, now is the time to investigate which drugs may improve clinical outcomes in COVID-19 by conducting well-designed clinical trials, rather than making assumptions based on preliminary data and low-quality clinical studies.[2] There are major trials underway in hospital wards and intensive care units, as well as in the community in the USA, Europe and Australia. Each trial will test different drugs or drug combinations, driven by locally available options.[3]

Hydroxychloroquine is registered in Australia for the treatment of patients with systemic lupus erythematosus, rheumatoid arthritis and malaria. It has proven benefit in these indications and is generally well tolerated by these patients. It is not yet registered for the treatment of COVID-19 in Australia and the drug toxicity profile in COVID-19 is currently unknown. It may prove to be dependent on both the patient population, the dose administered and the concomitant drug therapies. Without knowing the effective drug concentrations, non-optimised dosing may expose patients to serious adverse effects, such as seizures and cardiac toxicity.[4]

Some clinicians and consumers may believe that hydroxychloroquine should be available on compassionate grounds for patients with COVID-19 who are not eligible or do not give their consent for recruitment into a clinical trial.[5] Hydroxychloroquine should only be prescribed after the patient or their carer has been made aware of the drug's potential toxicities and its lack of proven efficacy in COVID-19, and consent has been given.

There are also proposals from some clinicians to take hydroxychloroquine prophylactically following high-risk exposure such as intubating or extubating infected patients. Although pre-exposure and post-exposure prophylaxis trials have already commenced, or will do so imminently, the use of hydroxychloroquine should be conserved for proven therapeutic indications or as part of a randomised controlled trial.[6]

Due to inappropriate prescribing and dispensing, hydroxychloroquine is now in short supply in Australia and globally. This has caused serious challenges for patients receiving ongoing treatment for chronic diseases such as lupus for which there often is not an effective alternative,[7] and even temporary withdrawal can lead to serious harm.[8] While patients with rheumatoid arthritis could be managed with alternative disease-modifying drugs, this is inconvenient as they need to have additional specialist consultations. It is encouraging that pharmacy and medical professional organisations are also conveying similar messages regarding the limited evidence of drug efficacy and safety in COVID-19, as well as the importance of ongoing access to essential treatments for chronic diseases.[9,10]

There may be a temptation to self-prescribe hydroxychloroquine or prescribe it for family and friends. Each state and territory has specific legislation that regulates this type of prescribing. The Good Medical Practice guide from the Medical Board of Australia cautions against prescribing for self, family, friends or coworkers. The Guide recommends 'seeking independent, objective advice when you need medical care, and being aware of the risks of self-diagnosis and self-treatment'.[11] In other words, all health professionals should have their own doctor. The guide also advises doctors against providing medical care to anyone with whom they have a close personal relationship because of the lack of objectivity, possible discontinuity of care and the risks to the doctor and patient.

Some may argue that in a pandemic, prescribing outside of the guidelines is justified. However, from a medico-ethical and possibly legal perspective, the answer should be 'no' when considering a request to prescribe for a family member or close friend.[12] If you

are asked for such a prescription, it is important to ask yourself:

- Have I made an objective and independent decision to prescribe the most suitable medicine for the condition in this situation?
- Am I able to provide appropriate care for my family or friend?
- Am I following my usual practice and scope in prescribing in this situation?
- Would my peers agree that this was consistent with good practice?
- Would our relationship survive, and could I be considered as having not executed my duty of care or even of being negligent if an adverse drug event occurred?

Prescribing medicines for COVID-19 lacks evidence, risks toxicity and may prevent others accessing essential treatments for chronic diseases. Using hydroxychloroquine or other unproven medicines as a possible standard of care for the treatment or prevention of COVID-19 raises ethical issues of resource allocation as well as beneficence. Drugs must be reserved for approved indications for which they are a first-line treatment. Conversely, while many are hopeful that hydroxychloroquine may prove to be the panacea that will help us lessen the effect of COVID-19 in the population, its use outside of a clinical trial should be avoided until more evidence is available.[13] <

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EDITORIAL

COVID-19 and the quality use of medicines: evidence, risks and fads

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Principles of ethical prescribing for self and others: hydroxychloroquine in the COVID-19 pandemic

The COVID-19 pandemic is rapidly evolving and determining the appropriate response is complex. The severity of COVID-19 and the limited evidence for any treatment have added to the complexity of clinical decision making and prescribing. A vaccine is not yet available, but decisions about treatment are needed now.

Fear in the community has resulted in people trying unproven remedies. These fads include consuming bleach,[1] and gargling warm salt water or vinegar.[2] Each fad has varying toxicity and none is of likely benefit. Consuming chloroquine from an aquarium product[3] and drinking methanol have been fatal.[4] High-dose vitamin C has been discouraged as a treatment for COVID-19,[5] but reports that it is being prescribed to,[6] and studied in,[7] patients with COVID-19 could confuse the public about its place in therapy. These examples highlight the need for balanced discussions of the harms and benefits of each proposed treatment.

Australian healthcare workers have the opportunity to learn from colleagues overseas with advice being received daily. There are many anecdotes about treatment, usually conveying a brief and narrow perspective. Each can consciously and subconsciously influence our clinical decisions.

Information about the purported effects of drugs in COVID-19 is rapidly changing. Most reports focus on what is new, rather than summarising what has been learnt to date. It is easy to miss when a treatment claim becomes discredited or raises new safety concerns.

Currently, supportive care is the mainstay of treatment for COVID-19. Suggested drug treatments have been based mostly on in vitro studies or biomarkers from observational studies. At best, preliminary data from these studies should be considered hypothesis generating and prompt more research, rather than guiding clinical management. Many clinicians are not experts in research methods, so we may not appreciate the limitations of the results based on the shortcomings of the methods used in some of these studies.

Over 300 trials including more than 50 drug or biological treatments for COVID-19 have been registered.[8] These will generate both hope and uncertainty. Currently the main approaches include inhibiting viral replication with chloroquine, hydroxychloroquine or antiviral drugs,[9] immune modulation by corticosteroids, tocilizumab or stem cells, and administration of convalescent sera.

Some studies that have been popularised by the media have been uploaded to online preprint servers without the rigour of peer review. This may not be apparent from an abstract or media report so a high level of scepticism is required.

A global survey of physicians in early April 2020 found that hydroxychloroquine and azithromycin were prescribed or seen to be prescribed by nearly 50% of respondents. However, only 38% perceived efficacy in COVID-19.[10] Some healthcare workers have prescribed hydroxychloroquine for themselves and their families. This represents extrapolation of the very low-quality evidence for treatment[11] to experimental use for prophylaxis.[12] The decision may have been their own, but it has been rumoured that some doctors were advised by their employer to self-prescribe hydroxychloroquine due to their increased risk of being infected by patients with COVID-19. This highlights the ethical questions about prescribing experimental treatments.[13] It is important to distinguish off-label from experimental prescribing.

Given the rate that the pandemic is evolving, the processes required to start a clinical trial may appear prolonged. However, these processes are necessary to develop a protocol, allocate resources and ensure patients are monitored to avoid treatment-related deaths. An experimental treatment should only be prescribed after informed consent is obtained.

The doses of some drugs being prescribed for COVID-19 are high compared to those used for their approved indications. Clearly, the greater the dose the greater risk of harm, and this is likely to be compounded in older patients with multiple comorbidities or those with viral myocarditis.

Some studies have used combinations of drugs which makes it difficult to assess their individual efficacy and toxicity. The combination of hydroxychloroquine and azithromycin is associated with cardiotoxicity, including a newly prolonged QTc interval of over 500 ms in 10–20% of participants.[14,15] A preprint publication of a retrospective study reported higher mortality in patients receiving hydroxychloroquine than those who did not.[16] Cardiotoxicity including ventricular tachycardia and death with higher doses of chloroquine prompted the early cessation of a Brazilian study.[17] Preventable drug-induced toxicity due to overdosage may have occurred in other

pandemics, including aspirin for influenza in 1918–19[18] and ribavirin for severe acute respiratory syndrome in 2003.[19]

In March 2020 there was much discussion that renin–angiotensin system inhibitors may increase the severity of COVID-19.[20-22] Much of this concern then subsided and it was recommended for patients taking these drugs to continue them.[20,22] The harm from stopping these drugs in patients with heart failure or other high-risk cardiovascular conditions is probably far greater than the unproven risk of severe COVID-19.[23,24] Subsequent studies confirmed that there was no increased risk from COVID-19 with renin–angiotensin system inhibitors,[25-28] confirming the earlier advice. There have also been concerns about non-steroidal anti-inflammatory drugs (NSAIDs) notably ibuprofen.[21] The current position is that NSAIDs can be used when indicated, but paracetamol is likely to be an acceptable alternative.[29-32]

Another risk from the increased prescribing of unproven drugs is that it creates a shortage of these drugs for patients who rely on them. For example, there has been a shortage of hydroxychloroquine for systemic lupus erythematosus, and reports of possible ivermectin efficacy in COVID-19 led to shortages within days. The shortages also impact on the supply of medicines for clinical trials. Regulators, funders and policymakers have needed to enforce or introduce regulations to prevent inappropriate prescribing and stockpiling. The Therapeutic Goods Administration and Pharmaceutical Benefits Scheme have now restricted who can prescribe hydroxychloroquine.[33,34]

COVID-19 is presenting a number of challenges. We should not compound the crisis by inappropriate prescribing based on inadequate evidence, which increases the risk of harm and causes drug shortages. At present all prescribing for COVID-19 is experimental. Healthcare professionals must constantly analyse the literature and stay up to date using trusted resources. We need to explain clearly the challenge of balancing harm and benefit to our patients, friends and family. The COVID-19 pandemic is an opportunity to improve the health literacy of the public and to emphasise the principles of the quality use of medicines to ensure drugs are used safely and effectively. <

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ARTICLE

Penicillin – getting prescribing right for children

SUMMARY

Penicillins are commonly prescribed to children. Recommendations in the product information may not be the most appropriate doses for children and may list clinical indications that are preferably treated with other antibiotics.

Reputable guidelines, for example Therapeutic Guidelines: Antibiotic, offer up-to-date advice on optimal choice, route, dosage and duration of oral penicillins in children.

In most instances, the child's weight should be used to calculate the dose in mg per kg without exceeding the maximum adult dose.

When prescribing higher weight-based doses of amoxicillin or flucloxacillin, check the volume of oral liquid required to complete a treatment course to ensure adequate supply.

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Introduction

Rates of antibiotic prescribing and dispensing for infants and young children are higher than for any other age group under 65 years.[1] Penicillins such as amoxicillin and the combination amoxicillin/clavulanate are among the most commonly dispensed antibiotics in primary care.

When indicated, it is critical that the optimal antibiotic choice, dosage, regimen and duration are prescribed for children. Australian guidelines, including Therapeutic Guidelines: Antibiotic,[2] provide up-to-date recommendations for prescribing oral penicillins in children. GPs may instead choose to order the dose recommended in the product information as this is freely available online and integrated into many electronic prescribing systems.[3] However, recommendations in the product information may not be the most appropriate doses for children (see Box). It may only include indications and doses approved by the Therapeutic Goods Administration at registration. As most oral penicillin products in Australia have been used for more than 20 years and are generally off-patent, up-to-date dosing information may not be included in the product information, particularly for children.

Prescribing in children

Many childhood infections do not require antibiotics at all, including:

- common self-limiting infections
- viral infections
- bacterial infections that require drainage or other physical treatment (e.g. cutaneous abscess, dental infections requiring timely dental treatment).

Box Examples of prescribing pitfalls for oral penicillins in children

Amoxicillin

A 2-year-old child weighing 12 kg has mild–moderate pneumonia amenable to treatment with oral antibiotics. The dose recommended in Therapeutic Guidelines is 25 mg/kg/dose or 300 mg eight hourly.

The recommended dose in the product information would equate to 13.3 mg/kg/dose or 160 mg eight hourly. If this was followed the child would receive approximately half of the dose recommended by current guidelines.

Amoxicillin/clavulanic acid

A 5-year-old child weighing 20 kg has otitis media refractory to amoxicillin alone and is treated with amoxicillin/clavulanic acid. The dose recommended in Therapeutic Guidelines is a 7:1 ratio of 22.5 mg/kg of amoxicillin (450 mg) with 3.2 mg/kg clavulanic acid given 12 hourly.

The product information recommends the 4:1 formulation of amoxicillin:clavulanic acid at a dose of 13.3 mg/kg of amoxicillin (265 mg) and 3.3 mg/kg of clavulanic acid given eight hourly. This dosing and frequency is different from current guidelines and the excess clavulanic acid increases the risk of gastrointestinal adverse effects.

Flucloxacillin

A 3-year-old child weighing 15 kg is receiving oral flucloxacillin as step-down therapy for osteomyelitis after discharge from hospital. Therapeutic Guidelines recommend 25 mg/kg/dose or 375 mg six hourly.

The product information recommends 125 mg flucloxacillin six hourly which is approximately a third of the dose recommended in current guidelines.

Shared decision making with parents is an effective approach to appropriately using antibiotics and reducing antibiotic overuse.

'Children are not little adults' is a common comment from those working in paediatrics. The epidemiology, clinical presentation and prognosis of some infections differ in children compared to adults. Understanding this is key to timely diagnosis and good antimicrobial stewardship. In addition, pharmacokinetics can be different in children. This was evident with oral penicillins from the very beginning – gastric acid secretion, intestinal motility and drug pH all affect absorption. Depending on age and whether a child is unwell, these can result in net increased or decreased absorption compared to an adult. However, the magnitude of these effects are greatest during the first two years of life.[4]

In paediatric studies, dosage requirements often exceeded the expected dose for body size.[4,5] Direct comparisons between paediatric studies were complicated by incomplete information about the age or weight of patients, use of different product strengths, teaspoon measures, and the 'rounding' of doses for convenient administration.[4,6]

Empiric prescribing should ideally be based on the likely pathogen and the pharmacokinetics and pharmacodynamics of the antibiotic. Dosing information for children is included in Therapeutic Guidelines, the AMH Children's Dosing Companion, and guidelines from children's hospitals.

When a penicillin is required, it should be prescribed at doses that are expected to safely maximise the time that the drug remains above the minimum inhibitory concentration for the pathogen. If available, reviewing cultures and the results of susceptibility testing ensures the correct drug with the narrowest spectrum is used.

Narrow-spectrum penicillins are active against *Streptococcus pyogenes* (Group A streptococcus). Phenoxymethylpenicillin has been used extensively for erysipelas, streptococcal tonsillitis and dental infections that require antibiotics.

Amoxicillin is active against susceptible *Escherichia coli*. Adding the beta-lactamase inhibitor clavulanic acid increases the ability to treat certain Gram-negative organisms.

For *Streptococcus pneumoniae* infections (other than meningitis) with reduced susceptibility to penicillin, increasing the penicillin or amoxicillin dose may be effective. Using amoxicillin/clavulanic acid does not provide additional benefit in this case, as penicillin resistance in *Streptococcus pneumoniae* is not mediated by a beta-lactamase.[7] For mild to moderate pneumonia, oral amoxicillin is recommended in Therapeutic Guidelines at 25 mg/kg dose eight hourly and in World Health Organization guidelines[8] at 40 mg/kg 12 hourly. It is non-inferior to parenteral options for this condition.

Amoxicillin/clavulanic acid is appropriate for treating beta-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella catarrhalis*. If a higher amoxicillin dose is required, children aged two months and over should be prescribed a formulation with a lower dose of clavulanic acid.

Duration of therapy varies by indication. Many common, uncomplicated infections may be treated with shorter antibiotic courses than are commonly given.[9]

Dosing by age or weight – practical problems

In many instances it is unclear if dosing principles and recommended age bands in the product information are based on convenience or arise for other reasons – these fail to account for growth and metabolic development occurring within each age band. At the margins of age bands, for example at age six or 12 years, the average child[10] might receive phenoxymethylpenicillin doses that either exceed the maximum or fail to meet the minimum dose for weight. For amoxicillin, this leads to substantial differences for children slightly above or below 20 kg.

Dose ranges are further widened for patients at the lowest and highest percentile weights for age, most obviously among 10–14 year-olds where the difference between the 5th and 90th percentile is greatest. Achieving adequate drug concentrations in overweight and obese patients is an increasing concern in countries such as Australia where around a quarter of children and adolescents (5–17 years) fall into this category.[11] Doses based only on age may be sub-therapeutic and result in treatment failure and an increased risk of resistance, or be excessively large doses based on a higher age band.[12] In most instances, the child's weight should be used to calculate the dose in mg per kg without exceeding the maximum adult dose.

Volume and pack size

Discrepancies between the dose and duration recommended in the product information and guidelines introduce new problems.[13] Older children may need additional tablets, and younger children may need a larger volume of oral liquid compared to what is provided in standard packs.[14]

Phenoxymethylpenicillin

When phenoxymethylpenicillin became available, doses in the range of 60 to 120 mg 3–6 hourly were commonly used for adults.[15-17] Doses were generally halved for children, but for severe paediatric infections these half doses were often doubled.[17-19] In the Australian product information, the same general principles continue to apply, which allow for a wide dose range. Twice-daily doses of phenoxymethylpenicillin for tonsillitis in children are not listed in the product information, even though this simplified regimen is commonly prescribed and reportedly achieves similar outcomes.[20] Therapeutic Guidelines recommends 15 mg/kg (up to 500 mg) 12-hourly phenoxymethylpenicillin for pharyngitis or tonsillitis requiring antibiotics.

Amoxicillin

Recommendations in the product information for amoxicillin suspensions – 250 mg/5 mL and 125 mg/5 mL – are generally unchanged from doses used in trials conducted in the 1970s. Paediatric doses are provided only for children weighing less than 20 kg.[21] The product information recommends doses of 6.6 mg/kg eight hourly (20 mg/kg/day) with doubling of the dose for severe infections, for infections with less susceptible organisms or for lower respiratory tract infections. It is likely doses this low are often inadequate – data from the USA on acute otitis media suggest 83% of *Streptococcus pneumoniae* are susceptible to amoxicillin at 40 mg/kg/day.[22] Twice-daily dosing at 60 mg/kg/day (given as 30 mg/kg/dose up to a maximum of 1 g 12 hourly) is licensed for use in acute otitis media in Australia. Prescribing amoxicillin for neonates remains off label in Australia, as are higher amoxicillin doses even though they have been studied and licensed overseas.[23] Therapeutic Guidelines[2] recommends 15 mg/kg doses eight hourly for urinary tract infections (with susceptible organisms) and 25 mg/kg eight hourly for pneumonia.

Amoxicillin/clavulanic acid

Clavulanic acid (clavulanate), a beta-lactamase inhibitor, is added to an amoxicillin backbone. Paediatric formulations of this combination in a 7:1 ratio (400 mg:57 mg in 5 mL) provide a higher amoxicillin component for indications such as acute otitis media. This optimises efficacy and minimises diarrhoea associated with too much clavulanic acid.[24] Despite this, products with a greater proportion of clavulanic acid (4:1, 125 mg:31.25 mg in 5 mL) continue to be recommended for children in the product information.

Flucloxacillin

Approved indications in Australia for flucloxacillin include pneumonia, and skin and bone infections. For children, the product information recommends prescribing half or a quarter of the adult dose depending on age. In early studies, flucloxacillin doses of 12.5 mg/kg for children produced similar concentrations to adults given doses of 500 mg. However, neonates had higher absorption than older children,[25] and infants aged under six months had better absorption than older children with liquid formulations.[26] Higher doses and weight-based doses that are recommended in many guidelines for bone infections in children are not included in the product information.

Conclusion

Evidence supporting optimal penicillin prescribing remains limited for children compared to adults. Dose recommendations available in the product information provide guidance which has often been superseded by regularly updated, evidence-based sources, such as Therapeutic Guidelines.

Prescribers should have access to evidence and updated guidelines to make decisions for children. Cooperation between regulators, pharmaceutical companies and software vendors is needed to improve this and support appropriate use of penicillins and other antimicrobials in the community. <

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ARTICLE

Treatment of systemic lupus erythematosus

SUMMARY

Systemic lupus erythematosus should be suspected in individuals with one or more classic symptoms. Diagnosis is made clinically and supported by serology.

Reducing sun exposure is central to the management of lupus.

Hydroxychloroquine is first-line treatment unless contraindicated and is useful in almost all manifestations of lupus. Other treatments are titrated against type and severity of organ involvement.

Monoclonal antibodies have a limited role in the management of lupus.

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Introduction

Systemic lupus erythematosus (also known as lupus) is a chronic, relapsing-remitting autoimmune disease characterised by autoantibody production. It may present at any stage of life, but is most common in women of childbearing age, with a female to male ratio of 9:1. Lupus has a wide spectrum of presentations, including skin, psychiatric and kidney manifestations.

When to suspect lupus

Lupus should be considered in any individual with one or more typical manifestations, but especially women of childbearing age. Classic symptoms include photosensitive rash, mouth ulcers, small joint arthritis, or unexplained cytopenias and venous or arterial clotting. Serositis and neurologic involvement are observed less commonly (Box).[1]

How to confirm diagnosis

The variable manifestations of lupus make diagnosis difficult and serology can be useful (see Box). Almost all patients (99%) have antinuclear antibodies at diagnosis. However, they are nonspecific and present in approximately 5% of the healthy population at titres of 1:320.[2] More specific for lupus is the presence of anti-double-stranded DNA antibodies, particularly when detected by the radionucleotide Farr assay. These are observed in approximately 70% of patients with lupus.[3] Anti-Smith antibodies are uncommon but specific for lupus and associated with nephritis and cytopenias.[4] Antiphospholipid antibodies are found in 40% of patients and are classically associated with an elevated risk of thrombosis and miscarriage.[5] Antibodies against the extractable nuclear antigens Ro(SSA), La(SSB) and ribonuclear protein are common but nonspecific in the diagnosis of lupus.

Antinuclear antibodies combined with lupus-specific antibody positivity can support the diagnosis. These are incorporated in the Systemic Lupus International Collaborating Clinics diagnostic criteria (Box).[1]

Pathogenesis

The pathogenesis of lupus is a composite of complex genetic risk and environmental influences. While immunologic abnormalities ranging from complement to B-cell dysregulation are reported, increased type 1 interferon activity is observed in 85% of patients at any point in time.[6] This is central to the disease. Reflecting this complex pathogenesis, several distinct biologic pathways have been targeted in the treatment of lupus.

Management of lupus

The management of lupus includes three goals:

- preventing flares and their symptomatic impact
- reducing chronic accumulation of organ damage
- minimising toxicity from immunosuppression.

All patients should minimise sun exposure and use hydroxychloroquine unless contraindicated. For lupus activity that is resistant to these measures, antiproliferative immunosuppressants and corticosteroids are effective. The choice of antiproliferative is influenced by the organ involved. Cyclophosphamide is used for severe life- and organ-threatening lupus. Biologic drugs have a limited role but drugs such as rituximab may be used for manifestations refractory to other treatments.

Non-drug approaches

Ultraviolet exposure can flare both cutaneous and systemic symptoms such as arthritis. Sunscreens (SPF 50+) should be used as well as avoiding exposure during peak hours.[7]

Smoking cessation may help with treatment-resistant skin lesions.[8] It may also mitigate the elevated cardiovascular risk associated with lupus.[9]

Box **Diagnostic criteria for systemic lupus***

Clinical criteria

Acute cutaneous – lupus malar rash, bullous lupus, toxic epidermal necrolysis variant of lupus, maculopapular lupus rash, photosensitive lupus rash

Chronic cutaneous – discoid lupus rash, hypertrophic (verrucous) lupus, lupus panniculitis, mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus

Oral or nasal ulcers – palate, buccal, tongue, or nasal in the absence of other causes

Non-scarring alopecia – in the absence of other causes

Arthritis – synovitis involving 2 or more joints, characterised by swelling or effusion or tenderness in 2 or more joints and at least 30 minutes of morning stiffness

Serositis – typical pleurisy for more than one day, pleural effusions, pleural rub or typical pericardial pain for more than one day, pericardial effusion, pericardial rub or pericarditis by ECG

Renal involvement – urine protein:creatinine ratio or 24-hour urine protein with >500 mg protein/24 hours or red cell casts

Neurological symptoms – seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, acute confusional state

Haemolytic anaemia – in the absence of other causes

Leucopenia – in the absence of other causes

Thrombocytopenia – in the absence of other causes

Immunological criteria

Antinuclear antibodies

Anti-dsDNA antibodies – above reference range (or >2-fold if tested by ELISA)

Anti-Smith antibodies

Antiphospholipid antibodies – positive lupus anticoagulant, false-positive rapid plasma reagin test, medium- or high-titre cardiolipin antibody, positive anti-b2-glycoprotein

Low complement C3, C4, CH50

Positive Direct Coombs test – in the absence of haemolytic anaemia

* For a positive diagnosis, patients must have 4 or more of the listed criteria, with at least 1 clinical and 1 laboratory criterion

dsDNA double-stranded DNA

ELISA enzyme-linked immunosorbent assay

Source: reference 1

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective for symptom relief in lupus-associated arthritis and myalgias.[10] However, they increase the risk of allergic reactions[11] and aseptic meningitis.[12] In the presence of lupus nephritis, they increase the risk of acute kidney injury[13] and death when used in patients with end-stage kidney disease.[14]

Hydroxychloroquine

Hydroxychloroquine should be used in all patients with lupus unless contraindicated. It is an antimalarial drug that inhibits toll-like receptors 7 and 9. These are potent drivers of type 1 interferon production.[15] Hydroxychloroquine is useful in both cutaneous and systemic lupus. Approximately half of patients with cutaneous lupus fail to respond to standard doses (200 mg daily) and may benefit from higher doses (400 mg daily).[16] In addition to improving skin symptoms, hydroxychloroquine reduces flares of systemic lupus[17] and lupus nephritis.[18] It also lowers cholesterol and thromboembolic risk in patients with antiphospholipid antibodies.[19,20] Consequently, sustained hydroxychloroquine therapy minimises accrual of organ damage[21] and glucocorticoid-induced osteoporosis, and improves overall survival.[22]

The major complications of hydroxychloroquine therapy are ocular. Transient and reversible corneal deposits occur in about 10% of people.[23] Irreversible retinopathy can also develop and typically manifests as visual disturbances, photophobia or light flashes. The risk of retinal toxicity is cumulative and may be as high as 20% at 20 years with recommended hydroxychloroquine doses.[24] A maximal daily hydroxychloroquine dose of less than 5 mg/kg (up to 400 mg/day) is recommended, along with regular screening by an ophthalmologist to detect toxicity before visual changes (Table 1).[24-26] Less common adverse effects include cardiac, cutaneous and neuropsychiatric manifestations.[27] Hydroxychloroquine is safe to use in pregnancy and should be continued.[28]

Corticosteroids

Almost all patients will be treated with corticosteroids at some point.[29] They are effective in controlling systemic lupus but their sustained use is limited by substantial toxicity. Corticosteroids are used transiently to control systemic disease flares or when disease activity cannot be controlled by other drugs alone. Due to toxicity, they should never be used on their own.

The adverse effects are dose-dependent and include an increased risk of infection, cancer, osteoporosis and avascular necrosis, steroid-induced diabetes, accelerated atherosclerosis and mood disturbances.[30] Cardiovascular risk is significantly increased in lupus and the use of corticosteroids increases this further.[31] Indeed, no study has established a safe lowest dose in systemic lupus so when possible they should be withdrawn.[32]

The toxicity of corticosteroids needs to be balanced against the threat of organ injury if they are not used. For mild disease, lower doses are often sufficient. High doses are typically reserved for debilitating or life-threatening involvement such as lupus nephritis or neuropsychiatric lupus (Table 2).[33] Once disease remission is achieved, the dose should be tapered.

For cutaneous lesions, topical corticosteroids are the mainstay of treatment. Higher potency creams have superior efficacy over low-potency creams.[34] However, they increase the risks of telangiectasia and skin atrophy and are used intermittently depending on the severity and location of the lesions. Topical steroids are useful for mouth ulcers but increase the risk of candidiasis.

Table 1 **Monitoring for patients receiving lupus treatments**

Drug	Monitoring
Hydroxychloroquine	Baseline fundal exam of the eye, then annual screening after 5 years treatment[24]
Corticosteroids	Baseline and annual bone densitometry[3] Annual diabetes check[3,25] Periodic ophthalmology review for cataracts and glaucoma
Azathioprine	TMPT activity before starting treatment Full blood count at 2–4 weeks for 2–3 months, then every 3 months
Methotrexate	Full blood count and liver function test every 2–4 weeks for 3 months, then every 2–3 months until 6 months. Monitor every 3 months when patient is stable[7,26]
Mycophenolate	Full blood count at 2–4 weeks, then every 3 months
Cyclophosphamide	Full blood count every 2 weeks for a month, then monthly
Rituximab	Optional: check CD19+ B cells to confirm depletion

TMPT thiopurine methyltransferase

Table 2 **Steroid doses and indications in lupus**

EULAR grading	Dose: prednisolone equivalent (mg)	Typical indications	Duration and tapering
Low dose	<7.5	Maintenance	If starting on low dose, give for 2–4 weeks. Tapering not required
Medium dose	7.5–30	Mild disease: cutaneous, musculoskeletal, haematological, or constitutional symptoms	Medium–high dose for 2–4 weeks then taper over 1–2 months
High dose	30–100	Induce remission of severe disease	
Very high dose	>100		
Pulse therapy	>250		

EULAR European League Against Rheumatism
Source: reference 33

Antiproliferative drugs

Three antiproliferative immunosuppressants are primarily used in systemic lupus – azathioprine, methotrexate and mycophenolate. For non-renal manifestations such as arthritis and rash where hydroxychloroquine or topical corticosteroids are insufficient, methotrexate is effective.[35] While evidence is stronger for methotrexate, azathioprine is also useful and has the benefit of being safe in pregnancy. Thiopurine methyltransferase activity should be tested before azathioprine is used to avoid bone marrow suppression in patients with a deficiency.

Mycophenolate is effective in non-renal disease that is refractory to corticosteroids,[36] and is superior to azathioprine.[37] However, it is contraindicated in pregnancy. For systemic lupus with kidney involvement, mycophenolate is superior to azathioprine so it is first-line maintenance therapy when tolerated.[38]

Cyclophosphamide

Cyclophosphamide is an alkylating drug that is beneficial in treating severe lupus. Oral regimens result in higher cyclophosphamide exposure and carry a greater risk of infection and bone marrow suppression than the intravenous preparation. High-dose mycophenolate is as effective as cyclophosphamide in controlling aggressive nephritis and is increasingly used as first-line therapy[38] given the lower rates of hair loss and infertility.

Biologic drugs

A range of new biological therapies has been investigated in patients with lupus. Many have not shown significant benefit to date.[39-48]

Rituximab

Rituximab is a B-cell depleting antibody against CD20. Despite initial reports of excellent responses to this drug, trials have failed to show a benefit in non-renal[39] and renal lupus.[40] However, it continues to be used in refractory disease and registry data suggest a benefit.[49,50]

Belimumab

Belimumab antibody inhibits B-cell activating factor (BAFF). This target has shown significant pre-clinical promise given its role in promoting autoreactive B-cell activation and proliferation.[51] Two multicentre trials, BLISS-52[43] and BLISS-76,[44] assessed the efficacy of belimumab at 52 and 76 weeks. While reaching statistical significance, both trials observed a modest reduction in overall disease activity at 52 weeks and no significant benefit at 76 weeks. The benefit was largely due to improvements in musculoskeletal and cutaneous symptoms.[52] Its role is in non-renal disease that is unresponsive to conventional drugs.

Anifrolumab

Anifrolumab blocks the interferon alpha receptor 1. Initial lupus studies observed benefits in disease activity. However, placebo-controlled trials (TULIP 1 and TULIP 2) failed to demonstrate benefit when conventional measures of lupus activity were used, and only marginally significant benefit when modified lupus scores were used.[53,54]

Pregnancy

Pregnancy can present challenges in women with lupus, so pregnancy planning and counselling are important.[55] Fertility rates are normal in lupus, unless compromised by cyclophosphamide[56] or worsening renal failure. Recent evidence is conflicting regarding increased disease flares during pregnancy.[57,58] However, the risks of pre-eclampsia[59] and miscarriage[60] are significantly higher. Secondary antiphospholipid syndrome confers added perinatal risk warranting specialist care.

When treating pregnant women, corticosteroids and azathioprine are generally safe. Mycophenolate, methotrexate and cyclophosphamide are contraindicated in pregnancy. Cyclophosphamide should be stopped three months before attempting to conceive and both men and women receiving cyclophosphamide should be on appropriate contraception. Egg harvesting or sperm banking should be considered before treatment.

Conclusion

Lupus has a wide range of clinical manifestations and should be considered as a diagnosis when two or more symptoms occur in women of childbearing age. All patients should receive hydroxychloroquine with appropriate monitoring. Antiproliferative drugs are useful for maintenance therapy, while high-dose steroids and cyclophosphamide are reserved for severe disease. The role of biologic drugs is an area of ongoing research. <

Conflict of interest: none declared

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ARTICLE

Lithium therapy and its interactions

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SUMMARY

Lithium is one of the most effective mood stabilisers for people with a mood disorder. However, many of these patients are also taking other medicines that could potentially interact with lithium.

To minimise the risk of relapse, it is usually necessary to maintain the lithium serum concentration between 0.6 mmol/L and 0.8 mmol/L.

Lithium clearance is easily influenced by drugs that alter renal function such as ACE inhibitors, angiotensin receptor antagonists, diuretics, and non-steroidal anti-inflammatory drugs.

It is therefore prudent for prescribers to monitor and adjust the lithium dose to avoid adverse effects or loss of efficacy.

Keywords
bipolar disorder, lithium, mood disorders

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Introduction

Driven by new research reinforcing the unique benefits of lithium, there has been a worldwide resurgence in the prescription of lithium. In clinical practice it is used predominantly to stabilise mood.[1] It remains one of the most effective options for bipolar disorder,[2] along with the newer atypical antipsychotics.[3] Lithium also serves as an effective adjunctive option for recurrent or resistant major depressive disorder and has anti-suicidal properties which are invaluable in the management of mood disorders.

Lithium is simple to administer and is usually well tolerated. Routine management of patients receiving lithium monotherapy is relatively straightforward.[4] However, complications can arise when other drugs are added that could potentially interact with lithium.

Regular monitoring of lithium plasma concentrations and other safety parameters is essential. Results should be communicated to the patient and everyone involved in their care. Aids are available to assist prescribers with lithium management, including an Australian tool called the 'Lithiumeter'.[4]

Indications for lithium

Patients with classic, episodic and remitting bipolar disorder with a family history and no psychiatric comorbidity are most likely to respond to lithium. Typically, lithium is effective in about a third of patients – with response rates up to two-thirds in those whose relatives have achieved good responses.[5] It is likely that people who commence lithium early in the course of their illness may have greater likelihood of response. In major depressive disorder, lithium is used to augment antidepressant drugs.

Lithium monitoring

Lithium has a very narrow therapeutic window for maintenance therapy. Too little lithium risks undertreatment of the mood disorder and increases the risk of relapse. Too much lithium increases the risk of both acute and chronic toxicity. Lithium concentrations should always be measured 12 hours after the last dose.

For the maintenance phase of treatment, recent guidelines recommend that patients maintain a serum concentration of 0.6–0.8 mmol/L to maximise therapeutic benefit.[6] For acute treatment in mania, serum concentrations should be increased to 0.6–1.0 mmol/L as tolerated. In depression, concentrations can be in the range of 0.4–0.8 mmol/L. In practice, target concentrations and monitoring practices are often inconsistent. Not all pathology laboratories use the same reference ranges, therefore noting whether the lithium concentration is consistent with the patient's presentation and the guidelines is essential.

As a part of optimising lithium dosing, clinicians may notice that a specific concentration achieves the most therapeutic benefit during euthymic periods and during manic and depressive episodes. Taking note of this is essential and helps to ensure stability of these patient-specific concentrations over time, particularly during each illness phase.

Maintenance of the therapeutic concentration (and adherence) is the strongest predictor of long-term stability. However, in some patients, stabilising their mood is not always possible with lithium alone. A trial with other mood stabilisers, such as adjunctive sodium valproate or an atypical antipsychotic, is often necessary.

Box Monitoring schedule for lithium therapy

Baseline assessments and follow-up of patients should be performed:

- during the early maintenance phase (e.g. baseline, 7 days, 14 days and 28 days) then at 3, 6 and 12 months, then annually

and

- when there are any changes in presentation
- following abnormal findings
- when altering the treatment regimen.

Regularly check the following:

- serum lithium concentrations and mood and stability over time
- renal function
  - electrolytes, urea, creatinine
  - estimated glomerular filtration rate
- thyroid and parathyroid function
  - thyroid stimulating hormone
  - calcium
- blood and cardiometabolic tests
  - full blood count, glucose, lipids, liver function tests
  - ECG
  - weight, BMI, umbilical girth
  - diet and eating behaviour
  - exercise and hydration
  - other comorbidities
- adverse effects
- cognition
- global functioning
- treatment adherence

Based on reference 4

Table Major adverse effects of lithium therapy

Toxicity	Adverse effect	Action
Acute	Any acute adverse effect or presentation	Measure lithium concentration
	Headache, fatigue	Consider stopping lithium
	Thirst, taste	Review medication
	Arrythmias	Hospitalisation
	Nausea, vomiting, diarrhoea, polyuria	Review hydration and consider haemodialysis
	Tremor	Monitoring and review medication
Chronic	Cognitive effects, ataxia, agitation, confusion, sluggishness	Monitor changes, optimise lithium concentrations, neurological referral
	Thyroid or parathyroid dysfunction	Monitor changes, optimise lithium concentrations, endocrinology referral
	Renal dysfunction	Monitor changes, optimise lithium concentrations, nephrology referral

A recommended monitoring schedule for lithium in a patient not taking other drugs is outlined in the Box.[4] Drug interactions are more likely to affect patients as they get older because of declining renal function and the accumulation of medical comorbidities. Close monitoring and dose adjustments are therefore often needed as patients get older.

In patients taking concomitant drugs, extra care should be taken because of the risk of drug interactions. Lithium concentrations should be closely monitored around the time of medication changes – at least just before and when the drugs have reached steady states. Lithium's half-life is about 24 hours, so a steady state is usually achieved after 5–7 days. A complete list of lithium drug interactions can be found at MIMS Online or Drugs.com.

Regular monitoring is required until a therapeutic concentration of lithium is reached and maintained, and any time that the patient presents with symptoms of lithium toxicity.[7] Conditions leading to haemodynamic and volume changes such as dehydration, febrile illness, gastrointestinal loss, drug interactions, perioperative management and surgery can affect lithium serum concentrations and levels should be rechecked in these circumstances.

Prescribers should contact the treating psychiatrist or consult a medicines information pharmacist if they are unsure how to manage a patient. Having up-to-date serum lithium concentrations at hand will assist.

Adverse effects of lithium

Regular long-term monitoring of lithium concentrations is essential to avoid both acute and chronic toxicity. Physical examinations and laboratory investigations should be performed at baseline and regular intervals after that (see Box).

Common acute adverse effects include tremor, polydipsia, polyuria, dysgeusia, nausea and diarrhoea (see Table). Prescribers can reassure patients that these adverse effects are usually transient after starting treatment. They are often dependent on the serum concentration of lithium and frequently subside within days or weeks. Nephrogenic diabetes insipidus (polyuria and polydipsia) is a common adverse effect of lithium.

Chronic adverse effects include subjective cognitive effects, thyroid and parathyroid dysfunction, and renal dysfunction (see Table). Some patients may report more mild neurocognitive effects such as 'brain fog', 'emotional greying', 'slowing', 'shakiness', anomia, and 'reduced creativity'. The higher the lithium concentration, the greater the risk of toxic presentations. In the long term, or with higher blood concentrations or repeated acute fluctuations, lithium leads to end-stage renal failure in 1% of patients (over 15 years treatment).[8] However, it should be noted that most patients do not experience renal adverse effects.

Common drug–drug interactions with lithium

The most common and noteworthy drug–drug interactions with lithium are pharmacokinetic in nature. The lithium ion is extensively absorbed in the gastrointestinal tract. The main determinant of serum concentrations is renal excretion, therefore the main drug interactions occur when co-administered drugs alter renal function, specifically modifying glomerular filtration and tubular reabsorption.

The most commonly prescribed drugs that have the potential to interact with lithium are ACE inhibitors, angiotensin II receptor antagonists (sartans), diuretics, and non-steroidal anti-inflammatory drugs (NSAIDs). Combinations of these are frequently used, so prescribers should be aware of their additive effects for a patient taking lithium.

ACE inhibitors and angiotensin II receptor antagonists

Several case reports and hospital admission studies have shown that ACE inhibitors and angiotensin II receptor antagonists can increase lithium serum concentrations and increase the chance of toxicity. Closer monitoring of lithium concentrations is needed when people start either of these drugs and the lithium dose will probably need to be reduced until a stable therapeutic concentration has been achieved. Closer monitoring is also required when these drugs are stopped.

Diuretics

When any diuretic is used, lithium concentrations must be carefully monitored. Thiazide and thiazide-like diuretics increase sodium reabsorption which decreases the clearance of lithium and significantly elevates lithium concentrations in serum. This is enough to fall out of the therapeutic range in many cases. As a rule of thumb, many prescribers halve the lithium dose then up- or down-titrate the dose with monitoring. Other prescribers avoid thiazide diuretics altogether.

Amiloride is recommended as a diuretic because it blocks entry of lithium through the epithelial sodium channel in the collecting duct. This reduces lithium accumulation and may improve kidney function in patients on long-term treatment.[9]

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.

Non-steroidal anti-inflammatory drugs

Patients on lithium therapy should be advised to avoid NSAIDs. Regular use is more problematic than episodic use. NSAIDs differentially alter lithium concentrations by multiple mechanisms, and one of these is to reduce prostaglandin E2 by inhibiting cyclo-oxygenase. This reduces vasodilation of the afferent arteriole which decreases blood flow to the glomerulus. This decreases glomerular filtration and consequently lithium excretion. If NSAIDs are indicated, they should be used under medical guidance with closer monitoring of lithium concentrations. Lower lithium doses may be required.

Other drugs

Acetazolamide for intraocular pressure, glaucoma and epilepsy has been shown to significantly increase lithium clearance.

Conclusion

Lithium has an important role in the treatment of mood disorders. Prescribers need to be mindful of its potential drug interactions and the impact they can have on patients. Improved knowledge of and confidence with monitoring will contribute to better patient outcomes. <

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NEW DRUGS

New drugs

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Abemaciclib

Approved indication: breast cancer

Verzenio (Eli Lilly)

50 mg, 100 mg and 150 mg tablets

Like palbociclib and ribociclib, abemaciclib is a small-molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6. These kinases are involved in cell cycle progression and are often overexpressed in hormone receptor positive (HR+) breast cancers. Blocking them leads to cell cycle arrest, senescence and apoptosis.

Abemaciclib is specifically indicated for HR+/human epidermal growth factor receptor 2 negative (HER2–) locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant. It can be given as initial endocrine-based therapy, or after previous endocrine therapy. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone agonist.

Abemaciclib has been assessed in three clinical trials of women with HR+/HER2– advanced breast cancer: MONARCH 1, 2 and 3 (see Table). MONARCH 1 was a single-arm, phase II trial in women who had failed two endocrine therapies and had already had 1–2 chemotherapy regimens. Women received abemaciclib monotherapy 200 mg twice daily.

At 12 months, the objective response rate was 19.7% (all partial responses), median progression-free survival was six months and the median overall survival was 17.7 months (see Table).[1]

The MONARCH 2 trial was a double-blind, phase III trial in 669 women who had progressed during endocrine therapy but had not received chemotherapy. They were randomised to receive fulvestrant in combination with abemaciclib (150 mg twice daily) or placebo. Median progression-free survival was significantly longer with abemaciclib than with placebo (16.4 vs 9.3 months)[2] as was median overall survival (46.7 vs 37.3 months).[3] The corresponding objective response rates were 35.2% and 16.1%.

MONARCH 3 was another double-blind, phase III trial. The 493 women enrolled had not received previous systemic therapy and most had metastatic disease at baseline. They were randomised to an aromatase inhibitor (anastrozole or letrozole) plus abemaciclib (150 mg twice daily) or placebo. Median progression-free survival was significantly longer with abemaciclib than with placebo (28.2 vs 14.7 months). The corresponding objective response rates were 48.2% versus 34.5%.[4]

The most common adverse effects with abemaciclib include diarrhoea (84.6% of patients), neutropenia (45.1%), nausea (43.5%), infections (43.6%),

Table **Efficacy of abemaciclib in HR+/HER2– advanced breast cancer**

Trial	Daily treatment	No. of patients	ORR	Median progression-free survival	Median overall survival
MONARCH 1[1]	abemaciclib monotherapy	132	19.7%	6 months	17.7 months
MONARCH 2[2,3]	abemaciclib + fulvestrant	446	35.2%	16.4 months	46.7 months
	placebo + fulvestrant	223	16.1%	9.3 months	37.3 months
MONARCH 3[4]	abemaciclib + aromatase inhibitor*	326	48.2.%	28.2 months	–
	placebo + aromatase inhibitor*	162	34.5%	14.7 months	–

* anastrozole or letrozole
HR+ hormone receptor positive
HER2– human epidermal growth factor receptor 2 negative
ORR objective response rate estimated as the total number of complete and partial responses divided by the number of patients

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.

fatigue (40.5%), anaemia (30.1%) and vomiting (27.7%). Hair loss occurred in 20.7% women. Hepatotoxicity and venous thromboembolism were also reported in the trials.

Diarrhoea was serious in 11.7% of cases. Onset was 6–8 days after the start of treatment and severe cases lasted for about a week. If this occurs, the abemaciclib dose should be interrupted until symptoms resolve. Fluids and an antidiarrhoeal medicine such as loperamide are recommended.

Neutropenia was serious in 28% of patients who were taking abemaciclib and fulvestrant, and fatal cases have occurred. Onset was a month after the start of treatment. Blood counts should therefore be measured at baseline and then monitored regularly.

Dose reduction or interruption may be required with serious adverse effects such as diarrhoea and haematologic and liver toxicities. As with other drugs in this class, abemaciclib can cause interstitial lung disease. In serious cases, the drug should be permanently discontinued.

The recommended starting dose of abemaciclib is 150 mg twice daily in combination with endocrine therapy. As the drug is metabolised in the liver, the dose should be reduced to one tablet a day in those with severe liver impairment. After oral administration, peak plasma concentrations are reached within eight hours and repeated dosing results in steady-state concentrations after five days. Abemaciclib's elimination half-life is 25 hours and most of the dose is excreted in the faeces.

Abemaciclib is metabolised by cytochrome P450 (CYP) 3A so concurrent use of strong inhibitors (e.g. clarithromycin, itraconazole, ketoconazole) and inducers (e.g. carbamazepine, rifampicin, St John's wort) is best avoided. If co-administration of a strong inhibitor cannot be avoided, the abemaciclib dose should be reduced.

Abemaciclib prolongs progression-free survival when used in combination with fulvestrant or an aromatase inhibitor in women with advanced HR+/HER2– breast cancer. As with palbociclib and ribociclib, diarrhoea is very common and may limit treatment. Severe neutropenia does not seem to be as common with abemaciclib as it was with palbociclib.

T manufacturer provided 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

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First published 24 April 2020

Acalabrutinib

Approved indication: mantle cell lymphoma, chronic lymphocytic leukaemia

Calquence (AstraZeneca)
100 mg capsules

Acalabrutinib is an oral small-molecule drug similar to ibrutinib for B-cell malignancies. It works by binding to Bruton's tyrosine kinase and blocking signalling through the B-cell receptor and cytokine receptor pathways. This inhibits the proliferation of B cells.

This drug is indicated for mantle cell lymphoma and chronic lymphocytic leukaemia. (The approval for mantle cell lymphoma is provisional pending more trials.) The recommended dose is one capsule twice a day as monotherapy. For chronic lymphocytic leukaemia acalabrutinib can also be given in combination with obinutuzumab.

Mantle cell lymphoma

The efficacy of acalabrutinib 100 mg twice daily was investigated in an open-label, single-arm, phase II trial of 124 patients with relapsed or refractory mantle cell lymphoma. All participants had been previously treated and some had had a stem cell transplant. After a median of 15.2 months, 81% of patients had responded to treatment and 40% had a complete response. The estimated overall survival rate at 12 months was 87%.[1]

Chronic lymphocytic leukaemia

The approval of acalabrutinib for chronic lymphocytic leukaemia appears to be based on two phase III, open-label trials that have not yet been published in full. One of the trials enrolled people with previously untreated disease. They were randomised to acalabrutinib plus obintuzumab, acalabrutinib monotherapy or chlorambucil plus obinutuzmab. After a median follow-up of 28.3 months, there was less progressive disease and fewer deaths in the acalabrutinib groups than in the comparator group (see Table).

The other trial assessed efficacy in patients with relapsed or refractory disease. They received acalabrutinib monotherapy or the investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab. After a median follow-up of 16.1 months, there was less disease progression with acalabrutinib than with the comparator, but the number of deaths were similar (see Table).

Pharmacology and drug interactions

Following oral administration, peak plasma concentrations of acalabrutinib and its active metabolite (ACP-5862) are reached within an hour. The median terminal half-life of the active metabolite is 6.9 hours and most of the dose is excreted in the

Table **Efficacy of acalabrutinib in chronic lymphocytic leukaemia***

Patients with previously untreated disease			
	Acalabrutinib plus obintuzumab (179 patients)	**Acalabrutinib monotherapy (179 patients)**	**Chlorambucil plus obinutuzumab (177 patients)**
Progressive disease	5%	11.2%	46.3%
Death	2.8%	3.4%	6.2%
Estimated progression-free survival at 24 months	92.7%	87.3%	46.7%
ORR	93.9%	85.5%	78.5%
Patients with relapsed or refractory disease			
	Acalabrutinib monotherapy (155 patients)	**Investigator's choice† (155 patients)**	
Progressive disease	12.3%	38.1%	
Death	5.2%	5.8%	
Estimated progression-free survival at 15 months	82.6%	54.9%	
ORR	81.3%	75.5%	

* based on data in the product information
† idelalisib plus rituximab or bendamustine plus rituximab
ORR objective response rate estimated as the number of complete and partial responses divided by the total number of patients

faeces. The drug is mainly metabolised by cytochrome P450 (CYP) 3A enzymes so co-administration with strong CYP3A inhibitors (e.g. itraconazole) and inducers (e.g. rifampicin) increase the risk of toxicity or reduce the efficacy of acalabrutinib and should be avoided. Dose adjustment of acalabrutinib may be needed with moderate CYP3A inhibitors such as erythromycin. Drugs that increase the pH of the stomach can decrease acalabrutinib concentrations. Proton pump inhibitors should be avoided and H_2-receptor antagonists should only be used two hours after the acalabrutinib dose. Antacids should be dosed separately by at least two hours.

Adverse events

The most common adverse effects with acalabrutinib in the trials included headache (22–40% of patients), diarrhoea (18–39%), fatigue (10–28%), muscle pain (15–37%) and bruising (12–34%). Cytopenias were very common and included neutropenia (21%), anaemia (10%) and thrombocytopenia (7%). Serious bleeding occurred in 3.6% of patients receiving acalabrutinib and one patient died. Concomitant use of antithrombotic drugs should therefore be avoided with acalabrutinib.

Atrial fibrillation was a concerning adverse effect with the related drug ibrutinib. In the combined safety cohort of the acalabrutinib trials, 1% of patients had grade 3 atrial fibrillation and 3% had milder events. ECG is recommended if patients develop palpitations, dizziness, syncope, chest pain or dyspnoea.

Infections were frequently reported in the chronic lymphocytic leukaemia trials and affected 57–69% of patients receiving acalabrutinib. Pneumonia was the most commonly reported serious infection. Hepatitis B reactivation and progressive multifocal leukoencephalopathy have also occurred with acalabrutinib.

Conclusion

Acalabrutinib seems to benefit patients with mantle cell lymphoma and chronic lymphocytic leukaemia. For both indications, over 80% of patients in the trials responded to treatment. In chronic lymphocytic leukaemia, acalabrutinib was associated with longer progression-free survival compared to the comparator treatments. It is not yet clear if the drug improves overall survival. Adverse effects are common and sometimes serious so may limit treatment.

T manufacturer provided the AusPAR and 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 and the Therapeutic Goods Administration.

NEW DRUGS

Aust Prescr 2020;43:98–9
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First published 24 April 2020

Ceftazidime/avibactam

Approved indication: specified infections

Zavicefta (Pfizer)
vials containing 2000 mg/500 mg as powder for reconstitution

Bacterial resistance to cephalosporins is increasing. The bacteria produce beta-lactamase enzymes which reduce the efficacy of beta-lactam antibiotics, such as penicillins and cephalosporins. Combining the antibiotic with an inhibitor of beta-lactamase can help to overcome bacterial resistance. One example is the combination of amoxicillin and clavulanic acid. Similarly, ceftazidime pentahydrate has been combined with the beta-lactamase inhibitor avibactam sodium. This combination aims to overcome resistance in serious infections caused by organisms such as the Enterobacteriaceae and *Pseudomonas aeruginosa*.

The formulation of ceftazidime and avibactam has to be reconstituted with water and then added to an infusion bag. This solution is then infused intravenously over two hours. The infusion is repeated every eight hours with the recommended duration of treatment being guided by the type of infection.

The activity of the combination is correlated with the concentration of free drug. The penetration of ceftazidime across the blood–brain barrier is poor, but this increases if the meninges are inflamed. Ceftazidime can cross the placenta and is excreted in breast milk. There is some evidence of reproductive toxicity with avibactam in animal studies.

The combination has a half-life of approximately two hours. Both components are excreted unchanged into the urine. Dose adjustment is required in patients with moderate or severe renal impairment.

An open-label trial assessed the efficacy of the combination of ceftazidime with avibactam in treating infections caused by Gram-negative bacteria resistant to ceftazidime. The 333 patients in the study mainly had complicated infections of the urinary tract, such as pyelonephritis, but some had complicated intra-abdominal infections. They received either the combination or the best available therapy, for example a carbapenem such as meropenem. When assessed 7–10 days after the final infusion there was a clinical cure in 91% of each treatment group.[1]

The double-blind RECLAIM trials compared ceftazidime/avibactam plus metronidazole to meropenem. RECLAIM 1 and 2 randomised 1066 patients with complicated intra-abdominal infections requiring surgical intervention or percutaneous drainage. It was possible to isolate the pathogens in 823 patients. In 111 patients there was a ceftazidime-resistant aerobic Gram-negative organism. When the 823 patients were assessed 28–35 days after randomisation there had been a cure in 81.6% of those treated with the combination and metronidazole compared with 85.1% of the meropenem group. The outcomes were similar in the patients with ceftazidime-resistant Gram-negative infections – 83% (39/47) versus 85.9% (55/64).[2]

A similar trial, RECLAIM 3, involved 441 patients in Asia. When they were evaluated 28–35 days after randomisation the proportion with a clinical cure was almost the same for the combination plus metronidazole as it was for meropenem (93.8% vs 94%). In 239 cases, the cause of the complicated intra-abdominal infection was identified as one of the Enterobacteriaceae. These patients were analysed in an intention-to-treat group. The clinical cure rate in this group was 83.2% with the combination plus metronidazole, and 88.8% with meropenem.[3]

The combination was also compared with meropenem in a study of nosocomial pneumonia. The double-blind REPROVE trial involved 817 patients including 246 with ventilator-associated pneumonia. Gram-negative bacteria, such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, were identified in 355 patients. In the patients who were clinically evaluable 21–25 days after randomisation there was a clinical cure in 77.4% (199/257) of the combination group and 78.1% (211/270) of the meropenem group. For an intention-to-treat population the corresponding results were 68.8% (245/356) and 73% (270/370). There were 38 deaths (9%) in the patients treated with ceftazidime/avibactam and 30 (7%) in the meropenem group.[4]

Ceftazidime/avibactam has been compared with doripenem, another carbapenem, in the treatment of complicated urinary tract infections, such as pyelonephritis. The two double-blind RECAPTURE trials randomised 1033 patients including 810 with identified bacteria. *Escherichia coli* was the most frequently isolated organism. The bacteria were resistant to ceftazidime in 19.6% of the patients. After five days of treatment, symptoms had resolved in 70.2% of the combination group and 66.2% of the doripenem group. At 21–25 days after randomisation infection had been eradicated in 77.4% of the patients treated with the combination and 71% of those infused with doripenem. The clinical cure rates were identical (89.3%) in the patients infected with ceftazidime-resistant bacteria.[5]

As ceftazidime has been available for many years its adverse effects such as hypersensitivity are well known. It is not yet clear what additional adverse effects the combination with avibactam may have. Based on analysis of 2024 patients who received ceftazidime/avibactam in clinical trials, adverse events were reported in 49.2%. Not considering deaths due to disease progression, 2% died with most deaths occurring in patients with pneumonia.[4] Common adverse effects include nausea, vomiting and diarrhoea. Some cases of diarrhoea may be associated with *Clostridioides difficile*.

Adding avibactam extends the range of bacteria that can be treated with ceftazidime. As it is important to reserve antibiotics against resistant bacteria, the use of ceftazidime/avibactam should be limited to the conditions studied in the trials. The combination has therefore been approved for complicated urinary tract infections, hospital-acquired pneumonia, and complicated intra-abdominal infections in combination with metronidazole. Although the overall outcomes were statistically non-inferior to meropenem for intra-abdominal infections, there was a trend favouring meropenem in patients with moderate renal impairment.[2] Close monitoring of renal function will be needed. It is important to remember that the combination will have little activity against Gram-positive bacteria.

T manufacturer provided the product information

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

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NEW DRUGS

Isavuconazole

Aust Prescr 2020;43:100-101
https://doi.org/10.18773/austprescr.2020.035

Approved indication: invasive fungal infections

Cresemba (Pfizer)
100 mg capsules, vials containing 200 mg powder for injection

Isavuconazole, which comes in the form of a prodrug isavuconazonium sulfate, is a triazole antifungal indicated for adults with invasive aspergillosis. It is also approved for the rare condition of invasive mucormycosis when amphotericin B is not appropriate. Like other drugs in the class, it works by inhibiting the synthesis of ergosterol which is an essential part of the fungal cell membrane.

The approval of isavuconazole is based on two main clinical studies – the SECURE trial[1] and the VITAL trial.[2] The SECURE trial was a phase III non-inferiority study comparing isavuconazole with voriconazole. It enrolled patients with invasive fungal disease mainly caused by *Aspergillus* species (e.g. *A. fumigatus, A. flavus, A. niger* and *A. terreus*). Some patients had other fungi isolated including unidentified filamentous fungi. Over 80% of the patients had a haematological malignancy, 20% had had a stem cell transplant and 66% had neutropenia at baseline.

Patients randomised to isavuconazole (n=258) were started on the intravenous formulation (200 mg three times a day), then continued or switched to capsules (200 mg daily) on the third day. Patients assigned to voriconazole (n=258) were given the drug intravenously on days one and two (6 mg/kg twice daily then 4 mg/kg twice daily) and then continued (4 mg/kg intravenously twice daily) or switched to oral voriconazole (200 mg twice daily) on day three. After a median of 45 and 47 days of treatment, all-cause mortality rates for isavuconazole and voriconazole were similar – 19% versus 20%. The corresponding treatment response rates in patients with proven or probable invasive aspergillosis were 35% and 36%.[1]

The VITAL trial was an open-label, single-arm study that enrolled 37 patients with proven or probable invasive mucormycosis. This included previously treated and treatment-naïve patients. Fungi identified at baseline included *Mucorales* moulds, *Mucor* species, *Rhizomucor* species, *Rhizopus oryzae* and *Lichteimia corymbifera*. Participants received the same isavuconazole dosing regimen as in the SECURE trial for a median of 84 days. By the end of the trial, 14% of the patients had a complete response to treatment. All-cause mortality was 43%.[2]

In a safety cohort of 403 patients, the most common adverse effects related to isavuconazole included nausea (7.4% of patients), vomiting (5.5%), dyspnoea (3.2%), abdominal pain (2.7%), diarrhoea (2.7%), injection-site reactions (2.2%), headache (2%) and rash (1.7%).

Skin, eye and hepatobiliary disorders were less common with isavuconazole than with voriconazole. In the SECURE trial, elevated liver laboratory tests were reported in 17.1% of patients in the isavuconazole group and 24.3% in the voriconazole group. Liver function should be tested before and during treatment. Isavuconazole is not recommended in those with severe liver impairment.

As isavuconazole shortens the QTc interval, it is contraindicated in patients who have familial short QT syndrome.

Isavuconazole is a pregnancy category D drug and is not recommended during pregnancy. In animal studies, it was associated with dose-related increases in fetal rib abnormalities. It is also not recommended during lactation as there was evidence of its excretion in the milk of lactating rats.

Isavuconazole has many potential drug interactions so it is prudent to consult the product information before prescribing in patients taking other medicines. Isavuconazole should not be given with concomitant ketoconazole, high-dose ritonavir (>200 mg/12 hourly) or drugs that strongly induce cytochrome P450 (CYP) 3A4/5 (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, St John's wort). It is also contraindicated with moderate CYP3A4/5 inducers (e.g. efavirenz, nafcillin, etravirine). Concomitant use with mild inducers should also be avoided.

Isavuconazole may increase exposure to drugs that are metabolised by CYP3A4/5 such as tacrolimus, sirolimus and ciclosporin. Therapeutic monitoring and dose adjustment of these drugs may be needed. Dose adjustment may be needed for substrates of P-glycoprotein as toxicity may be a concern, particularly with drugs that have a narrow therapeutic index such as digoxin, colchicine and dabigatran.

This antifungal comes in the form of a water-soluble prodrug, isavuconazonium sulfate, which can be given intravenously or orally. Following administration, it is rapidly hydrolysed to isavuconazole by esterases in plasma. Maximum concentrations of this active metabolite are reached within 2–3 hours of oral administration. Food does not affect absorption. It is mainly metabolised by CYP3A4/5 and uridine diphosphate-glucuronosyltransferases. The product information recommends that no dose adjustment is required in renal or hepatic impairment. The drug has not been studied in severe hepatic impairment.

Isavuconazole appears to be non-inferior to voriconazole for patients with invasive aspergillosis.

It was also of benefit in some patients with invasive mucormycosis. However, the trial was small with no comparator and the activity of isavuconazole on individual fungi was difficult to assess.[2] It is not known how isavuconazole will compare to other azole antifungals. The safety and efficacy of isavuconazole in children has not yet been established.

T manufacturer provided the AusPAR

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

NEW DRUGS

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First published 24 April 2020

Stiripentol

Approved indication: Dravet syndrome

Diacomit (Emerge Health)
250 mg and 500 mg capsules
250 mg and 500 mg powder for oral suspension

Dravet syndrome is a severe myoclonic epilepsy in infancy. It usually emerges in the first year of life. The seizures are difficult to control and the infants develop intellectual disability. Stiripentol has been approved as an adjunctive treatment for infants with generalised tonic-clonic and clonic seizures which are not controlled by valproate and a benzodiazepine.

Stiripentol is an aromatic alcohol which is unrelated to the structure of other antiepileptic drugs. It increases activity in the GABAergic system, but it also interacts with anticonvulsant drugs. Stiripentol inhibits cytochrome P450 (CYP) 1A2, 2C8, 2C9, 2C19, 2D6 and 3A4. It therefore increases the plasma concentrations of antiepileptic drugs including carbamazepine, clobazam, phenytoin and valproate. There are many other potential pharmacokinetic interactions, including with benzodiazepines.

Stiripentol is well absorbed, but there is extensive first-pass metabolism. While they are not the main method of metabolism, CYP1A2, 2C19 and 3A4 are involved. The clearance of stiripentol decreases after several doses probably because it inhibits its own metabolism. A steady state is established after 2–5 days. Most of the metabolites are excreted in the urine. The elimination half-life is 4.5–13 hours.

As Dravet syndrome is rare, the trials of stiripentol have involved small numbers of patients. The two main trials of efficacy involved a total of 64 patients. In these double-blind trials stiripentol was added to optimised treatment with clobazam and valproate. The recommended daily dose was 50 mg/kg. An infant was considered to have responded to treatment if there was at least a 50% decrease in the frequency of seizures.[1,2]

One of these trials was in France. It randomised 21 children (average age 9.4 years) to stiripentol and 20 to placebo. In the first two months of the trial 15 (71%) in the stiripentol group responded compared with one (5%) in the placebo group. Nine of the children taking stiripentol became seizure free.[1]

The other trial was in Italy and involved 23 children with an average age of 9.1 years. After two months, eight children responded to stiripentol (66.7%). Only one (9.1%) in the placebo group responded. Three of the children taking stiripentol became free of seizures.[2]

During the trials there were more adverse events in the children taking stiripentol, compared to placebo. More frequent effects included drowsiness, agitation, irritability, hypotonia, nausea and vomiting. There was also loss of appetite and weight loss. Elevation of gamma-glutamyltransferase has been reported so liver function should be checked every six months, as should a full blood count because of the risk of neutropenia.

While it is difficult to know if the effect is due to its interaction with clobazam and valproate, stiripentol reduced seizures more than a placebo did. When starting stiripentol it should be given two or three times a day with the dose being gradually increased. The doses of clobazam and valproate may need to be reduced if adverse effects emerge. Long-term efficacy and safety data are limited. For example, does the weight loss, which was seen in 24% of the children taking stiripentol, have a long-term effect on growth?

T manufacturer provided 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 and the Therapeutic Goods Administration.

Correction

Faecal microbiota transplantation: indications, evidence and safety [Correction]

Aust Prescr 2020;43:103
https://doi.org/10.18773/austprescr.2020.032

The article on faecal microbiota transplantation (Aust Prescr 2020;43:36-8) has been corrected. View corrected article.

The conflict of interest statement was inadvertently omitted during the production process. It should have read:

Robert V Bryant has received speaker fees, grants and research support from AbbVie, Ferring, Janssen, Shire, Takeda and Emerge Health. These fees were paid to his employer to support research. He is also a board member and shareholder of BiomeBank.

Samuel P Costello has received speaker fees, grants and research support from Ferring, Janssen, Shire and Microbiotica. He is also a board member and shareholder of BiomeBank.

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