Research Review Speaker Series™

Psoriatic arthritis and HCV elimination from NZ (GP CME Rotorua)

Making Education Easy

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About the speakers

Dr Doug White (BSc[Hons], MBChB[Hons], MRCP [UK], DipMSM, FRACP) is consultant rheumatologist at Waikato DHB and senior lecturer at the University of Auckland. Prior to this, he has practised in Rotorua, Christchurch, Brisbane and in the UK. Since joining the rheumatology department in 2010, Doug has established a clinic for people with ankylosing spondylitis that he runs with physiotherapy and nursing support. He contributes to national and international research on ankylosing spondylitis and is particularly interested in aspects of service provision that influence patient care.

Prof Ed Gane (MBChB, MD, FRACP, MNZM) is Chief Hepatologist and Deputy Director at the NZ Liver Transplant Unit, and a Professor of Medicine at the University of Auckland. Prof Gane has been actively involved in many international clinical trials of therapies for chronic viral hepatitis, and in a range of national, regional, and international advisory boards in this therapeutic area. He has published more than 200 scientific papers and serves on the editorial committee for several major journals. Recently he received the Health Research Council of NZ's Beaven and Lilley medals for outstanding contributions to clinical research, and was appointed as a Member of the Order of New Zealand for Services to Medicine.

Abbreviations used in this review

ALT = alanine aminotransferase
DAA = direct-acting antivirals
DMARD = disease-modifying antirheumatic drug
GP = general practitioner
GT = genotype
HCV = hepatitis C virus

This publication is a summary of two presentations made at the Abbvie Breakfast Session on June 11 as part of the Rotorua GP CME 2016 meeting. Dr Doug White spoke on the role of primary healthcare providers in identifying patients with possible psoriatic arthritis early in their disease and making appropriate specialist referral for such patients, thereby improving time to diagnosis and patient care. Prof Ed Gane presented data on DAA (direct-acting antiviral) therapies and their ability to provide a cure for chronic HCV (hepatitis C virus) infection which is well tolerated. Importantly, these regimens are now available in NZ, and in combination with efforts to prevent disease transmission will be important in the elimination of HCV from NZ.

JOINING THE DOTS IN PSORIATIC ARTHRITIS

Dr Doug White, Rheumatologist

Epidemiology of psoriatic arthritis

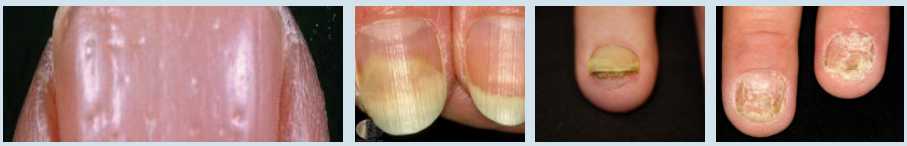
Cutaneous psoriasis is estimated to affect 2–4% of Western populations, and of these, ~30% will develop psoriatic arthritis.[1,2] An increased awareness of the prevalence of psoriatic arthritis among patients with psoriasis is important for an appropriate diagnosis. Males and females are equally affected (unlike other inflammatory rheumatic diseases), and the peak age of onset is 30–55 years. Compared with patients with psoriasis, those with psoriatic arthritis have slightly but significantly greater body surface area involvement (9.6% vs. 7.7% [p=0.015]), longer disease duration (21.7 vs. 19.1 years [p=0.006]), and are almost twice as likely to have nail disease (84% vs. 46%).[2,3] Other predictors of psoriatic arthritis include psoriasis located in the perianal region, the gluteal cleft, and the scalp and postauricular area, and lifestyle factors such as obesity and smoking.[4,5]

The average delay in diagnosis of psoriatic arthritis is 5 years. Early diagnosis is important for preventing severe deformities requiring surgery and to preserve long term function. Compared with patients diagnosed early (within 2 years), those diagnosed later have significantly more damaged joints, significantly greater radiographic damage, significantly more axial and peripheral disease and worse physical function outcomes.[6,7]

Presenting features

Family history in psoriatic arthritis is very relevant, and is one of the CASPAR diagnostic criteria. Psoriatic nail changes include pitting (often subtle), onycholysis, subungual hyperkeratosis and dystrophy (figure 1). Psoriatic nail dystrophy is often mistaken for onychomycosis, and it is important to consider psoriatic arthritis in the differential diagnosis of such patients. Nail disease is relevant as it is a manifestation of enthesitis; the enthesis is the site of ligament and tendon insertion into bone.[8] Extensor tendons insert close to the nail bed, and inflammation there is the cause of nail disease. Enthesitis is therefore a key pathology of psoriatic arthritis, which can be present even in asymptomatic individuals.

Figure 1. Spectrum of psoriatic nail changes

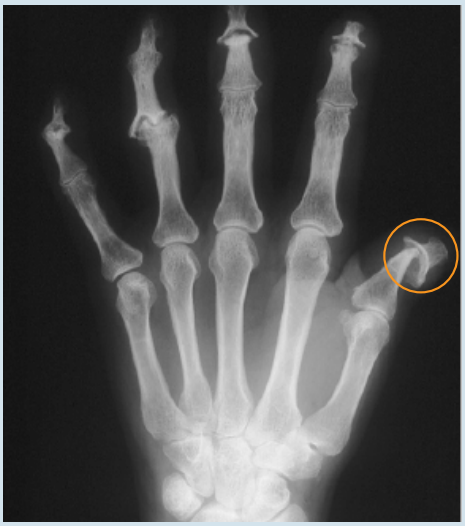


Pitting	Onycholysis	Subungual hyperkeratosis	Dystrophy

At initial presentation of psoriatic arthritis, the most common pattern of joint involvement is the oligoarticular form (~60%), often affecting knees and ankles.[9,10] However, psoriatic arthritis can also present symmetrically affecting small joints of the hands and feet (similar to RA), spondylitis, enthesitis (Achilles tendon problems, plantar fasciitis) and dactylitis.[9–12] Dactylitis is probably an under-recognised but useful clinical sign, which is also a marker of disease severity. It is also a useful diagnostic marker, as in addition to spondyloarthritis, only gout, sarcoidosis and infection are within the differential diagnosis.

Radiographic changes due to psoriatic arthritis, unlike those of rheumatoid arthritis, show characteristic bony proliferation, usually around the enthesis, and can demonstrate predominant distal interphalangeal joint involvement. They include the textbook example of 'pencil in cup' deformity (figure 2), osteolysis, spondylitis, ankylosis and spur formation.[13]

Figure 2. 'Pencil-in-cup' deformity in psoriatic arthritis



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Comorbidities

Patients with psoriatic arthritis are also susceptible to a range of comorbidities, including anxiety/depression (22.2–36.6%), CV disease (14%), hyperlipidaemia (20.7%), fatty liver disease (28.1%), obesity (30%), sacroiliitis (25–78%), type 2 diabetes (12%) and uveitis (4–18%).[14–18] Elevated serum uric acid levels can contribute to diagnostic difficulties. Psychiatric problems reported by patients include helplessness (87%), self-consciousness (89%) and embarrassment (87%), and these can have profound effects on patients.[19] Therefore, GPs have an important role to play in helping to manage these comorbidities.

Treatment options

Patient surveys showed that 59% of patients with psoriatic arthritis were receiving no treatment or topical treatment only, and 78% were receiving treatment that may not inhibit irreversible joint damage, suggesting a treatment gap.[20] The 2015 treatment schema provided by GRAPPA is quite complex, but it does nicely illustrate that treatment is directed at the clinical manifestations. Also in the NZ setting, the schema cannot be implemented as outlined due to unavailability of a number of the included drugs, so our algorithms are more straightforward and are outlined below.

EULAR treatment recommendations for psoriatic arthritis[21]

- NSAIDs (nonsteroidal anti-inflammatories) may be used to relieve musculoskeletal signs and symptoms.
- Conventional synthetic DMARDs (e.g. methotrexate, sulphasalazine or leflunomide) should be considered at an early stage for patients with peripheral arthritis and structural damage in the presence of inflammation.
- Local injections of glucocorticoids should be considered as adjunctive therapy; oral steroids should be avoided to minimise the risk of a withdrawal flare.
- TNF (tumour necrosis factor) antagonists should be commenced in those with an inadequate response to conventional synthetic DMARDs.

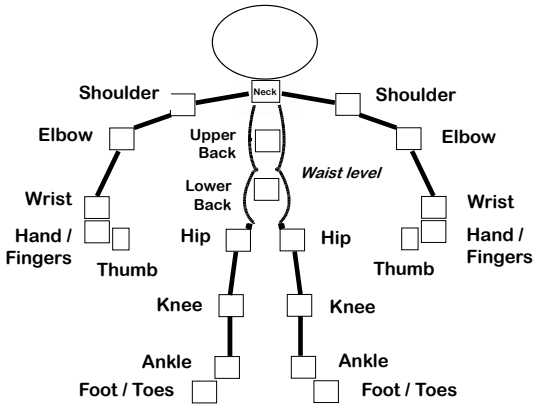
Screening/referral

There are a number of screening tools/questionnaires available for psoriatic arthritis, including PEST (Psoriatic Epidemiology Screening Test), EARP, TOPAS, PASE and PASQ. Despite considerable variability in length and complexity among these tools, most perform well with >70% sensitivity.[22] The PEST tool is a good option due to its brevity, with sensitivity of 94% and specificity of >75% (figure 3).[23] It includes five questions, which capture core clinical manifestations, and a homunculus for patients to complete to indicate which joints are affected. A score of ≥3 is indicative of psoriatic arthritis, but a lower score should not necessarily discourage referral. Other valuable information to include in a referral covers the impact on the patient, past treatments and relevant investigations (see below).

Figure 3. PEST screening tool for psoriatic arthritis [23]

	No	Yes
Have you ever had a swollen joint (or joints)?		
Has a doctor ever told you that you have arthritis?		
Do your finger nails or toenails have holes or pits?		
Have you had pain in your head?		
Have you had a finger or toe that was completely swollen and painful for no apparent reason?		

In the drawing below, please tick the joints that have caused you discomfort (i.e. stiff, swollen or painful joints).



Valuable information to include in psoriatic arthritis referrals

- Current musculoskeletal symptoms and their impact on function
- History of psoriasis (skin and nail), including past and current treatments and examination findings
- Important comorbidities
- Current medications and any previous treatments for arthritis and psoriasis
- Relevant investigation results (e.g. C-reactive protein, rheumatoid factor and anti-CCP, ANA, radiology reports, etc)
- Other relevant information (e.g. PEST score)

'Double Whammy' programme

Abbvie's 'Double Whammy' programme, for which Dr White was involved in the development, includes a booklet designed for healthcare practitioners, which includes clinical images, questions and information for assisting in identifying and managing patients with psoriatic arthritis. The second component of the initiative is a website, www.DoubleWhammy.co.nz, with patient information.

TAKE-HOME MESSAGES

Psoriatic arthritis is variable and unpredictable, ranging from mild and nondestructive to a severe, debilitating and erosive arthropathy.

Specialists and GPs can work together to improve outcomes by identifying patients earlier, as even short delays in diagnosis can lead to loss of function.

Skin, joints, other disease manifestations and comorbidities should be considered and managed when treating patients with psoriatic arthritis.

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ELIMINATING HCV IN NZ – NO LONGER A DREAM

Prof Ed Gane, Hepatologist

HCV infection is the silent epidemic of the 21st century, affecting ~50,000 New Zealanders and 150 million individuals globally.[1,2] HCV is a blood-borne virus that can be transmitted via contaminated blood products and infected needles if shared by intravenous drug users. Since screening of blood donors was introduced in NZ in 1992, there have been no cases of transfusion-related HCV infection recorded, and recreational injection drug use accounts for almost all cases of chronic HCV infection in NZ and Australia, with a few cases attributed to tattooing and body piercing outside licensed parlours. It is important to acknowledge that successful treatment of people who inject drugs should prevent HCV transmission, and therefore engagement of this largely marginalised section of society is needed for elimination of HCV from NZ.

The peak age of HCV infection is 15–25 years, reflecting the peak age of recreational drug use. Two NZ pilot studies in 2011–2013 of ~1000 patients from Wellington and the Bay of Plenty with newly diagnosed HCV infection showed that the median age of diagnosis was 45–50 years, i.e. 25–30 years after initial infection (figure 4).[2] Fibroscans performed on 788 newly diagnosed patients demonstrated 12% had severe fibrosis and 11% already had established cirrhosis. All HCV GTs (genotypes) are present in NZ, but GTs 1a and 1b are the most common, occurring in 56% of 6130 patients in one study, followed by GT-3 at 35%. While GT-6 is rare overall, it has risen to ~5% of all patients in the greater Auckland region due to immigration.

It is estimated that around half of the individuals in NZ with HCV infection are undiagnosed, and the duration of infection prior to diagnosis is 20–30 years for most individuals. As such, a number of patients have liver disease on diagnosis. The high rate of cirrhosis is reflected in a very expensive health burden, with steady increases in the number of both liver transplants and liver cancers attributable to HCV infection over the last two decades.[3] Based on an aging untreated cohort of 50,000 patients with HCV infection, epidemiological modelling has projected that the number of deaths from liver failure or liver cancer would treble by 2030.[2,4]

The best way to prevent the serious complications of HCV infections and to reduce the associated costs is to cure HCV infection through successful antiviral therapy – even cirrhosis will regress when the virus has been eliminated.[5] However, <1% of patients with HCV infection are being treated every year with funded interferon-based therapy, despite improvements in efficacy to >50% with the addition of boceprevir in 2013.[6] This is because all of these interferon-based therapies are poorly tolerated and require weekly injections for up to a year. Many patients and their doctors have elected to wait for funding of the new DAAs, which have few side effects, efficacy of >95% and treatment durations of only 8 or 12 weeks. Because of the high costs of DAAs, the initial proposal was to restrict funding for these oral treatments to patients with advanced liver disease. However, this would have only a minimal impact on the numbers, with cirrhosis and complications of hepatocellular carcinoma, hepatic decompensation and liver-related death continuing to climb. In contrast, if 10% of patients were treated with the new DAAs, it has been projected that the numbers for all liver-related complications would decline and that chronic HCV infection could be eliminated HCV from NZ within 15 years (figure 5).[2]

Figure 4. Age at diagnosis of chronic HCV in NZ[2]

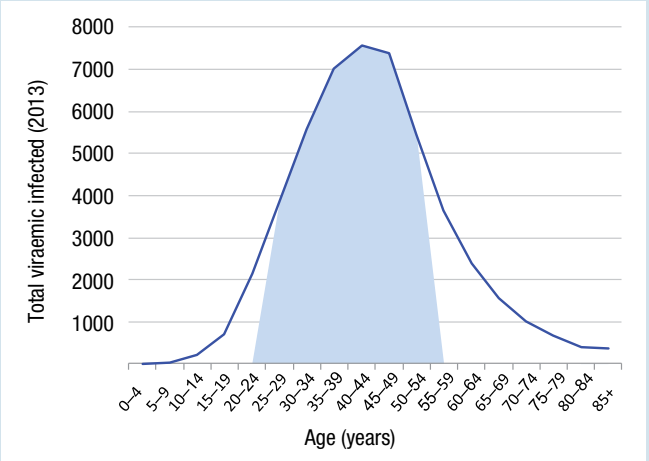
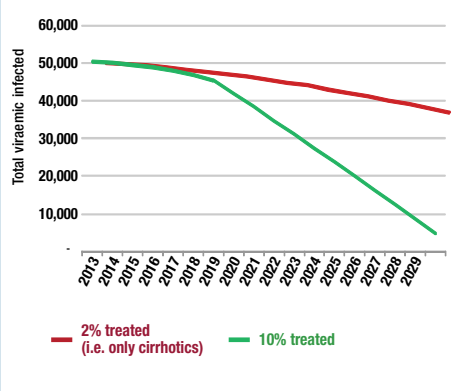


Figure 5. Projected numbers with chronic HCV in NZ[2]



Eliminating HCV in NZ

Because HCV transmission is almost entirely due to injection drug use, successful treatment of people who inject drugs will expedite the elimination of HCV from this country, potentially in 10 years.[7] There are three main areas that need to be addressed to achieve this. Firstly, undiagnosed individuals need to be identified. Primary-care and community groups have an important role in testing for HCV infection in undiagnosed patients, and point-of-care testing in prisons where the prevalence is particularly high is necessary. Secondly, funding DAA treatment for all HCV infections is needed by 2020. Thirdly, the number of patients treated needs to be quadrupled by 2020, and this will only be achieved by moving treatment from hospitals to primary care. Treatment as prevention in prisons, etc., will also be important.

VIEKIRA PAK/VIEKIRA PAK-RBV

Australia has already started an elimination strategy, which is likely to treat >25,000 individuals per year (considerably more than the planned 12,000) and eliminate HCV by 2025. The elimination strategy has just started in NZ, with an announcement from PHARMAC in June that two treatments with >90% cure rates will be funded, namely Harvoni (ledipasvir/sofosbuvir) for patients with advanced cirrhosis and VIEKIRA PAK (coformulated paritaprevir/ritonavir/ombitasvir copackaged with dasabuvir, with or without ribavirin) for all patients with GT-1 disease, including those with compensated cirrhosis. Certain specialists are able to prescribe VIEKIRA PAK and VIEKIRA PAK-RBV (VIEKIRA PAK with ribavirin) from July 1st, 2016, and all relevant prescribers, including GPs, will be able to prescribe VIEKIRA PAK from October 1st, 2016. This is to allow time for additional educational support and guidance to be put in place.

The components of VIEKIRA PAK target three different steps in HCV replication (figure 6). [8–10] It is administered twice daily and provided to the patient in daily blister packs containing two tablets of coformulated paritaprevir 75mg boosted with ritonavir 50mg plus ombitasvir 12.5mg and a single dasabuvir 250mg tablet to be taken in the morning with food, and a second dasabuvir 250mg tablet to be taken at night with food (figure 7). Each monthly carton contains 4 weeks of treatment, and the duration of treatment for most patients is 12 weeks, although some may require 24 weeks.

Figure 6. Mechanisms of action of the component drugs in VIEKIRA PAK (adapted from Lindenbach & Rice, 2005)[8–10]

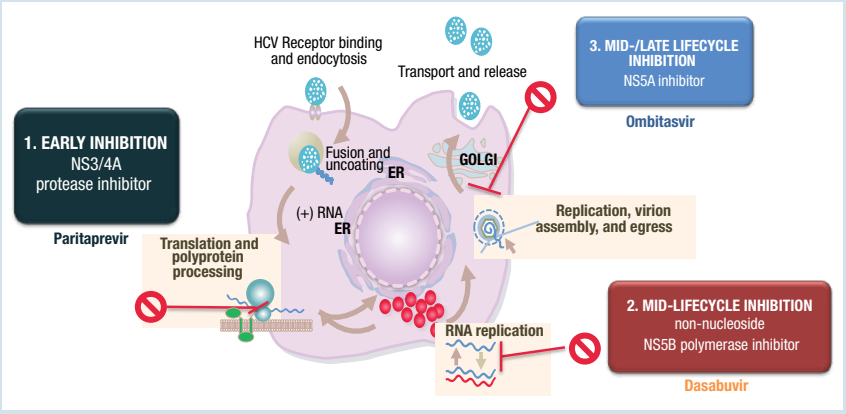


Figure 7. VIEKIRA PAK blister pack

VIEKIRA PAK and VIEKIRA PAK-RBV indications

VIEKIRA PAK and VIEKIRA PAK-RBV are indicated and funded in NZ for all patients with GT-1 HCV infection, including those with compensated cirrhosis – a 12-week course of VIEKIRA PAK is all that is required for patients with GT-1b without cirrhosis.[9,10] For all patients with GT-1a and for cirrhotic patients with GT-1b, ribavirin is added at bodyweight-based dosing (400mg in morning and 600mg in evening if <75kg; 600mg morning and evening if >75kg). Extending the treatment duration to 24 weeks can be considered for the most difficult-to-treat patients with GT-1a HCV infection, cirrhosis and previous null response to peginterferon/ribavirin treatment. Note that the approved treatment durations are the same as in Australia, Canada and Switzerland, but differ from the US FDA label.

Efficacy of VIEKIRA PAK

Pooled data from clinical trials show that VIEKIRA PAK-RBV is 96% effective on average across all non-cirrhotic patients with GT-1a HCV, regardless of previous treatment experience. The cure rate in patients with GT-1b is 100% (figure 8).[9,10] The cure rates for patients with cirrhosis are slightly lower, but remain >90%. Real-world data have confirmed that the adherence and cure rates are similar to those seen in clinical trials.[11,12] Note that the vast majority (99%) of patients who will be treated in NZ will be treatment-naïve.

Safety of VIEKIRA PAK and VIEKIRA PAK-RBV

Safety data from the SAPPHIRE I and II clinical trials have shown slightly increased adverse event rates in patients treated with VIEKIRA PAK-RBV, versus placebo, particularly for fatigue, nausea and pruritus, all recognised side effects of ribavirin. [9,10] However, the adverse event rates were low in patients who received VIEKIRA PAK without ribavirin (table 2). In patients without cirrhosis, most adverse events have been grade 1, serious adverse event rates were low and discontinuation rates were <1% (similar to placebo).[13–17] In patients with cirrhosis, adverse events were generally mild or moderate, with a 5.5% serious adverse event rate, and the discontinuation rate was still low at 2.1%; the hepatic decompensation rate was 1% and unrelated to study drugs.[17,18]

During the clinical trials, around 1% of VIEKIRA PAK recipients experienced increases in ALT levels to >5 times the upper limit of normal – the main risk factor was concomitant oestradiol oestrogen, which is now a contraindication for VIEKIRA PAK.[9,10] ALT elevations are typically seen during the first 4 weeks of treatment with VIEKIRA PAK, and are generally asymptomatic and transient.[13–16]

Bilirubin level elevations to >2 times the upper limit of normal are observed in 0.4% of VIEKIRA PAK recipients and 5.2% of VIEKIRA PAK-RBV recipients.[9,10] These increases are predominantly increases in indirect bilirubin related to either transporter inhibition (paritaprevir) or increased haemolysis (ribavirin), and are not accompanied by ALT level elevations. Nevertheless, monthly liver function monitoring is recommended.

Figure 8. Pooled trial data of efficacy of VIEKIRA PAK in patients with GT-1 HCV infection [9,10]

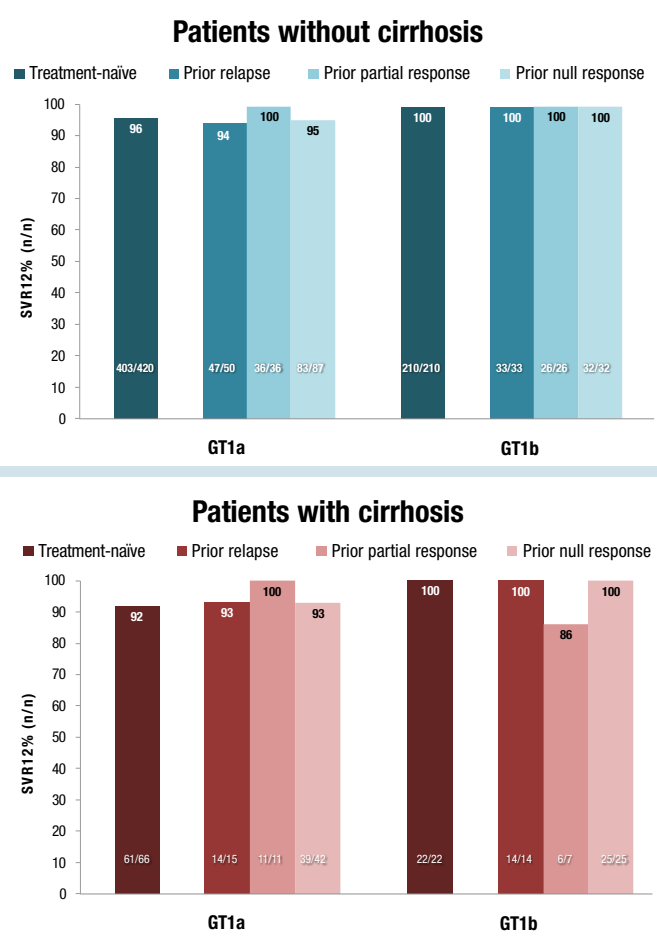


Table 2. Adverse events in clinical trials of VIEKIRA PAK and VIEKIRA PAK-RBV in patients without cirrhosis [9,10]

	SAPPHIRE I and II		PEARL II, III and IV	
Adverse event	**VIEKIRA PAK-RBV** 12 weeks (n=770)	**Placebo** 12 weeks (n=255)	**VIEKIRA PAK-RBV** 12 weeks (n=401)	**VIEKIRA PAK** 12 weeks (n=509)
Fatigue	263 (34%)	67 (26%)	120 (30%)	135 (26%)
Nausea	172 (22%)	38 (15%)	63 (16%)	43 (8%)
Pruritus	121 (16%)	11 (4%)	48 (12%)	31 (6%)
Insomnia	108 (14%)	19 (7%)	49 (12%)	26 (5%)
Asthenia	104 (13%)	17 (7%)	36 (9%)	20 (4%)
Anaemia	41 (5%)	0	30 (7%)	1 (0.2%)

The most frequent laboratory abnormality with VIEKIRA PAK-RBV is ribavirin-induced haemolytic anaemia. All patients receiving VIEKIRA PAK-RBV should have monthly monitoring of haemoglobin levels. If the haemoglobin level falls to <100 g/L in patients with no cardiac disease, the ribavirin dosage should be reduced to 600 mg/day, and the agent should be discontinued if the haemoglobin level falls to <85 g/L; see datasheets for information regarding ribavirin dose reduction in patients with stable cardiac disease. Caution also needs to be exercised in patients with renal dysfunction or vascular disease. Almost all (98.5%) of patients who required ribavirin dose reduction achieved cure, which was comparable with patients with no dose reduction.

Precautions for VIEKIRA PAK and VIEKIRA PAK-RBV [9,10]

- Contraindicated in Child-Pugh C and not recommended in Child-Pugh B cirrhosis
- Caution if albumin <32 or platelets <100 cells/μL
- Not indicated for HCV GTs other than GT-1
- Not recommended during pregnancy or breastfeeding; VIEKIRA PAK-RBV is contraindicated due to ribavirin
- Safety and effectiveness in patients aged <18 years or >70 years have not yet been established – studies are ongoing
- Risk of hepatotoxicity with ethinyloestradiol-containing oral contraceptives – consider changing contraceptive agent or method
- There are important interactions with drugs that are metabolised by CYP3A, are moderate or strong inducers of CYP3A, or are strong inducers or inhibitors of CYP2C

Drug-drug interactions

All patients should undergo a careful medicines review for possible drug-drug interactions prior to starting VIEKIRA PAK or VIEKIRA PAK-RBV. All DAAs interact with drug metabolising liver enzymes or transporters, and ribavirin is associated with additional drug interactions (table 3). There are several resources available for identifying possible drug-drug interactions. The Medsafe-approved VIEKIRA PAK datasheet or VIEKIRA PAK-RBV datasheet should be used in the first instance. Another useful resource is the University of Liverpool website, which includes a searchable alphabetical list of drugs and drug classes – this can also be downloaded as an easy-to-use smartphone app. The manufacturer, AbbVie, also has data on file built up through its clinical development programme and postmarketing experience, and can be contacted directly on 0800 900030 (helpline) or via email. There were >1200 medications permitted and managed in Abbvie's phase 2 and 3 VIEKIRA PAK trials, with <1.5% excluded due to prohibited medications, and the company is continuing to evaluate drug-drug interactions with a range of agents (data on file).

Table 3. Drug-drug interactions for VIEKIRA PAK and VIEKIRA PAK-RBV components

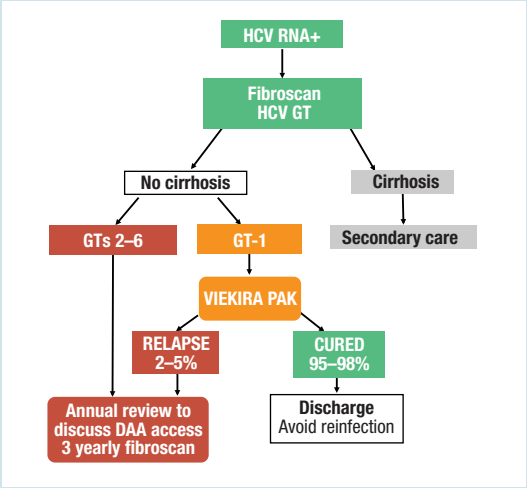
No restrictions	Caution/dose adjustment/clinical monitoring[1]	Contraindicated/ not recommended
Abacavir	Alprazolam	Atorvastatin[3]
Buprenorphine	Amiodarone	Carbamazepine
Dolutegravir[2]	Amlodipine	Colchicine in renal or hepatic impairment
Duloxetine	Atazanavir	Efavirenz
Emtricitabine	Cyclosporine	Ergotamine and its derivatives
Escitalopram	Darunavir, darunavir/ritonavir	Ethinyloestradiol-containing products
Lamivudine	Diazepam	Fusidic acid
Metformin	Digoxin	Gemfibrozil
Methadone	Fluticasone	Oral midazolam
Naloxone	Flecainide	Phenobarbital
Norethisterone	Furosemide	Phenytoin
Paracetamol	Ketoconazole	Quetiapine
Raltegravir	Lidocaine (systemic)	Rifampicin
Sulfamethoxazole	Mexiletine	Rilpivirine[2]
Tenofovir	Omeprazole	Ritonavir
Trimethoprim	Pravastatin	Sildenafil[4]
	Propafenone	Simvastatin
	Rosuvastatin	Salmeterol
	Tacrolimus	St. John's wort *(Hypericum perforatum)*
	Warfarin	Terfenadine
		Triazolam

1. Refer to Medsafe-approved Data Sheets
2. Registered but not reimbursed in NZ
3. Liverpool website but not NZ Data Sheet
4. Contraindicated for treatment of pulmonary arterial hypertension; for erectile dysfunction, reduced dose frequency is recommended

Community HCV infection treatment algorithm

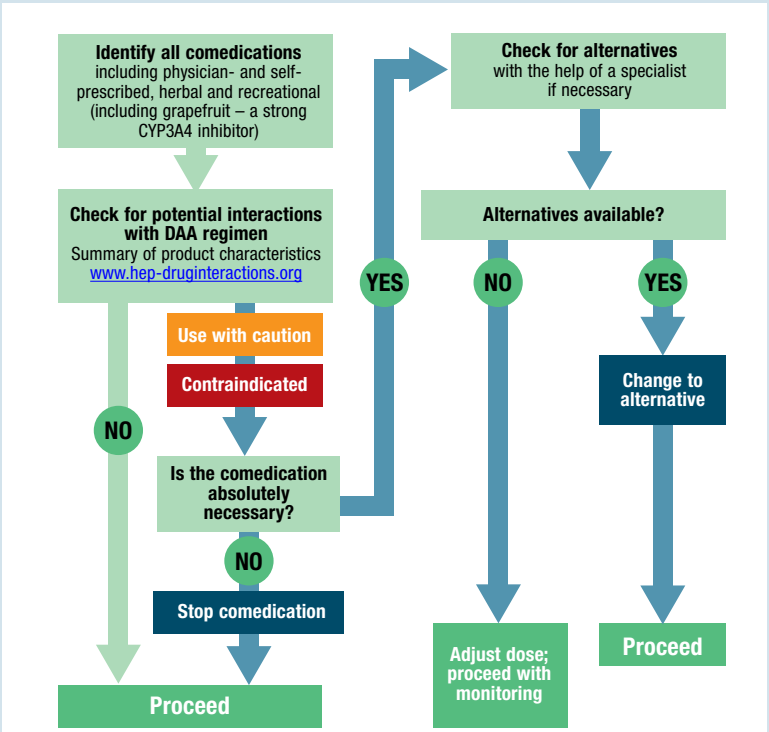
The Ministry of Health is working on a treatment algorithm (figure 9) to disseminate to community healthcare groups by September/October this year. Fibroscans will be available via e-referral without a specialist appointment. Of note, other oral treatments are likely to become available for use in primary care within 1 year for the 2–5% of patients with GT-1 HCV infections for whom VIEKIRA PAK treatment is unsuccessful. Monitoring includes full blood counts, liver function test at day 1 and again at weeks 2, 4 and 8. HCV RNA is only retested at post-treatment week 12 – if negative, no more testing is necessary, unless the patient is engaging in high-risk behaviours for reinfection.

Figure 9. Proposed algorithm for the treatment of HCV infection in the community



To assist with monitoring for drug-drug interactions, AbbVie Care will organise for the training of pharmacies to identify issues with patients' other medications, which the pharmacies will then on-report to the doctor prescribing VIEKIRA PAK. There will also be good algorithms to follow to ensure potentially harmful drug-drug interactions are avoided (figure 10).

Figure 10. Algorithm to help identify and manage drug-drug interactions with VIEKIRA PAK and VIEKIRA PAK-RBV (courtesy of David Back)



TAKE-HOME MESSAGES

- VIEKIRA PAK/VIEKIRA PAK-RBV is an important first step to eliminate HCV infection in NZ
- There is a high certainty of cure
  - SVR12 of 97% for patients with GT-1 HCV infection, with or without cirrhosis, including previous nonresponders to peginterferon/ribavirin
- Low rate of virological failure (<2%)
- Well tolerated with low discontinuation rates (1%) and predictable mild, manageable adverse effects that are mainly related to ribavirin

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