

NEW HEPATITIS C ANTIVIRAL DRUGS

Date: Tuesday 25 February 2014
Time: 1.30 am – 4.30 pm
Venue: Sirius Building, Furzer St
Woden, Canberra

1. Welcome & Introductions

The Pharmaceutical Benefits Advisory Committee (PBAC) Chair, Dr Suzanne Hill, welcomed all meeting participants and thanked them for their time and participation in the meeting. The Chair reminded non-departmental attendees that an Undertaking of Confidentiality declaration must be signed if discussions were to include in-confidence material. All participants indicated that confidential material will not be disclosed.

Participants were informed that a record of the meeting will be publically available on the PBS website.

2. Background

Following introductions, the PBAC Chair informed participants that this hepatitis C virus (HCV) stakeholder meeting would help inform the PBAC of the:

- New treatment options and their place in therapy in chronic hepatitis C (CHC) treatment;
- Patient numbers and consideration of whether there should be target populations;
- Data collection – the need to collect (if any) and what to collect;
- The appropriate models of clinical care; and
- If there is a need for further diagnostic testing to be available and funded.

3. Direct Acting Antiviral (DAA) HCV Presentation

Professor Paul Desmond presented an update on current clinical practice in the treatment of CHC and the changing drug treatment landscape precipitated by the new direct acting antiviral oral (DAA) therapies. The presentation covered the following points:

- The prevalence and incidence of HCV in Australia and the distribution by genotype at St Vincent's hospital in Melbourne;
- The genotype I cure rate¹ when treated with boceprevir and telaprevir with peginterferon and ribavirin (triple therapy);
- The effectiveness of second generation antiviral protease drug, simeprevir with peginterferon and ribavirin (QUEST and PROMISE studies);
- The clinical outcomes of sofosbuvir, a nucleotide polymerase inhibitor in combination with peginterferon and ribavirin (NEUTRINO study);

¹ cure rate was defined as sustained virological response (SVR) at 24 (12) weeks post treatment

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- Current clinical studies that are focussing on interferon-free therapies for treatment naïve genotype I HCV patients; and
- The clinical outlook for genotype 2 and genotype 3 patients treated with sofosbuvir and ribavirin.

Treatment of genotype 1 patients with boceprevir or telaprevir with peginterferon and ribavirin yielded a sustained virological response rate (SVR) in approximately 65-75% of subjects. Patients experienced more anaemia with boceprevir and more rash with telaprevir. Both treatment regimens were noted to have frequent daily dosing schedules (i.e. three times daily), in addition to interferon side-effects.

It was noted that the new drug simeprevir was approved by the US Food & Drug Administration (FDA) in November 2013 for use in combination with peginterferon and ribavirin. This combination therapy offers the patient convenience advantage of once daily dosing and is not expected to cause anaemia or rash side effects. In December 2013, the FDA approved sofosbuvir, plus peginterferon and ribavirin for genotype I therapy. Clinical trial outcomes indicate that the therapy is well-tolerated and only requires a short treatment period of 12 weeks for all patients. A sustained virological response (SVR) of 80% was achieved even in patients with cirrhosis.

Interferon-free therapies were discussed in the context of potential DAA combinations. Meeting participants noted four drug manufacturer were currently trialling all oral combinations for genotype I and it was expected that these combination therapies would be available within the next two years.

A general summary of the presentation was that new generation DAAs are soon to be available in the market with the convenience of oral-only dosing and fewer side-effects but with improved efficacy.

4. Utilisation data on PBS listed medicines for HCV

The Drug Utilisation Sub-Committee (DUSC) Secretary, Dr Alicia Segrave, presented the following:

- An overview of drug utilisation trends in HCV therapies before the listing of boceprevir and telaprevir on the PBS on 1 April 2013;
- Current drug utilisation patterns of existing HCV treatments.

The presentation recalled past comments from the May 2012 hepatitis stakeholder meeting regarding patient numbers, utilisation data, patient selection for treatment and clinical trials. These 2012 comments included:

- 3 000 and 4 000 patients with CHC were treated each year;
- The data obtained from the Department of Human Services was not genotype specific and was subject to unreliable items code selection;
- The selection of patients to withhold from current treatment in the expectation that future treatments could be trialled in such patients (i.e. 'warehousing') was occurring with genotype I patients;

- Clinical trials, familiarisation and compassionate use programmes could be underway prior to the listing of boceprevir and telaprevir.

In the first six months of direct acting antiviral (DAA) use (1 April 2013 to September 2013), it was noted that:

- The data collected was differentiated into patients with genotype 1, naïve or experienced patients;
- The proportion of Australian patients with genotype I HCV was 55%² and of these 41% were treated with DAAs;
- 72% of total patients treated with DAAs were treatment naïve;
- A comparison of historical trends were unavailable to inform future treatment trends;
- There has been minimal switching between boceprevir and telaprevir;
- The duration of pack, number of scripts, and course of prescription varied between the HCV therapies;
- Only 6 months of data was available for analysis;
- Data anomalies may have arisen due to the possibility of incorrect PBS item code selection (e.g. the Continuing treatment PBS item code for treatment-experienced patients may have been selected when the Continuing treatment PBS item code for treatment-naïve patients should have been selected);
- In summary, the limited amount of data confirms what was expected in terms of drug utilisation.

5. Who is likely to receive treatment with the new oral DAAs?

This question was asked by the PBAC in the context of its desire to recommend PBS restrictions that not only limit Government subsidy to patient populations in which the drug/s are considered to be cost-effective, but also to recommend restrictions that are aligned with clinical best practice.

Total number of CHC patients versus number of treated patients

It was recalled that at the May 2012 stakeholder meeting, the number of treated patients was estimated to be between 3,000 – 4,000 patients. The capacity of the Australian healthcare system to treat patients with CHC infection at the May 2012 stakeholder meeting was estimated by experts to be approximately 5,000 patients due to the limited number of specialist physicians and specialised treatment centres.

One expert considered that once all-oral treatment regimens become available, in theory, every patient with CHC could be treated due to the high response rates seen with the new DAAs.

It was believed that the current total hepatitis C patient population is approximately 230,000. Approximately 80,000 of these patients may be considered to be currently active in illicit drug-injecting behaviours and therefore are at risk of re-infection. It was further postulated by one expert

² Dore G.J., Law M., MacDonald M. et al., Epidemiology of Hepatitis C virus infection in Australia. *Journal of Clinical Virology* 2003; 26(2): 171-84.

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that hepatitis c infection could be eradicated by 2027 if active drug injectors were treated – an effect driven mainly by a decreased community viral load. This theory was also claimed to be in line with HIV disease modelling.

Estimating the number of patients likely to be treated with the new DAAs was considered difficult and uncertain because of the competing factors that would drive an increase in prescribing and factors that would constrain drug utilisation. Factors that may drive an increase in hepatitis drug utilisation were considered to be:

- The shorter treatment duration (12 weeks) with the new DAAs – this would appear to have advantages in aiding treatment compliance;
- All-oral treatment regimens may allow prescribing by General Practitioners;
- Increased patient interest and acceptance of treatment through reduced pill burden and/or the absence of injections;
- Improved gains in SVR with the new oral DAAs; and
- Increased patient safety/reduced levels of side-effects with the new oral DAAs.

The factors that would constrain a rapid growth in hepatitis C drug utilisation were considered to be:

- The TGA registered indications of the new DAAs with respect to how broadly or limited the patient populations are in terms of genotype;
- ‘Warehousing’ of patients is not expected to occur because unlike the triple treatment therapy, where patients were intolerant to interferon and thus willing to wait for newer treatment, the double therapy had better tolerance and a better toxicity profile;
- Disease severity assessment may still be a rate limiting factor as genotyping and measurement of viral load are laboratory investigations that may be less likely to be done by primary healthcare centres compared to tertiary healthcare clinics;
- The speed at which models of patient care and support are updated may not be as quick as expected;

Therefore, it was accepted that patient numbers would be unlikely to change from 3,000 – 5,000 to 200,000 plus treated patients in the short term. Instead, once the new all oral therapies are available, it may be reasonable to expect 10,000- 15,000 patients to be treated in the next 3 to 4 years, dependent on timing of TGA registration and PBS reimbursement.

TGA registration and PBS reimbursement processes

In light of the numerous sponsors with HCV drugs that are at different stages of commercialisation present at this meeting, the PBAC Chair outlined the general regulatory and reimbursement framework in Australia and commented that it would be useful to have some efficiency in planning

the timing of the various submissions to the PBAC and the TGA. In particular, the PBAC Chair noted that:

- The PBAC is required to consider not only clinical effectiveness but also cost-effectiveness against similar therapies, unlike the US FDA or TGA which focus on efficacy;
- Following PBAC recommendation, the drug would still need to be processed for listing and that any time delay between a PBAC recommendation and final listing is beyond the PBAC's control; and
- The PBAC would also consider issues of equity of access as part of their deliberations.

Laboratory testing

In response to the question of whether fibroscans are an integral part of CHC clinical care and what is optimal for patient care in terms of laboratory testing, clinicians agreed that the scans are useful in patients 40 years and older, and, in patients with advanced disease, to ascertain the degree of fibrosis and cirrhosis for triaging and monitoring purposes. Fibroscans were particularly important in patients F23 and above but in the main, there was a consensus that mandatory fibroscan testing was not desirable. Experts commented that a large proportion of patients should be monitored but that fibroscans are not necessary to start drug treatment in CHC patients as fibroscans are not the sole diagnostic consideration. Other diagnostic methods such as liver biopsy were also noted to be used in practice.

It was noted that fibroscans are largely available in practice at the moment but that reimbursement is not currently provided through the Medical Benefits Schedule and that a submission is being considered by the Medical Services Advisory Committee. If fibroscans are considered to be part of routine clinical management of CHC patients, it was noted that any assessment of the cost-effectiveness of the DAAs would need to factor in the costs of fibroscans. In addition, if patients were moved to primary care settings, it was commented that there may not be enough fibroscans to meet demand at the moment.

Priority groups for treatment

Clinicians were of the view that it would be inappropriate to treat all patients initially with the new oral DAAs and considered those who relapsed and non-responders would be high priorities for treatment or for continued treatment.

Whether there should be an age threshold for the commencement of treatment was raised by the PBAC. It was noted that treatment would be likely to be restricted to patients over the age of 18 because of the lack of clinical and safety data for those aged 18 years and under. Final TGA registration details would ultimately decide this.

³ METAVIR score F0=no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with few septa
F3 = numerous septa without cirrhosis ; F4 = cirrhosis

Resistance

The PBAC raised the question of whether there is need to be concerned with the potential development of HCV resistance to the new or existing CHC drug treatments, noting that resistance is generally a concern with all antimicrobials.

Comment was made that a percentage of the genotype I subtype A patients may be sensitive to simprevir, but the prevalence of this sub-type varied by region and is low in Australia (i.e. 5-7%). Therefore, one expert commented that polymorphism testing may be needed.

Re-infection of treated patients was recognised as a possibility. However clinicians considered that the frequency was low; 2-3% per annum, and can be contained in vulnerable groups through appropriate models of care and education.

In summary, experts commented that ‘resistance’ issues had not occurred with combination therapies and that resistance is not a long term or major issue.

6. Models of patient care

What setting/s should patients be treated in?

In response to whether the DAAs would be listed under current Section 100 Highly Specialised Drugs Program arrangements, it was noted that Section 85 General Schedule listing is the default for drug listings on the PBS and that reasons that justify listing of drugs elsewhere in the Schedule of Pharmaceutical Benefits would need to be taken into consideration by the PBAC when considering submissions to list. It was commented that General Schedule listings can equally require training and education commitments for listing and that although current treatments are listed as Section 100 items, thereby requiring patients to be treated in a tertiary setting with access to specialised facilities, the PBAC would consider whether the new oral DAAs and existing DAAs would need to remain as Section 100 items in due course.

The PBAC sought comment on how a possible transition from Section 100 listing model of care to a General Schedule listing (i.e. a wider, community based access) model of care could be facilitated. One expert suggested that current specialists could take up any initial extra prescribing due to the short-duration of treatment and increased ease in treatment with the new oral DAAs. Another expert commented that due to the complexity of CHC, general practitioners will not want to treat such patients. However, other experts commented that expansion of patient treatment and care by primary practices can be achieved but expected this to happen gradually as data on efficacy, safety and general treatment experience arising from patients treated in tertiary health settings with the new oral DAAs would first be needed before confidence in the expansion into primary health settings could occur.

Attendees noted treatment practice would be affected not only by the availability of the drugs but also disease severity, co-morbidities, the patients’ ability to tolerate interferon, vein health, clinical

knowledge about the new therapies and other social factors such as patient support network for a particular course of treatment, and the patients' level of comfort in seeking treatment. The latter two are recognised as barriers to treatment and could affect patient numbers or demand and adherence.

Clinicians noted it would be unlikely that all patient care can be outsourced to general or specialised clinics as the ability to transfer care is linked to the stage of disease and its progression. F1 patients may be able to move to general population after 12 week treatment with the new generation DAAs but it is likely that F2-F4 patients' who have co-morbidities would require continued treatment at tertiary institutions.

Attendees noted clinical care pathways are being developed with infrastructures being put in place to administer antiviral education and therapeutic programmes. In the short-term there is no expectation of a change in the current model of care. Longer term, there would be increased capacity for speciality care centres with shared cared models and a focus on vulnerable groups such as drug and alcohol users and prisoners with HIV. A parallel issue is to improve current social barriers to CHC treatment in terms of patient stigmatisation and patient support.

What changes in treatment regimen/practice are expected?

It was noted that changes in the current clinical treatment algorithm (i.e. a move from triple therapy to targeted treatment or a stepwise treatment regimen) would be influenced by the timing of the regulatory approval for dual or triple therapy. It was reasonable however to expect a stepwise progression. There was general agreement that there would not be a major switch from current triple therapy to the new oral DAAs if a population approach is taken, that is genotype 1, and 2 is expected to be the initial focus of treatments as per clinical studies, followed at a later stage by genotype 3, 4 and 6.

How should patient expectations be managed?

With regards to managing patient expectations, participants noted that the majority of the CHC population remain unaware of the advances in CHC treatment. Hence patients would need to be educated about the available treatments. It was commented that those patients who are aware of the new therapies would be keen to access interferon free therapies.

7. Data collection

Purpose and options for data collection

It was commented that it would be helpful if data was available on:

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- SVR rates obtained in practice;
- Why a treatment was stopped in practice;
- What co-medications were administered in practice;
- Number of patients treated; and
- What side-effects have emerged in practice.

It was noted that data collection can provide a vital tool in monitoring a product's safety and efficacy and to inform on whether Government expenditure has been justified.

Departmental representatives noted that a national data collection initiative for boceprevir and telaprevir had previously been proposed but that such a registry had not been progressed. Departmental representatives commented that data collection in the context of post-PBS subsidy needs to be different from what the TGA collects in terms of standard pharmacovigilance practice and that more consideration should be given to this aspect of data collection. Further to this, comment was made to emphasise that a national data collection system would be ideal compared to sponsor/tertiary specific databases.

The need to give careful, thoughtful consideration to what the objectives of data collection are, was also emphasised amongst meeting participants. Some preliminary objectives of data collection were postulated as the following:

- 1) To confirm that the drugs are working;
- 2) To capture the real-life natural history of the disease to ascertain whether the new drugs are making a real difference. Mapping the disease's impact and the burden of disease could be achieved;
- 3) To ascertain re-infection rates.

It was commented by industry that it was not clear if every objective could be met by data collection. The Chair emphasised that data collection does not imply that future submissions to list new DAAs are to be considered only through a managed entry scheme.

Comment was made that the implications on data collection if GP clinics began prescribing CHC drug treatments were currently unknown.

The PBAC noted a general willingness of professional organisations in assisting in collection and provision of data to Government and sponsors.

The possibility of having standardised utilisation data, approved by the PBAC's Drug Utilisation Subcommittee was raised but it was considered that more thought would need to be given on how to achieve this. As a start, an agreed list of objectives and a standard way of collecting data, would need to be agreed to.

Concluding remarks

In summary if it was possible, all CHC patients would ideally be treated. In reality this is not possible due to budgetary considerations. A number of unknowns exist including the uncertainties of the number of HCV drug combinations that could become available, and their cost-effectiveness. To some degree, access to these new therapies would depend on the asking prices set by the respective drug companies. The tight fiscal constraints faced by the government were noted and while the PBAC may recommend a drug as being cost-effective, listing of medicines is essentially a two-step process and Government would need to decide if it would subsidise these new high cost products.

Participants appreciated the opportunity to discuss the issues, and thanked the Chair for sharing information and for being open to the discussions.

The Chair thanked all present for their interest and participation in the meeting.

The meeting closed at 3.50pm