Minutes of the

Adverse Drug Reactions

Advisory Committee

315th meeting

29 May 2009

[redacted] Principal Medical Adviser, TGA, joined the Meeting by telephone for discussion of item 10.1.1 – The report of the Gardasil Expert Panel.

1 Administrative arrangements

1.1 Conflict of Interest Statements

Members presented their Conflict of Interest statements to the Chairman who referred to them as necessary during the meeting and then passed them to the Secretariat to be kept with the agenda.

1.2 Welcome and apologies

The Chairman welcomed Members and TGA staff to the Meeting and noted apologies received from [redacted].

1.3 Date and Venue of the Next Meeting

The 316th meeting of the Australian Adverse Drug Reactions Advisory Committee was scheduled for the 17th July 2009 at the Qantas Meeting Rooms, Sydney Airport. Other ADRAC Meeting dates in 2009 were noted: 11th September (a change in date from 4th September was confirmed at this Meeting), 30 October, and 11 December.

2 Minutes of the 314th (Apr 09) Meeting

The Minutes of the 314th ADRAC Meeting (held 17 April 2009), as amended by the Chairman, were accepted.

10.1.1 Final report of the Gardasil Expert Panel

Background

The Gardasil Expert Panel (GEP) was established by the TGA in August 2008 to undertake an evaluation of the safety of the human papilloma virus vaccine, Gardasil, following receipt by the TGA of a small number of reports of symptoms of demyelination occurring after immunisation. In particular, the Panel was asked to consider whether the reports represented a safety signal that required further investigation, in which case the Panel was also asked to consider the mechanism through which the effect may be mediated and to advise on how the risk of occurrence could be minimised. The Panel was also asked to consider whether the overall balance of the safety and efficacy of Gardasil had changed significantly since marketing approval.

The report was provided to ADRAC for information and comment. The sponsor's response to the report, an updated TGA statement on Gardasil (dated 5 May 2009) and written comments from an ADRAC Member were also provided.

Discussion

A Member raised the following issues in relation to specific aspects of the report:

Demyelination events

Background rates of MS are known in older adolescents and in adults but there is limited information on background rates in girls aged 15-18 years, who are the main recipients of the vaccine and in whom most of the MS-like events after Gardasil have been reported. Demyelination conditions are less common in younger populations than in older populations. Therefore, there was uncertainty if cases observed in 15-18 year old females represented the background rate. It was also notable that in 2007/2008 there was an increase, compared with earlier years, in the number of MRI scans ordered for all females aged < 25 years and for females aged 25-34 year in Victoria. The reasons for the increase are unknown but it would be interesting to analyse the data for the 15-18 year old group to determine if there is a relationship with HPV immunisation status.

Regarding the inclusion of preliminary data from the USA's Vaccine Safety Datalink Rapid Cycle analysis, it was considered there was currently insufficient data available to allow the detection of very rare adverse reactions.

Case ascertainment of demyelination

Regarding case ascertainment, the Member noted that ADRAC had reviewed several reports describing unusual and/or multiple neurological symptoms following immunisation with HPV vaccine. While some of these were likely to be due to conversion-type reactions, it was important that there were systems in place to allow the systematic follow-up of all such cases so that some overall analysis was possible. Ideally, these cases should be followed up as far as possible to determine the final diagnosis, the results of all laboratory and clinical investigations and the outcome. Specific criteria for follow-up should be developed and implemented for all cases suggesting neurological disorder.

Analysis of urticaria and skin rash

It was important that reports of skin rash or urticaria be assessed in terms of onset time relative to vaccination as this would assist in determining causality and in distinguishing between urticarial rash and other skin rash. Not all rashes were urticarial and some rashes change with time. Therefore, obtaining information on onset time was critical.

Analysis of anaphylaxis

The assessment of the report with regards to anaphylaxis was accepted.

Conclusion and recommendations for surveillance

This appeared to be based on two stages. Stage 1 involved the establishment of systems to generate and collect greater numbers of reports of adverse events following HPV vaccination; stage 2 involved the establishment of clinical studies (case-control or other epidemiological studies) to determine causality. Stage 1 was not yet in full development. It was important to define the details of the "enhanced passive" and "active" surveillance programs that were intended to generate increased reporting. Links with the established HPV register would enhance the levels of available data and thereby assist in causality analyses.

General discussion

Members were advised that the views of the GEP and ADRAC regarding the association between HPV vaccine and demyelination events would be used to inform TGA recommendations to the areas of the Department that had carriage of the HPV program.

The current view is that there may be a signal indicating a higher rate of demyelinating events in females receiving HPV vaccine using the WHO definition of a signal as *reported information on possible casual relationship between AEFI and vaccine, relationship previously unknown or incompletely documented* (http://www.who.int/vaccines-documents/DocsPDF05/815.pdf). However, information to determine if this signal is associated with the HPV vaccine does not currently exist.

Where there is a suggestion of a possible vaccine-associated signal, it is necessary to take investigative actions in addition to those afforded by the spontaneous reporting system. ADRAC strongly endorsed the recommendations of the GEP regarding the need to establish causality studies, and individual Members were keen to provide input into the methodology of such studies. Case ascertainment through passive, active and enhanced passive reporting should be encouraged (similar to APSU activities).

ADRAC also considered that data from all existing sources should be used as part of the causality analyses. Liaisons should be established with the group running the HPV registry, AusImmune group (for determining background rates of demyelination events in specific sub-populations, as this group has a mechanism for case ascertainment in place), health outcome data from the various States….

A Member re-iterated the view that information on the background rate of demyelinating events in females aged 15-18 years was critical for assessing whether there is an association between HPV vaccine and demyelinating events in this sub-group. However, in addition to the missing "denominator" information, Members suspected that the actual incidence of demyelinating disease in

females receiving HPV vaccine (ie, the "numerator") was greater than that suggested by the current reporting rate. In the 6 month period since the GEP report was finalised, only one additional case of demyelination with HPV vaccine had been reported. However, it was unlikely that a connection would be made between the development of demyelinating disease and a vaccine administered some months previously. Further, patients with demyelinating disease were often under the care of various specialists and the focus on reporting may get lost.

ADRAC agreed it was likely that there were unreported cases of demyelinating disease in females who had been vaccinated with HPV vaccine. The numbers of such cases were likely to be small (in the order of 10-20 rather than 100-200) and it was considered unlikely that this would constitute a major public health problem. In order to obtain comprehensive information on the number of cases, all neurologists and allied specialists (such as ophthalmologists) who treat the complications of demyelinating disease would need to be surveyed about their patients and their patient's vaccination history. This information would then be useful to help decide if a case-control study was justified or warranted.

A Member commented that demyelinating events were typically reported in association with vaccines, especially following the mass introduction of a new vaccine. Therefore, it would be useful at the outset before a new vaccine is introduced to have systems in place to allow these events to be recorded and monitored comprehensively and systematically. The detail of these structures and programs was a matter for those responsible for administering vaccination programs. However, health practitioners, local Government authorities, hospital staff and private research organisations should be included and involved in these programs.

Members considered or discussed the preferred methods that should be used to investigate associations between vaccines and specific disorders. Data linkage was useful for causality assessments because it provided access to large amounts of data. However, this type of system would not be useful for assessing disorders that did not require hospital treatment and were instead dealt with mostly by private health practitioners.

In relation to the demyelinating events after HPV vaccine, Members suggested that the first step would be to survey all specialists involved in the care of patients with this type of disorder. If additional cases are identified, a formal epidemiological study with an appropriate follow-up period (at least 6 months) could be conducted to establish whether or not there is in fact a signal.

Members also considered whether HPV vaccine might also be involved in provoking relapse of demyelinating events. Both new-onset and relapse were important to investigate. The most convincing evidence of this would be obtained from a controlled study of those in remission, but this would be unethical.

There is a background MS flare rate which could confound such studies, but the impact of this could be minimised by conducting a very large randomised study. A time-series approach might also be informative. In this situation, those in remission from the disorder of interest could be assessed 1 month after vaccination compared with 1 month after some other (control, objective) event (eg, Xmas).

It was noted that studies were underway to determine whether there is an association between HPV vaccine and rheumatoid arthritis flare.

Overall, ADRAC strongly recommended that prospective enhanced surveillance structures should be put in place at the same time any large-scale public health program is initiated to allow comprehensive monitoring of the safety of that program.

[redacted]

10.2 Vaccine reports

During the period from 24 February to 12 April 2009, 203 reports of vaccine adverse reactions were lodged. This represents about 19.6% of the reports lodged for the period.

Reports of vaccines other than HPV vaccine

169 of the vaccine reports describe reactions to vaccines other than single-injection HPV vaccine (8 of these describes reactions to HPV vaccine plus another [redacted] vaccine).

118 of the reports were received from States, Territories or Local Government Councils, 39 were from health professionals, 8 were from sponsors; and 4 were from the AMEL. 114 reports related to children, 53 related to adults and age was not stated in 2.

All case reports for vaccines received during the period covered by this Meeting were provided to the Committee.

HPV vaccine reports:

34 of the vaccine reports described reactions to HPV vaccine when given as a single vaccine. These were received from QLD (9), VIC (6 – including 1 from the AVN), NSW (7), WA (2), SA (3), ACT (4), NT (2). One report of 7 from the sponsor did not identify the originating State.

Number of reports and events

The number of reports received in association with the majority of the vaccines is shown below:

Vaccine	No. reports	Vaccine	No. reports
[redacted]			
		Human papilloma virus	34

[redacted]

Other events

Summarised details of other specific reactions associated with vaccines are shown in the Tables, below.

Seizures/convulsions (7 reports) **Note: onset time (if stated on report) is in days; an onset time of 0 indicates the reaction occurred on the day of vaccination**						
Case Number State	**Sex**	**Age**	**Onset Time**	**Outcome Description**	**Reactions**	**Vaccine/s**
[redacted]						
249321 SA	F	13	8	Recovered	Gardasil	Convulsion, loss of consciousness, pallor
249349 VIC	F	12		Recovered	Gardasil, [redacted]	Convulsion, loss of consciousness, urinary incontinence
[redacted]						
249816 VIC	F	12		Recovered	Gardasil, [redacted]	Convulsion, loss of consciousness

Other serious neurological cases (9 reports)						
Case Number State	**Sex**	**Age**	**Onset Time**	**Outcome**	**Trade Name Description**	**Reactions**
[redacted]						
249101 State not identified	F	18		Not yet recovered	Gardasil	Cerebrovascular accident
[redacted]						

249100 NSW (sponsor)	F	24		Not yet recovered	Gardasil	Multiple sclerosis, sensory loss, swelling, dizziness, headache, paraesthesia, muscular weakness, photopsia, tachycardia, malaise

10.3.2 Possible neurological reactions after HPV vaccine (Gardasil)

Report 249971 (ACT)

This describes a 16 year old girl who received her second HPV dose and about 1 month later developed hand tremor, loss of balance, slurred speech, tiredness, headache, difficulty sleeping and poor mobility. The symptoms were on-going 4 months later and resulted in the girl being absent from school for long periods.

The symptoms were treated with antidepressants, sodium valproate and propranolol but these were withdrawn because they made the girl tired and unsteady. The patient was referred to two different neurologists. MRI and CT scans were unremarkable but investigations were ongoing.

One neurologist has suggested the disorder was *"migraine associated dysfunction"*; the other *"does not believe symptoms are related to Gardasil. .. has not found a cause for her symptoms, but .. it is possible that they do not have a physical basic apart from exaggerated physiological tremor… it is unlikely that there is a serious neurological disorder."*

Members agreed that the severity of the disorder warranted follow-up to the greatest extent possible. It was possible there was a psychological component underlying the disorder. However, given the age of the girl and the impact this disorder had on her life, investigations were warranted to attempt to conclusively rule in or out central and/or peripheral demyelination and other neural disorders, and any involvement of vaccines.

10.3.3 Relapse of neurological disorder after HPV vaccine (Gardasil)

Report 249100 (NSW).

A few hours after her second dose of HPV vaccine, a 24 year old female experienced light-headedness, pain, swelling, intermittent, sudden sharp headache associated with pre-syncope, and photo scintillations, from which she apparently recovered. Six days later she felt unwell and developed paraesthesia around her left elbow and weakness in her left arm. She was admitted to hospital but no evidence of neurological disorder was found on CT scan and she was discharged. Four days after discharge the patient developed light-headedness and dizziness and was again admitted to hospital. CT scan of the head, MRI and cervical spine x-ray were all normal but physical examination showed patchy sensory loss in her left arm.

The patient was reported to have been diagnosed with MS (confirmed by CT brain) 3 years prior to receiving Gardasil. She had been stable for 2 years before she suffered a relapse of symptoms within 24 hours of her second Gardasil dose. The relapse episode lasted four months.

Members noted the absence of objective evidence of neurological disease. It was also noted the patient had pre-existing liver disease and was taking several medications prior to receiving Gardasil. Members were not convinced this was a case of MS-relapse.

10.3.4 Cerebrovascular accident after HPV vaccine (Gardasil)

Report 249101 (sourced by the sponsor from a newspaper article; State not identified).

This described an 18 year old female football player who reported becoming “sicker and sicker” after each dose of HPV vaccine and she ultimately suffered a “stroke without the bleed” and was hospitalised for 3 months.

Members considered there was no objective information available to allow assessment of any involvement of HPV vaccine in this case.

10.3.5 Allergy symptoms after HPV vaccine (Gardasil)

Report 249845 (VIC).

The day after administration of Gardasil (dose 2), a 17 year old female developed throat tightness (relieved 1 hour after administration of salbutamol) and rash (lasting 2-3 hours) on her arms and torso.

Members noted the patient had a history of asthma. On the basis of the respiratory symptoms and presence of generalised rash, there was a Level 2 degree of certainty, according to Brighton classification criteria, that this was a case of anaphylaxis. **However, Members suggested follow-up information should be obtained for case 249845 to allow a more definitive assessment.**

[redacted]

[redacted]

11.2.1 HPV vaccine and atrioventricular septal defect

Report 249154

A 21 year old who became pregnant soon after removal of an intrauterine device was found at gestation week 17 to have a fetus with atrioventricular septal defect. The mother was immunised with HPV vaccine "some time between conception and implantation"; the report contained no information regarding any concomitant drugs.

This is the 6th report involving fetal neonatal events in women who have received HPV vaccine. The other 5 reports do not describe fetal malformations/variations (there are 2 reports of abortion and 1 each of unintended pregnancy (interaction with OCP), premature labour and exposure during pregnancy).

HPV vaccine is in pregnancy Category B2. No adverse effects on reproduction are known with this vaccine.

An association with HPV vaccine in report 249154 was considered unlikely.

[redacted]

[redacted]

- Six minutes of stuff for Doctors 06 May – HPV vaccine

[redacted]