Expert Panel Consensus Position Statement regarding the Use of Rh(D) Immunoglobulin in Patients with a Body Mass Index ≥30

Background

CSL Behring has updated the Rh(D) Immunoglobulin-VF Product Information (PI) to include a recommendation that the clearance of fetal cells and the presence of Rh(D) antibody be confirmed post-administration in patients with a BMI ≥ 30. This change came into effect from 22 December 2014. CSL Behring also updated the Rhophylac PI to recommend intravenous administration of this product in patients with a BMI ≥30.

The update to the Rh(D) Immunoglobulin-VF PI has generated questions from healthcare professionals regarding the implications of this change on clinical and laboratory practice. To support the healthcare community, an expert panel was convened by the Australian Red Cross Blood Service and the National Blood Authority on 22 May 2015 in order to discuss this matter and develop appropriate actions.

Members of the Expert Panel included:

- Associate Professor Stephen Robson and Professor Michael Permezel representing the Royal Australian & New Zealand College of Obstetricians and Gynaecologists (RANZCOG)
- Deborah Pidd representing the Australian College of Midwives (ACM)
- Simon Benson and David Roxby representing the Australian & New Zealand Society of Blood Transfusion (ANZSBT)
- Dr Marija Borosak representing the Royal College of Pathologists of Australasia (RCPA)
- Dr Helen Savoia representing the Expert Working Group and Clinical/Consumer Reference Group - Patient Blood Management Guidelines: Module 5 – Obstetrics and Maternity
- Dr Joanne Pink, Dr Janet Wong and Dr Chris Hogan representing the Australian Red Cross Blood Service (Blood Service)
- Dr Peter Flanagan representing the New Zealand Blood Service (NZBS)
- Michael Stone and Leia Earnshaw representing the National Blood Authority (NBA)
- Dr Darryl Maher, Annmarie Pendleton and Guilio Barrese representing CSL Behring*

**CSL Behring attended the meeting and presented data, but did not contribute to the Consensus Assessment and Recommendations.*

The following is a record of the outcomes from this meeting.

The Evidence

Recognition of the potential for lack of effect of Rh(D) immunoglobulins administered intramuscularly (IM) in those with a high BMI arose following a number of pharmacokinetic studies conducted in pregnant women[1-4]. These studies investigated several Rh(D) immunoglobulins manufactured by different companies. The data from these studies indicate pregnant women with a high BMI have significantly lower serum peak levels (Cmax) of Rh(D) immunoglobulin when Rh(D) immunoglobulins are given IM compared to those with a BMI within the normal range. This phenomenon was observed across all the Rh(D) immunoglobulins studied. In the published literature, no studies had been conducted to identify if a link existed between the lower Cmax and an increased risk of lack of effect.

Pharmaceutical companies have passive post-marketing adverse event surveillance systems in place which may detect less common adverse events that have not been identified in clinical studies. It is important to note that data collected via such systems have several limitations including the potential for under-reporting and biased reporting as well as providing incomplete information. CSL Behring's analysis of the cases in its post-marketing adverse event database showed the proportion of all reports consistent with reduced effect was approximately 4 fold higher in patients with BMI ≥ 30 compared to non-obese patients. Nevertheless, the absolute number of reports of lack of effect (such as failure to detect the presence of Rh(D) immunoglobulin post-administration, maternal Rh(D) alloimmunisation, or the baby developing signs consistent with haemolysis) was small relative to the number of doses of Rh(D) immunoglobulin used. Whilst the absolute number of reports of lack of effect in obese women was small, CSL Behring considered the data sufficient to suggest that IM administration in obese patients (defined as BMI ≥30 or weight >90kg) may be associated with an increased risk of lack of effect.

As the evidence was insufficient to determine the mechanism by which this potential lack of effect may be occurring, CSL Behring felt it was prudent to recommend that patients with BMI of ≥30 should be monitored to ensure an effective dose had been administered.

References

1. Woelfer B, Schuchter K, Janisiw M, et al. *Post-delivery levels of anti-D IgG prophylaxis in D– mothers depend on maternal body weight.* Transfusion. 2004; 44: 512-517.
2. Bichler J, Schöndorfer G, Pabst G, et al. *Pharmacokinetics of anti-D IgG in pregnant RhD-negative women.* BJOG. 2003; 110; 39–45.
3. Tiblad E, Wikman A, Rane A, et al. *Pharmacokinetics of 250 µg anti-D IgG in the third trimester of pregnancy: an observational study.* Acta Obstet Gynecol Scand. 2012; 91: 587-92.
4. MacKenzie IZ, Roseman F, Findlay J, et al. *The kinetics of routine antenatal prophylactic intramuscular injections of polyclonal anti-D immunoglobulin.* BJOG. 2006; 113: 97-101.

Consensus Assessment and Recommendations

1. Whilst there is some evidence to suggest that intramuscular administration of Rh(D) immunoglobulin may be associated with an increased risk of lack of effect in patients with a BMI ≥30, the meeting participants, having assessed the available evidence, considered that the data are currently insufficient to support a change to clinical and laboratory practice at the present time.

    a. The number of passively reported cases of possible lack of effect of Rh(D) immunoglobulin in patients with a BMI ≥30 are very small in comparison to the very large number of doses of Rh(D) immunoglobulin which have been administered. It is, however, acknowledged that there is likely to be significant under-reporting of cases of lack of effect and, in those cases that are reported, the patients' BMIs are not always recorded.

    b. There is currently no established relationship between lower post-administration serum anti-D levels and alloimmunisation rates or poor clinical outcomes.

    c. There is no national dataset of women who have developed Rh(D) alloimmunisation during pregnancy; however, surrogate data suggests that the number of pregnancies complicated by severe haemolytic disease of the newborn (HDN) is decreasing. Australian Institute of Health and Welfare (AIHW) data show that, in the ten year period

from 2003/04 to 2012/13, the number of neonatal exchange transfusions performed in Australia decreased from 124 to 29 per annum and intrauterine fetal transfusions decreased from 124 to 59. In addition, perinatal deaths due to specific perinatal conditions, including Rh(D) alloimmunisation, have decreased from 172 in 2004 to 159 in 2012. All of the serious outcomes for Rh(D) alloimmunisation are now very uncommon despite the fact that the proportion of women with a BMI ≥30 is progressively increasing and now comprises almost one third of all women giving birth in Australia. It is acknowledged, however, that there are many other factors at play, including the fact that the number of babies women have has decreased over the years.

d. The mechanism by which Rh(D) immunoglobulin works is not fully established and may relate not so much to maternal blood volume or serum concentration of anti-D as to the volume of fetal red cells and the amount immunoglobulin that is available to bind to those cells. Its mechanism of action may, therefore, not be analogous to therapeutic drug levels.

2. It is important that a recommendation is made to all Rh(D) negative pregnant women to receive Rh(D) immunoglobulin in accordance with the currently established guidelines.

3. The Blood Service/CSL Rh(D) immunoglobulin must be given by deep intramuscular injection. For women with a BMI ≥30, particular consideration should be given to factors which may impact on the adequacy of the injection, including the site of administration and the length of the needle used.

4. No specific additional testing is required because a woman has a BMI ≥30. Routine post-administration testing is not required unless there has been a large fetomaternal haemorrhage (FMH); in which case, testing should be in accordance with current established guidelines.

5. For women with a BMI ≥30 who experience a FMH of greater than 6mL, consideration may be given to administering any required additional doses of Rh(D) immunoglobulin via the intravenous route (i.e. use of Rhophylac) to increase bioavailability and facilitate the more rapid clearance of fetal cells.

6. Further research should be undertaken in this area, including examination of the bioavailability of Rh(D) immunoglobulin in patients with a BMI ≥30 and studies looking at the incidence and causes of Rh(D) alloimmunisation during pregnancy.

Next Steps

1. The *Frequently Asked Questions (FAQs) about the Use of Rh(D) Immunoglobulin*, which are currently available on the Blood Service www.transfusion.com.au website were reviewed and updated in light of the above recommendations.
2. A study to examine the bioavailability of Rh(D) immunoglobulin in patients with a BMI ≥30 will be considered.
3. The possibility of developing a registry or other data collection to capture patient outcomes, including alloimmunisation rates is also being assessed.
4. The need for review of the 2003 *Guidelines on the Prophylactic Use of Rh D Immunoglobulin (Anti-D) in Obstetrics* was referred to the NBA for consideration.