MARCH 2014, No. 16

Reaksi

DRUG SAFETY NEWS

Mission: This publication provides information and recommendations to healthcare professionals to enhance communication of drug safety updates, raise awareness of adverse drug reactions reported, and stimulate additional adverse drug reaction reporting.

This is a bimonthly publication by the Drug Safety Monitoring Centre, National Pharmaceutical Control Bureau (NPCB), Malaysia.

TO REPORT AN ADVERSE DRUG REACTION

Online

1. Visit www.bpfk.gov.my.
2. Click on ADR Reporting and Product Complaints.
3. Click to report as a healthcare professional online or via hardcopy.
4. Submit the form once completed.

Mail

1. Print out and complete the ADR form available from our website.
2. Mail or fax to:
   The Drug Safety Monitoring Centre, Centre for Post Registration of Products, National Pharmaceutical Control Bureau, Ministry of Health, PO Box 319, Jalan Sultan, 46730 Petaling Jaya, Selangor.

Telephone

03-7883 5400
(ext. 8460/ 8461/ 8463)

Fax

03-7956 7151

In This Issue:

Pure Red Cell Aplasia related to use of Erythropoietin Stimulating Agents

The National Pharmaceutical Control Bureau (NPCB) has assessed the benefit-risk profile of erythropoietin stimulating agents (ESAs) particularly in relation to the adverse event Pure Red Cell Aplasia (PRCA). PRCA is a progressive, severe anaemia with sudden onset, characterised by the absence of erythroblasts, while white blood cells and platelets remain normal[1].

Epoetin-associated PRCA is a rare adverse drug reaction (ADR) resulting from cross-reaction between anti-erythropoietin antibodies (AEAB) and endogenous erythropoietin. Immunogenicity of ESAs can be influenced by many **factors**, such as the manufacturing process, storage conditions, route of administration, frequency and duration of treatment[2].

Product Information

ESAs are generally approved for the treatment of anaemia in patients with chronic renal failure, concomitant chemotherapy, Human Immunodeficiency Virus (HIV) patients treated with zidovudine, and for erythropoiesis stimulation in certain procedures such as autologous blood donation or during surgery. The first ESA was registered in Malaysia in 1996. There are currently five brands of ESAs (***Table 1***) approved by the Drug Control Authority (DCA), with a total of 35 products of various strengths. However, Eprex® and Recormon® have been on the market the longest and make up about 98% of the local ESA usage currently.

Table 1: Brands of ESAs Registered in Malaysia

Brand Name	Active Ingredient	Year of Registration with DCA	Product Registration Holder
Eprex®	epoetin alfa	1996	Johnson & Johnson (M) Sdn. Bhd.
Recormon®	epoetin beta	2002	Roche (M) Sdn. Bhd.
Mircera®	methoxy polyethylene glycol epoetin beta	2008	Roche (M) Sdn. Bhd.
Binocrit® (biosimilar to Eprex®)	epoetin alfa	2011	Novartis (M) Sdn. Bhd.
Nesp®	darbepoetin alfa	2011	Smart Medicine Sdn. Bhd.

Background

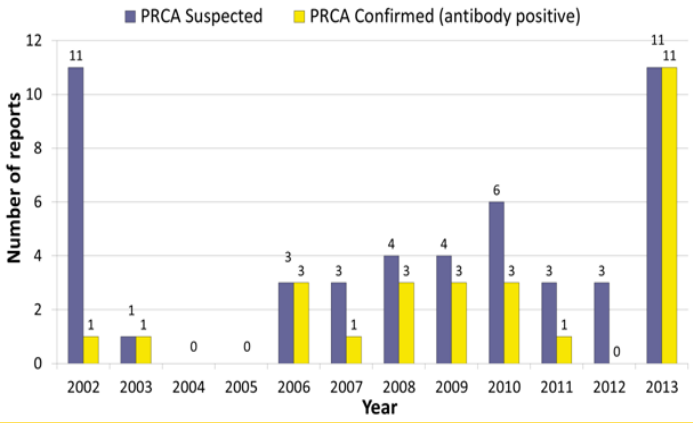
Between 1999 and 2004, there were 191 cases of epoetin-associated PRCA identified **globally,** 95% involving haemodialysis patients who received Eprex®. Investigations revealed the increased immunogenicity could be due to change of stabiliser, leaching from uncoated rubber stoppers, and breaks in the cold chain process. The prescribing information was revised to state that Eprex® should only be administered intravenously in chronic renal failure patients and storage conditions should be strictly maintained[3].

In Malaysia, the NPCB has received a total of 135 ADR reports related to ESAs, with 172 adverse events since 2000[4]. Majority of the events (67%; 116 events) comprised of red blood cell disorders, with 30% (51 events) specifically involving suspected PRCA. AEAB testing was conducted, with the results as shown in ***Graph 1***.

Of the 51 cases of suspected PRCA, 53% (27 cases) tested positive for AEAB, with **89%** (24 cases) involving **subcutaneous administration**.

All the confirmed PRCA cases involved the products Eprex® and Recormon®, as these were the only brands available until 2008. Besides **lower usage** of the other brands, **under-reporting** of ADRs related to ESAs is also suspected.

Graph 1: Malaysian ESA-related PRCA reports (2002-2013)



In 2013, NPCB observed a sudden increase in ESA-related PRCA reports (***Graph 1***). This possible safety signal was investigated, but no specific cause was identified. However, an average 70% increase in the overall usage of ESAs was noted from 2010 to 2013.(***Note:*** As of the date of this publication, no reports of ESA-related PRCA have been received by the NPCB for the year 2014).

Risk Minimisation Actions

The benefit-risk profile of ESAs remains positive provided the following risk minimisation measures are adhered to:

1) *Antibody testing*
   - All product registration holders provide antibody testing for suspected PRCA cases in accordance with the established procedures and checklists.
2) *Storage and handling*
   - ESAs must be stored according to conditions listed in the product package inserts (temperature 2-8°C).
   - Patients and healthcare professionals must be fully instructed regarding storage and handling of these products.
3) *Route of administration*
   - Intravenous (IV) route: preferable for chronic renal failure patients, especially those on haemodialysis with ready intravenous access
   - Subcutaneous (SC) route: **higher immunogenic potential**[1] but may be used when IV access is not readily available, e.g. peritoneal dialysis patients[3,5].
4) *Patient monitoring*
   - Monitor for signs and symptoms of PRCA
   - Investigate further if haemoglobin level progressively drops despite ESA treatment
   - Bone marrow examination and erythropoietin antibody measurement should be reserved for cases in which there is a reasonable suspicion of antibody-mediated PRCA.

The NPCB will continue to monitor the safety profile of ESAs, in particular related to PRCA to ensure early detection of safety signals and implementation of regulatory action if necessary.

Advice for Healthcare Professionals

- Treatment with ESAs must be initiated under supervision of experienced physicians for the approved indications only.
- Storage conditions listed in the product package inserts must be strictly adhered to. ESAs must always be stored between 2-8°C.
- Patients on regular haemodialysis with IV access available: use IV administration of ESAs
- All ADRs suspected to be related to ESA use should be reported to the Drug Safety Monitoring Centre, NPCB.

References:

1. Eckardt KU and Casadevall N (2003).*Pure red-cell aplasia due to anti-erythropoietin antibodies.* Nephrol Dial Transplant 18: 865–869.
2. Schellekens H (2002). *Bioequivalence and the immunogenicity of biopharmaceuticals*. Nat Rev Drug Discov 1: 457–462.
3. Eprex Malaysian Package Insert [Version: 12 February 2009].
4. The Malaysian National Adverse Drug Reaction database, NPCB. [Accessed: 2 March 2014]
5. Rath T, Mactier RA, Weinreich T and Scherhag AW (2009). *Effectiveness and safety of recombinant human erythropoietin beta in maintaining common haemoglobin targets in routine clinical practice in Europe: the GAIN study.* Curr Med Res Opin 25(4): 961-970.