ISSN: 0219 - 2152 Dec 2017 Vol.19 No.3

ADVERSE DRUG REACTION NEWS

HSA Health Sciences Authority

Contents

- Risk of hepatitis B virus reactivation with ibrutinib 1-2
- AE Case in Focus : Test Yourself 2
- Biomedical informatics sessions by Research Assistant Prof Robert Carroll, Vanderbilt University School of Medicine 3
- A quick guide to biosimilar products 4-5
- An epidemiological analysis of thrombocytopenia following childhood vaccination in Singapore 6-7
- List of Dear Healthcare Professional Letters 7
- Answers to AE Case in Focus: Test Yourself 8

RISK OF HEPATITIS B VIRUS REACTIVATION WITH IBRUTINIB

Key Points

- Overseas cases of hepatitis B virus (HBV) reactivation have been reported in patients who received treatment with ibrutinib
- Healthcare professionals should be aware of the risk of HBV reactivation associated with ibrutinib and ensure that HBV status of patients who require ibrutinib treatment is established before initiating treatment

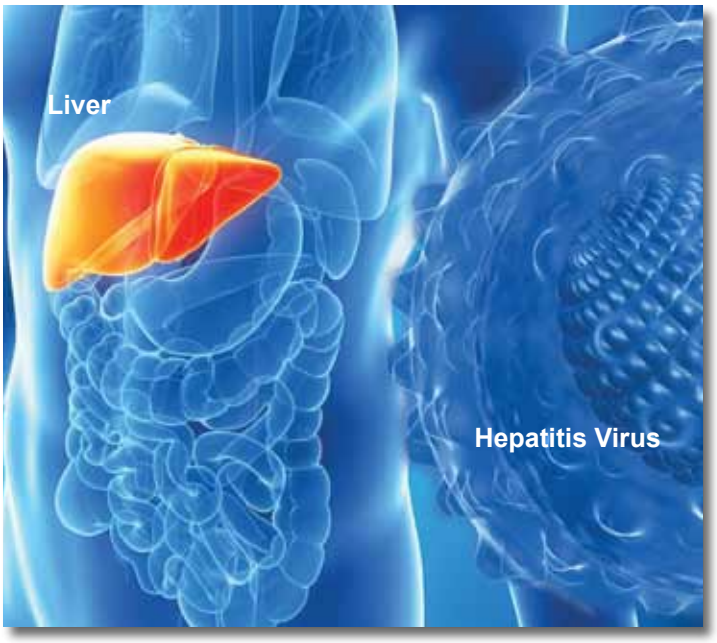
HSA would like to bring to the attention of healthcare professionals the potential risk of hepatitis B virus (HBV) reactivation associated with ibrutinib treatment. This risk was identified by the European Medicines Agency (EMA) following its review of overseas cases of HBV reactivation in patients who received treatment with ibrutinib.

Ibrutinib (Imbruvica®, Johnson & Johnson Pte Ltd), registered locally in July 2015, is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK). It is approved for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, chronic lymphocytic leukaemia (CLL), including CLL with 17p deletion, and Waldenström's macroglobulinaemia.

BTK is an important signalling molecule of the B-cell antigen receptor (BCR) pathway implicated in the pathogenesis of several B-cell malignancies, including MCL and B-cell CLL. The inhibition of BTK by ibrutinib blocks BCR signalling, thus interfering with malignant B-cell proliferation and survival.

Review by the EMA[1, 2]

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) conducted a routine review examining the safety profile of ibrutinib, which identified cases of HBV reactivation in ibrutinib-treated patients. This cumulative review took into consideration available data from clinical trials, scientific literature, as well as postmarketing adverse drug reaction reports of HBV reactivation in patients receiving ibrutinib treatment.



EMA's review of cumulative data available till November 2016 identified eight cases of HBV reactivation in which the role of ibrutinib was considered possible or probable. In other cases, the role of ibrutinib in the onset of HBV reactivation could not be clearly established due to confounding by prior or concomitant treatment regimens known to be associated with the development of viral reactivation. The remaining cases had insufficient information to allow for meaningful causality assessment. None of the cases of HBV reactivation had led to fulminant liver failure requiring liver transplantation. However, there was one report with a fatal outcome, which was attributed to HBV reactivation and concurrent metastatic melanoma of the liver, lung and spleen.

Based on review of the available information, the EMA's PRAC concluded in June 2017 that the benefit-risk balance of ibrutinib in relation to its approved indications remained unchanged. However, the PRAC recommended that healthcare professionals establish the HBV status of patients prior to initiating treatment with ibrutinib. In patients with positive hepatitis B serology, consultation with a hepatic disease expert is recommended before initiating treatment with ibrutinib. The PRAC also advised that patients with positive hepatitis B serology who require ibrutinib, be monitored and managed according to local medical standards of care, so as to minimise the

risk of HBV reactivation. A letter to healthcare professionals was issued across the European Union (EU) in July 2017 to inform them about this new safety information. The EU product information for ibrutinib would also be updated to include warnings on the risk of HBV reactivation and to include HBV reactivation as an uncommon adverse reaction.

Local situation and HSA's advisory

To date, HSA has not received any local adverse reaction report of HBV reactivation in patients receiving treatment with ibrutinib. Johnson & Johnson Pte Ltd has informed HSA that the Singapore package insert for Imbruvica® will be updated to include safety information regarding the risk of HBV reactivation. In view of the higher prevalence of hepatitis B in Singapore than in Europe, and the potentially serious outcomes caused by HBV reactivation in immunosuppressed patients, healthcare professionals should ensure that HBV status is established before initiating treatment with ibrutinib. They are also advised to closely monitor patients with positive hepatitis B serology who require ibrutinib and institute appropriate therapy as indicated to minimise the risk of hepatitis B reactivation.

References

1. *https://www.gov.uk/drug-safety-update/ibrutinib-imbruvica-reports-of-ventricular-tachyarrhythmia-risk-of-hepatitis-b-reactivation-and-of-opportunistic-infections*
2. *https://assets.publishing.service.gov.uk/media/598dbe0740f0b6794e62337e/Imbruvica_DHPC_170617.pdf*

AE CASE IN FOCUS: TEST YOURSELF

Clinical case

A female patient in her 30s was diagnosed with seropositive non-erosive rheumatoid arthritis (RA). She was on regular follow-up to monitor her condition and symptoms of any adverse drug reaction. Her medical condition had been well controlled with sulfasalazine 1g orally twice daily. Three months after sulfasalazine was initiated, her pre-clinic consult blood tests showed a significant drop of her white blood cells (WBC) to 0.91 x 10^9/L with undetectable neutrophils [baseline WBC 4.95 x 10^9/L; absolute neutrophil count (ANC) 2.89 cells/μL]. The patient was called back and was admitted to hospital for severe leucopenia with agranulocytosis. Her vital signs were stable, and she was generally well on admission, exhibiting no clinical symptoms or signs of infection. Sulfasalazine was stopped immediately upon admission. Two full blood count (FBC) tests were conducted on the first two days of admission and the results showed an increasing trend of her WBC: 1.14 x 10^9/L (ANC 0.17 cells/μL) and 1.76 x 10^9/L (ANC 0.21 cells/μL) respectively. In addition, the results for tests to check for viral infection (cytomegalovirus and parvovirus) were negative and liver function test (LFT) values remained within normal limits. The patient was given one dose of Granulocyte Colony-Stimulating Factor (GCSF) 300μg to stimulate the bone marrow to produce granulocytes. The patient responded positively to the treatment, and her WBC rose to 2.43 x 10^9/L (ANC 0.97 cells/μL) the next day. During her inpatient stay, other than the complaint of mild right wrist stiffness that started two days after sulfasalazine was discontinued, she was otherwise well and was discharged after four days.

Question:
What could have caused severe leucopenia with agranulocytosis in this patient?

HSA would like to take this opportunity to thank Dr Andrew Green, Preventive Medicine Senior Resident, NUHS for contributing this article and Prof Chng Hiok Hee, Senior Consultant, Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital for her professional inputs.

Answers can be found on page 8

BIOMEDICAL INFORMATICS SESSIONS BY RESEARCH ASSISTANT PROFESSOR ROBERT CARROLL, VANDERBILT UNIVERSITY SCHOOL OF MEDICINE

In May 2017, HSA's Vigilance and Compliance Branch organised a series of talks on biomedical informatics. Research Assistant Professor Robert Carroll from the Department of Biomedical Informatics at Vanderbilt University School of Medicine was invited to share about his research using electronic health records (EHR) data tied to DNA biobanks*. The eMERGE (Electronic Medical Records and Genomics) Network is a United States network of nine hospital systems which combines EHR systems with DNA bio-repositories to perform research which examines the association between genetics and phenotypes extracted from EHR.

Key topics covered

These sessions were attended by participants from academia, healthcare institutions and public health organisations who are interested in the field of biomedical informatics. Research on EHR is done at Vanderbilt University using patients' data that are continuously de-identified and updated to create a mirror image of the EHR known as the Synthetic Derivative. This is linked to BioVU, a collection of de-identified DNA samples via a pseudo-identifier. As such, a valuable resource is created for investigators to study genotype-phenotype* associations, thus facilitating research relating to precision medicine, genome-driven diagnostics and therapeutics.

Another topic that was shared included methods that used EHR data to predict patients' disease states and drug responses in order to phenotype individuals. One of these methods is called Natural Language Processing (NLP), which can be applied to convert unstructured clinical text documents into computable, structured data. In the area of pharmacovigilance, preliminary studies have been conducted using NLP to extract information on diseases, related symptoms and drug concepts from clinical text, and using statistics to find correlations between drugs and their known adverse events.

Assistant Professor Carroll also shared on the different clinical terminologies (e.g., SNOMED-CT*, MedDRA*, ICD-10*) available and the existing tools that can map to these terminologies due to the inconsistency of the terminologies used across EHR systems. These mapping tools will enable information to flow across systems and to facilitate the electronic exchange of clinical health information.

Conclusion

In line with international developments, HSA has ongoing initiatives in the area of using de-identified EHR for the detection of safety signals. These sessions have provided HSA and our collaborators a good learning opportunity to continue to develop our pharmacovigilance capabilities in the field of bioinformatics. With new insights imparted on the use of biomedical informatics tools, participants were challenged to explore the use of these tools for potential application in safety signals detection locally. HSA will continue to work with relevant stakeholders and explore various methodologies on the use of healthcare analytics data to further enhance public health surveillance.

* Useful definitions

DNA biobank	A repository of extracted DNA samples that serve as a resource for studies of genotype-phenotype associations
Genotype	Specific genetic constitution at a given location (e.g., what allele a person has at a given location)
Phenotype	An observable trait resulting from genes and the environment, and an interaction of the two
SNOMED-CT	Systematised Nomenclature of Medicine - Clinical Terms
MedDRA	Medical Dictionary for Regulatory Activities
ICD-10	International Classification of Disease 10th Revision

HSA staff and Research Assistant Professor Robert Carroll (fifth from the left on the top row)

Participants from academia, healthcare institutions and public health organisations at the session

HPRG's Group Director, Assoc. Professor Chan Cheng Leng presenting a token of appreciation to Research Assistant Professor Robert Carroll

A QUICK GUIDE ON BIOSIMILAR PRODUCTS

In recent years, the expiration of patents on many biologics has led to the availability of biosimilars in the market. Biosimilars are highly similar versions of biologic medicines which unlike chemical generics are very complex and difficult to reproduce exactly. As more biosimilars are approved and used in Singapore, HSA would like to update healthcare professionals on what biosimilars are, the regulatory requirements for registration and the post-market safety surveillance measures. The FAQs below provide answers to common questions asked.

1. What are biologic medicines?

Biologics are medicinal products produced in living organisms. Unlike small molecule chemical medicines such as paracetamol, for which the manufacturing process can be replicated to produce an identical copy ("generics"), biologics are large complex molecules produced by living cells through highly specific processes. Even a slight change in the manufacturing process may vary the structure of the biologic compound and consequently impact the efficacy, safety and quality of the biologic medicine.

2. What are biosimilar medicines?

Biosimilars are "follow-on" versions of innovator biologic medicines. These "follow-on" versions are required to demonstrate similarity in physical and chemical characteristics, biological activity, safety and efficacy to the first approved biologic medicine, also referred to as the reference biologic product (RBP). The route of administration, dosage form and the strength of the biosimilar product should be the same as the RBP. Biosimilar product is not identical but similar to the RBP.

3. Are biosimilar medicines the same as generic drugs?

Biosimilar medicines are not the same as generic chemical drugs. The active ingredient in generic drug is identical to the reference chemical drug, whereas for biosimilars, it is not identical to the RBP. This is because generic medicines are easy to duplicate due to their simple and well characterised structure, but biologics are difficult to duplicate due to their complex structure and manufacturing processes. Therefore, a biosimilar product can only be similar to the RBP but not identical.

Biosimilars and generics generally undergo abbreviated clinical development riding on safety and efficacy data of the innovator reference product, but the process for biosimilars is more complicated than the generic drug. For chemical drugs, the manufacturer of a generic must demonstrate that the generic drug is bioequivalent to the reference chemical drug and no clinical efficacy or safety studies are usually required. However, the bioequivalence approach for chemical drugs cannot be appropriately employed for biosimilars. Biosimilar manufacturers must demonstrate comparability to RBP in terms of physicochemical and biologic characteristics as well as safety and efficacy to demonstrate that there are no clinically meaningful differences between the RBP and the biosimilar product. The amount of clinical data required for a biosimilar product may vary depending on the complexity of the active ingredient, its characterisation, the approved indications etc. (refer to FAQ 2 and 4).

4. How are biosimilar products approved?

Biosimilar products are required to go through a scientifically rigorous pathway based on a stepwise head-to-head comparability to the RBP in terms of quality of product (physical and chemical characteristics), non-clinical studies (toxicity and functionality) and clinical studies (safety, efficacy and immunogenicity). The comparability studies are designed to show similarity and demonstrate that there are no clinically meaningful differences between the RBP and biosimilar product.

A biosimilar product may ride on the safety and efficacy of the RBP to obtain approval for one or more indications approved for the RBP without head-to-head comparison in clinical studies for each indication. This is based on the overall evidence taking into account the physicochemical similarity demonstrated through analytical and functional assays (structure, molecular weight, binding assays, etc.) that the biosimilar works in the same way as the RBP, as well as clinical studies conducted in the most sensitive clinical setting which allows the bridging of the efficacy and safety to other indications.

5. Can a biosimilar be used interchangeably with the RBP?

Interchangeability means the ability to change patient's treatment between the RBP and the biosimilar, while achieving the same treatment response and safety profile in each individual patient.

A biosimilar should be comparable to the RBP in efficacy and safety, although their clinical effects may not be identical. To demonstrate that interchanging between RBP and the biosimilar does not change the clinical response in the individual patient, specific clinical studies need to be conducted. These involve patients receiving initial treatment of either the RBP or the biosimilar and subsequently crossing over to the other treatment. Patients are then assessed if the clinical effect achieved by the initial treatment is maintained after crossing over to the subsequent treatment. Not all companies may conduct interchangeability studies. Please refer to the package insert of approved biosimilars for information on the relevant clinical studies. The package inserts are available on HSA website, Infosearch - Register of Therapeutic Products.

If a clinician decides to change a patient's treatment to a biosimilar, careful monitoring of clinical response of the individual patient is advised.

6. What are the biosimilars approved in Singapore?

There are five biosimilar products approved in Singapore:

Biosimilar	Reference Biologic Product	Active ingredient	Approval date
SciTropin A	Genotropin	Somatropin	March 2009
Nivestim	Neupogen	Filgrastim	July 2012
Zarzio	Neupogen	Filgrastim	March 2015
Basaglar	Lantus	Insulin glargine	August 2016
Remsima	Remicade	Infliximab	March 2016

7. What are the important information required when reporting adverse events (AEs) associated with biosimilars?

Please refer to the table below for important information required when reporting an AE associated with biosimilars:

Information required	Details required	Rationale
Patient's details	Initials, gender, age/date of birth	To identify duplicate reports
Reporter's details	Name, place of practice, contact number	To obtain follow up information if necessary
Details of adverse event	Date of onset/latency, concise description of adverse event (e.g., type of rash)	For causality assessment
Suspected biosimilar	**Brand name**, active ingredient, dose, therapy dates, indication, **batch/lot number**	To identify brand or batch/lot related issues
Concomitant health product(s)	Brand name/active ingredient	To identify any confounders
Other relevant information	Pre-existing conditions, known allergies, lab results etc.	
Outcome	Recovery status, sequelae	
Seriousness of event	The event is classified as 'serious' if it fulfills any of the criteria below: • Patient died due to reaction • Life threatening • Congenital anomaly • Involved or prolonged in-patient hospitalisation • Involved persistent or significant disability or incapacity • Medically significant	
Treatment given	Yes/No. If yes, please specify	

It is important to provide the **brand name** and **batch/lot number** of the biosimilar in the AE reporting form*. Due to the characteristics of biologic medicines (refer to FAQ 2 and 3), variations in the production process may lead to variability between different batches/lots of the same product. Hence, clear identification of the product based on the brand name and batch/lot number is needed to detect brand- or batch/lot-specific AEs.

8. What are the post-marketing measures put in place to monitor the safety of biosimilars?

The current post-market vigilance systems for detecting safety issues relating to RBPs are applicable to biosimilars. These may include:

- Reporting of serious AEs associated with biosimilars to HSA by product registrants (companies) or healthcare professionals;
- Timely update by product registrants on significant safety issues and safety-related regulatory actions taken by overseas agencies;
- Submission of benefit-risk evaluation reports relating to the biosimilar by product registrants (when required);
- Conduct of post-marketing safety studies by product registrants (when required).

Risk minimisation activities to mitigate the risks known to be associated with RBPs will generally be adopted for biosimilars. These may include:

- Warnings and precautions in package inserts (e.g., cautionary statement on the risks associated with switching of products during treatment);
- Provision of educational materials for physicians and/or patients (when required).

In conclusion, the availability of biosimilars in the market has provided a cost-saving treatment option for patients on biologic therapy. However, due to the limited post-market safety experience at the time of registration, healthcare professionals are strongly encouraged to be vigilant of any suspected serious AEs associated with biosimilars and report them to the Vigilance and Compliance Branch of HSA via our AE reporting form* or by providing the details submitted through the following channels:

Email : HSA_productsafety@hsa.gov.sg

Phone : (65) 6866 1111

Electronic reporting:
http://www.hsa.gov.sg/ae_online

Mail:
Vigilance and Compliance Branch
Health Products Regulation Group
Health Sciences Authority
11 Biopolis Way
#11-03 Helios
Singapore 138667

Fax : (65) 6478 9069

***HSA AE Reporting Form is down-loadable from HSA's website:**
http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Safety_Information_and_Product_Recalls/Report_Adverse_Events_related_to_health_products.html

Useful Information

Doctors, dentists and pharmacists can claim continuing education points for reading each issue of the HSA ADR News Bulletin. Doctors can apply for one non-core Continuing Medical Education (CME) point under category 3A, dentists can apply for one Continuing Professional Education (CPE) point under category 3A and pharmacists can apply for one patient-care Continuing Professional Education (CPE) point under category 3A per issue of the bulletin.

AN EPIDEMIOLOGICAL ANALYSIS OF THROMBOCYTOPENIA FOLLOWING CHILDHOOD VACCINATION IN SINGAPORE

Key Points

- An increase in cases of infant thrombocytopenia following vaccination was detected in KK Women's and Children's Hospital (KKH) in 2014 and 2015
- Apart from being temporally-related to hepatitis B and BCG vaccines, investigations did not find any clear causative link to the vaccines
- Active surveillance and monitoring of vaccine adverse events are important in providing reassurance and maintaining confidence in public health vaccination programmes

The Health Sciences Authority (HSA) has worked in collaboration with KK Women's and Children's Hospital (KKH) to establish a sentinel site to perform active surveillance for adverse events following immunisation (AEFI).[1] Unlike a spontaneous adverse event (AE) reporting system that relies on doctors to report suspected AEs to HSA, in an active surveillance system, potential AEFI are proactively identified from patients' medical records and vaccination history when patients are first admitted into the hospital. Through this program, an increase in the cases of thrombocytopenia in infants less than one year of age was observed in the year 2014 and 2015. The team conducted an epidemiological analysis of paediatric thrombocytopenia cases classified as temporally associated with vaccination during the period of January 2012 to December 2016 to investigate the increase in thrombocytopenia cases.

Methodology

A search for thrombocytopenia cases was conducted in the HSA-KKH Inpatient Surveillance of Post Immunization Reactions (HK-INSPIRE) database, which is the repository for AEFI cases collected from daily hospital surveillance. All thrombocytopenia events in patients admitted to KKH that had been classified as being temporally associated with vaccination (onset within 35 days) from January 2012 to December 2016 were analysed.

Thrombocytopenia was defined as having a platelet count of less than $150x10^9$/L. All 'possible-and-above cases' defined in accordance with World Health Organization Uppsala Monitoring Centre (WHO-UMC) causality assessment system[2] were included. Cases where routine infective screens were positive were excluded.

The cases were analysed in terms of temporal trends, interval category (vaccination versus onset date), patient's basic demographics, median of the platelet count, the brand name of the suspected vaccine(s), vaccine dose and batch number, where available.

Results

There were 27 thrombocytopenia cases classified as temporally associated with vaccination during the period of January 2012 to December 2016. Thirteen of the cases met the inclusion and exclusion criteria. Figure 1 shows the increase in thrombocytopenia cases from July 2014 onwards. The rate of increase in cases returned to baseline by October 2015 and there had been no unusual sudden increase in cases from October 2015 to December 2016.

Majority of these cases involved patients who were less than 6 months old (85%) and were females (62%). The median platelet count was 54 $x10^9$/L, with a range of 2 - 115 $x10^9$/L. Seven (7/13) of the patients developed thrombocytopenia within seven days of vaccination. The presenting symptoms included generalised macular rash, petechiae, blood streaks in stools or bruising.

The vaccines that were temporally associated with thrombocytopenia were hepatitis B (Engerix-B®, GlaxoSmithKline) and BCG vaccines (three different brands were implicated). Seven cases (7/13) involved the first dose of hepatitis B vaccine and BCG vaccine. There were also four cases and two cases that were temporally linked to the second and third doses of hepatitis B vaccine respectively (Figure 2). For hepatitis B vaccine, a total of nine batches were associated with cases of thrombocytopenia. One of the batches (AHBVC319BB) was linked to three cases but two of these patients were receiving their second and third doses. The available vaccine batch numbers of the cases were different for BCG vaccines except for one batch number which was involved in two cases. Based on the above, the issue was assessed as not likely to be batch-related.

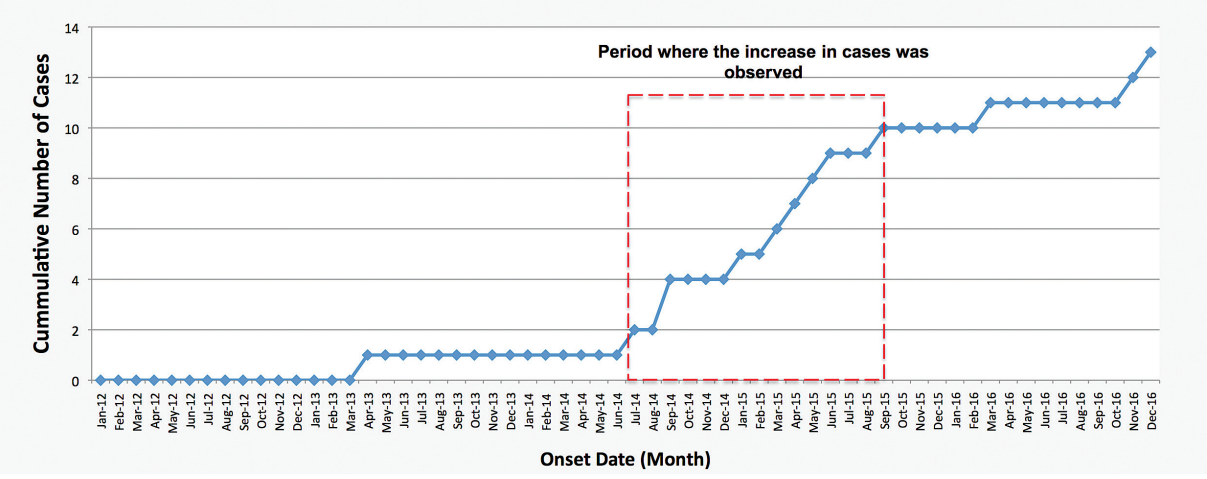


Figure 1. Cumulative number of thrombocytopenia cases classified as 'possible-and-above' from January 2012 to December 2016 in KKH

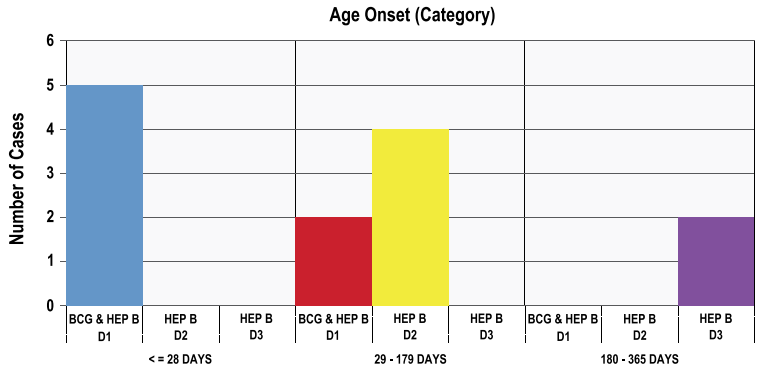


Figure 2. Distribution of age, vaccine type/dose and interval between vaccinations to detection of thrombocytopenia

Observations and conclusions

Based on the available information, it was observed that there was a cluster of thrombocytopenia cases temporally linked to hepatitis B with/without BCG vaccination from July 2014 to September 2015. The rate of increase in cases plateaued by October 2015 and no unusual spike in cases was observed from October 2015 to December 2016. All of the patients recovered from the thrombocytopenia episodes with no mortality or morbidity detected.

Investigations into the cause of the increase did not detect any obvious causative link with hepatitis B or BCG vaccine apart from a temporal association. The BCG vaccine was considered less likely to be causally-related since it was implicated in only seven out of 13 cases and different brands were involved in these seven cases. The investigation was therefore focused on Engerix-B®. No significant manufacturing changes or specific safety issues were identified by the company in the review period. Assessment of overseas reports captured in the company and WHO's global pharmacovigilance databases (Vigibase) and checks with regulatory agencies overseas also did not identify any safety concerns with the hepatitis B vaccine and thrombocytopenia.

The final analysis showed that spikes in a clinical event with a temporal link to the receipt of vaccination(s) does not necessarily equate to a causal link. While the causation for thrombocytopenia in these cases remains undetermined, idiopathic thrombocytopenia is known to occur in neonates. This incident demonstrated the importance of active surveillance and monitoring of vaccine AEs in providing reassurance and maintaining confidence in the public health vaccination programmes.

References

1. *Vaccine 2014; 32(39): 5000-5005*
2. *http://apps.who.int/medicinedocs/en/d/Jh2934e/15.html*

The contents of this article was adopted with permission from a poster presentation at the 9th KKH Scientific Meeting 2017 and edited for the purpose of the bulletin. The editorial team would like to thank Dr Yung Chee Fu, Ms Oh Bee Khiam, A/Prof Chong Chia Ying, Dr Natalie Tan and A/Prof Thoon Koh Cheng for contributing the above article.

LIST OF DEAR HEALTHCARE PROFESSIONAL LETTERS ON SAFETY CONCERNS ISSUED BY HSA, PHARMACEUTICAL AND MEDICAL DEVICE COMPANIES (1 SEPTEMBER 2017 TO 30 NOVEMBER 2017)

For details of the DHCPL, please log on to MOHAlert via your professional board's website.

Therapeutic products

23 Oct 2017	**PREGNYL (human chorionic gonadotrophin)** Update to its Singapore product package insert to include a new contraindication and additional information to the warnings
30 Nov 2017	**Dengvaxia® (CYD dengue virus serotype 1,2,3 and 4)** Advisory and update to its Singapore product package insert on assessing the dengue serostatus of an individual before vaccination. This advisory is due to a review of the results from a supplemental exploratory study to further assess the long-term safety and efficacy of Dengvaxia®

Medical devices

29 Sep 2017	**Covidien Endo GIA™ Black Radial Reload with Tri-Staple™ Technology** Voluntary recall of specific lots due to device cartridge disengagement during use due to manufacturing error
16 Oct 2017	**LENTIS Foldable Intraocular Lenses** Voluntary recall of specific lots due to lens opacification issues
20 Oct 2017	**DELTA XTEND™ Reverse Shoulder System Modular Centered and Eccentric Epiphysis Implants** Urgent recall of specific lots due to out-of-specification manufacturing issue and advisory to cease use of all affected devices
6 Nov 2017	**Endologix Nellix® EndoVascular Aneurysm Sealing System** Update to the Instruction For Use (IFU) due to new information on patient selection criteria, options for secondary interventions in patients who have specific Nellix-related complication and information related to off-label use
9 Nov 2017	**Stryker rHead Radial Implant System** Voluntary recall of affected device due to a review of current data which was found to be inconclusive to continue supporting the performance of the device
23 Nov 2017	**ACETABULAR CUP INTRODUCER (32mm)** Voluntary recall of specific lots due to reports of melting of the nylon ejector slug during the autoclave process
28 Nov 2017	**Eluvia™ 150mm and Innova™ 180mm & 200mm Stent Systems** Voluntary recall due to elevated complaint rates for partial stent deployment
28 Nov 2017	**Anaconda™ Longer Leg Iliac Stent Graft System** Updates on complaints of detachment of the delivery system sheath from the collar during stent deployment. Risk to patient is assessed to be negligible

ANSWERS TO AE CASE IN FOCUS: TEST YOURSELF

Sulfasalazine

Sulfasalazine is a disease-modifying antirheumatic drug (DMARD) and is indicated for the treatment of rheumatoid arthritis (RA) and inflammatory bowel diseases.[1] In the treatment of RA, sulfasalazine has been shown to reduce swelling, alleviate pain, and prevent progression of joint damage.[2] It is postulated that these benefits are largely attributed to its active metabolite, sulfapyridine, although the parent molecule may also play a role.[3] Studies have suggested that sulfasalazine may exert its disease-modifying effects by inhibiting the secretions of inflammatory cytokines such as interleukin (IL)-8,[4] osteoclast formation via modulatory effects on the receptor activator of nuclear factor-kappa B (NFkB),[5] or tumour necrosis factor (TNF)-alpha expression via apoptosis of macrophages.[6]

Leucopenia and agranulocytosis adverse effects

While sulfasalazine is usually quite well tolerated, there are adverse effects (AEs) associated with its use.[3,7] The AEs can either be idiosyncratic (e.g., hypersensitivity-related) or dose-related.[8] It is estimated that leucopenia occurs in 2% of RA patients on sulfasalazine and the incidence is lower for agranulocytosis.[3] Women are twice as likely to suffer from agranulocytosis as compared to men, and its incidence rises sharply with age and polypharmacy.[9,10] More specifically to RA, concurrent use of sulfasalazine and etanercept has been shown to cause greater depression of neutrophil counts than that which occurs when either drug is used alone.[11]

While symptoms associated with dose-related leucopenia tend to be mild and transient, fatalities due to agranulocytosis or other types of blood dyscrasias have been previously observed.[12-14] Agranulocytosis caused by a hypersensitivity reaction usually presents within days or weeks after beginning the drug, with septic symptoms developing acutely and are often severe.[3,8] In contrast, patients with dose-related agranulocytosis are commonly asymptomatic (such as the case above) or may present with "flu-like" symptoms e.g., fever, chills, sore throat, malaise with immediate or an insidious onset, depending on the time course of neutropenia development.[3,15]

Generally, the condition of non-idiosyncratic, dose-related leucopenia or agranulocytosis improves upon lowering the dose or discontinuation of the suspected drug. Furthermore, a number of non-randomised studies have reported encouraging results with the use of GCSF in patients with drug-induced agranulocytosis: shorter recovery times,[16,17] less antibiotics use,[18,19] and shorter lengths of hospitalisation compared to controls.[19]

Local reports

To date, HSA has received ten reports of leucopenia and three reports of agranulocytosis associated with the use of sulfasalazine from 2003 to 2016. All the AE reports listed sulfasalazine as the only suspected drug. Out of the reports, all patients were female except for one patient who was a male. Their ages ranged from 32 to 78 years old.

Precautions

AEs arising from sulfasalazine use may be moderated by slow initiation of drug therapy and by serial monitoring of specific laboratory tests (mainly full blood count (FBC), liver function test (LFT), creatinine) with the first three months after initiating treatment being the most intensive.[3] Bone marrow depression and leucopenia have been reported within the first three months of starting sulfasalazine treatment.[1] Accordingly, the American College of Rheumatology Guidelines for the treatment of RA recommends performing FBC with differentials and LFT before starting therapy, then every 2 to 4 weeks for the first 3 months of therapy, followed by every 8 to 12 weeks for the subsequent 3 months, and then once every 3 months thereafter or as clinically indicated to permit early detection of AEs.[20] Studies have shown that such intense screening measures have been able to detect progression of haematological abnormalities prior to the development of symptomatic infection, leading to prompt interventions, and thereby reducing morbidity and mortality.[11]

HSA's advisory

HSA strongly encourages healthcare professionals to be vigilant to possible serious AEs when patients on sulfasalazine presents with 'flu-like' symptoms and to report any adverse events suspected to be associated with its use to the Vigilance and Compliance Branch of HSA. Your support of the national safety monitoring programme is invaluable in safeguarding public health.

References

1. *Singapore package insert for Salazopyrin EN-Tablet. Approved Oct 2013.*
2. *https://www.rheumatology.org/i-am-a/patient-caregiver/treatments/sulfasalazine-azulfidine*
3. *https://www.uptodate.com/contents/sulfasalazine-in-the-treatment-of-rheumatoid-arthritis*
4. *Exp Mol Pathol. 2002;73:84*
5. *Arthritis Rheum. 2004;50:3831*
6. *Arthritis Rheum. 2000;43:1941*
7. *Rheumatology. 1997;36, p.382*
8. *Therapy of Systemic Rheumatic Disorders. 1998*
9. *The Drug Etiology of Agranulocytosis and Aplastic Anemia. 1991*
10. *Pharmacoepidem Drug Safety. 1993;25*
11. *https://www.uptodate.com/contents/drug-induced-neutropenia-and-agranulocytosis*
12. *Br Med J (Clin Res Ed). 1986; 293(6544):420–423*
13. *Drugs. 1986;32 Suppl 1:49-53*
14. *Eur J Clin Pharmacol. 1992;43:215-8.*
15. *Pharmacotherapy: A Pathophysiologic Approach 9 ed., eChapter 24;pg 363-65*
16. *JAMA. 1994;271:935-938*
17. *Thyroid. 1997 Aug;7:575-8*
18. *Br J Haematol. 2010;150:3-8*
19. *Arch Immunol Ther Exp (Warsz). 1996;44:255-8*
20. *Arthritis Rheumatol. 2016;68:1-26*

Please send your enquiries, comments and suggestions to:

Vigilance and Compliance Branch
Health Products Regulation Group
Health Sciences Authority
11 Biopolis Way, #11-01,
Helios, Singapore 138667

Tel : (65) 6866 1111
Fax : (65) 6478 9069

Website: http://www.hsa.gov.sg
Email: HSA_productsafety@hsa.gov.sg