AMERICAN COLLEGE OF RHEUMATOLOGY
POSITION STATEMENT

SUBJECT: Pharmacovigilance

PRESENTED BY: Committee on Rheumatologic Care

FOR DISTRIBUTION TO: Members of the American College of Rheumatology
Food and Drug Administration
Medical Societies
Centers for Medicare and Medicaid Services
Managed Care Organizations/Third Party Carriers
Members of Congress
Arthritis Foundation

POSITIONS:

1. The American College of Rheumatology (ACR) supports robust pharmacovigilance to support the safety of medications used in rheumatology.

2. The ACR supports the ongoing development of the Sentinel System by the Food and Drug Administration (FDA).

3. The ACR recognizes the vital role of healthcare providers in actively monitoring patients for adverse events, and reporting any serious adverse events through MedWatch.

4. When reporting adverse events related to biologics, the ACR urges the reporting of full product information, including biosimilar suffix, lot information, and indication for using the drug.

5. The ACR recommends pharmacovigilance systems be readily available and easy to use for patients given the current partial reliance on patients for spontaneous reporting of adverse events.

BACKGROUND:

Pharmacovigilance is the science of detection and assessment of adverse effects from drugs, with particular emphasis on effects not recognized prior to licensing.[1] Pharmacovigilance is important because most new drugs receive marketing approval after testing in a limited (frequently less than 1000) number of patients for a limited time period.[2] At time of marketing the safety profile of any new drug is incomplete. After marketing, the drug is used in a much larger and more diverse population, allowing for the detection of rare adverse events, as well as events that are more common in particular sub-populations of patients. Pharmacovigilance is also important in detecting bad lots of drug or other unexpected changes to a drug's safety profile.

Pharmacovigilance in the U.S.

Pharmacovigilance, as a formal activity, is primarily carried out by drug manufacturers and the drug regulatory agency of each country (specifically, the FDA in the United States). The FDA's Office of Surveillance and Epidemiology (OSE) is charged with evaluating product risks and promoting the safe use of products by the American people. Within this Office are three divisions including the Division of Drug Risk Evaluation (DDRE).[3]

New drugs are often approved in the United States with very few patient-years of exposure; therefore, the FDA takes a continuous life-cycle approach to monitoring drugs for safety. Detection of adverse events essentially occurs in 2 ways: Detection of new adverse events can come from reports of individual cases (voluntarily from patients or health professionals, and mandatorily by manufacturers); or through aggregation of observational data in large databases.

The FDA has several programs for monitoring trends in drug safety. The oldest of these is the **Adverse Event Reporting System (AERS)**. This was originally developed in 1969 as the Spontaneous Reporting System and migrated to AERS in 1997.[4] This program collects information on individual reports of adverse drug reactions. The majority of these reports come from manufacturers due to mandatory reporting requirements as they become aware of this information.

Additional information enters AERS from voluntary, direct reports from patients and medical professionals through the MedWatch program. Through MedWatch, health care professionals and consumers may submit electronic reports to AERS when they find a problem with a drug, medical device, biologic agent, or other FDA-regulated product.

Additional programs relevant to pharmacovigilance and managed by the FDA include:

REMS: The Food and Drug Administration Amendments Act of 2007 gave the FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks in everyday use. These programs range from medication guides for patients, to restricted prescription and distribution networks. See current examples at REMS@FDA.[5]

Safe Use Initiative: This is a system of private and public collaborations with the healthcare community. Its goal is to reduce preventable harm by identifying specific medication risks and developing, implementing and evaluating cross-sector interventions with partners who are committed to safe medication use.
https://www.fda.gov/Drugs/DrugSafety/SafeUseInitiative/default.htm

Sentinel Initiative: This is a linked, sustainable system that uses existing automated databases from multiple sources to actively monitor drug safety and rely less on spontaneous case reports. A pilot phase – Mini-Sentinel – was completed and the full system was implemented in 2016.[6] It is particularly important with the advent of accelerated approval of drugs. Sentinel is a distributed system – all data stay in their existing environments, not a central database. FDA identifies safety questions and sends them to participating partners. Data partners (e.g.

potentially RISE for ACR) may then evaluate data in their own systems with appropriate privacy protections and forward results to FDA for aggregation.

Pharmacovigilance in the International Setting

The United States also participates in pharmacovigilance on a world-wide level. After nearly 10,000 babies were born with birth defects associated with thalidomide, the World Health Organization (WHO) developed a pharmacovigilance program called Programme for International Drug Monitoring (PIDM) in 1968. Within this program, pharmacovigilance is performed at the national level, with countries reporting adverse events through a protocol called Individual Case Safety Reports. As of January 2016, 127 countries, including the United States, report to the PIDM. Data are stored at the Uppsala Monitoring Centre in a database called VigiBase.

Additional examples of international pharmacovigilance bodies are noted in the appendix.

The Importance of Pharmacovigilance in the Biosimilar Era

Due to the complex manufacturing processes of biopharmaceuticals, biosimilars are not identical to their reference products or even between two different biosimilar manufacturers. This may result in differences in adverse events and/or immunogenicity between originator and biosimilar products. As such, adverse event reporting with biologics (including biosimilars) should include the drug name suffix. Furthermore, lot number should be included in the medical record of all patients receiving biologic medications to allow for detailed post-marketing analyses and attribution of adverse events to the correct biologic.

For robust pharmacovigilance of biosimilars to occur, there must be the ability to track the products to the manufacturer. Under the FDA's final naming guidance, all biological products must bear a non-proprietary name that includes a unique four-letter suffix. The ACR additionally advocates for inclusion of lot number for each medication to improve tracking. As the US healthcare system relies heavily on spontaneous reporting of adverse events from patients and/or health care providers, it is essential that the non-proprietary name and lot number is collected when adverse events are reported to ensure that any post-marketing adverse events are attributed to the correct medication.

Healthcare providers should be educated to include the biologic product's suffix in all prescriptions; if the suffix is missing, the pharmacist should clarify the desired biologic product to be dispensed. This will help prevent inappropriate substitutions. All substitutions from the reference product to a biosimilar, or between biosimilars, should be made under the full knowledge and guidance of the health care provider, in accordance with applicable laws in the jurisdiction.

Given the extrapolation of indications that may occur for biosimilar drugs, the indication for which the biosimilar was prescribed should be collected during adverse event reporting to identify potential at-risk populations for a specific adverse event.

Pharmacovigilance systems need to be readily available and easy to use for patients given the current partial reliance on patients for spontaneous reporting of adverse events.

Rheumatology Providers and Pharmacovigilance

Pharmacovigilance requires the active participation of a variety of stakeholders including patients, healthcare providers, pharmacies and pharmaceutical companies. The ACR recognizes the importance of the active participation of rheumatology healthcare providers in monitoring patients for adverse events, and reporting any serious adverse events through MedWatch. A serious adverse event as defined by the FDA includes an event resulting in death or a life threatening event; an event resulting in hospitalization, disability or permanent damage, or congenital anomaly/birth defect; an event that required medical or surgical intervention to prevent permanent impairment of a body function; or any other serious medical event which may jeopardize the patient.[1] The ACR strongly encourages all rheumatology healthcare providers to report any such adverse events through the FDA website.[7]

REFERENCES:

1. Pitts PJ. 21st century pharmacovigilance: efforts, roles, and responsibilities. Lancet Oncol 2016;17:e486-92.

2. Downing NS, Shah ND, Aminawung JA, et al. Postmarket safety events among novel therapeutics approved by the U.S. Food and Drug Administration between 2001 and 2010. JAMA 2017;317:1854-63.

3. https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm119101.pdf

4. https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm

5. https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm.

6. http://www.fda.gov/safety/fdassentinelinitiative/default.htm

7. https://www.fda.gov/Safety/ MedWatch/HowToReport/DownloadForms/ucm149236.htm

Appendix

In the European Union (EU), two major pieces of legislation in 1995 and 2012 formed the framework for the European Medicines Agency (EMA). The EMA is responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU. The EMA will license medications for use in the EU, implement pharmacovigilance legislation, submit safety updates, and develop GVP (Good PV practices) standards reports. Data are collected and stored in the EudraVigilance data-warehouse system overseen by the Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC will provide recommendations on

pharmacovigilance and risk management. The PRAC is made up of experts in medicine safety from Member States, with each Member State sending 2 representatives. Brexit will result in the UK losing its two members to the EMA/PRAC. The EMA works closely with the FDA and WHO.

In the United Kingdom (UK), pharmacovigilance is managed by the Medicines and HealthCare products Regulatory Agency or MHRA. MHRA is the executive agency of the Department of Health in the UK. MHRA is responsible for medications and device safety and efficacy in the UK and develops the GPvP (standards document for good practices of pharmacovigilance). MHRA will submit a yearly report called Pharmacovigilance Assessment Report (PPAR) for health providers. To report an adverse drug reaction or a problem with a medical device, patients and providers may submit a Yellow Card report via the Yellow Card Scheme on MHRA website.

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