

Name:	Nicole Pratt
Affiliation:	University of South Australia
Email:	nicole.pratt@unisa.edu.au
Presentation type (select one):	Poster

Utilising the power of the OHDSI network to generate large scale evidence of the safety of biologics

Nicole L. Pratt, PhD¹, Libby E. Roughead, PhD¹, Michael Ward, PhD¹, Lisa Kalisch Ellett, PhD¹, Andrew Milburn, PhD¹, Marc A. Suchard, MD, PhD², Martijn Schuemie, PhD³

¹University of South Australia, Adelaide, South Australia, Australia; ²UCLA School of Public Health, Los Angeles, California, USA; ³Janssen R&D, Titusville, New Jersey, USA

Abstract

Biologics are increasingly becoming an integral part of treatment and the ongoing development of these medicines particularly for chronic disease will see more of these medicines being used by a much wider patient population. The expiration of patents for existing biologics will lead to the introduction of lower-cost biosimilar medicines, furthering increasing the expected utilisation of biologics in clinical practice. Despite knowledge that adverse events are more frequent for biologics than conventional products and that new biologics have had three times more safety regulatory warnings than conventional medicines, there are no estimates of the global harms from biologics. We propose a study which will build an active post-market surveillance approach to monitor the use and adverse events associated with biologic medicines in the real-world setting.

Introduction

Biologic medicines are predominately immune-based therapies used to treat a wide range of disease including cancer, diabetes, multiple sclerosis, heart attack, asthma, inflammatory bowel disease and autoimmune disorders such as rheumatoid arthritis. While clinically effective, the unique mechanisms of action of biologics can result in unpredictable and life threatening adverse events. Expanding indications, off-label use, use of multiple biologics for multiple diseases, and sequential use of biologics further exacerbates the potential for adverse events. Due to the limitations of pre-market clinical trials, some serious safety concerns have only emerged as populations have become increasingly exposed to biologics in the post-market setting. For example, in South Australia, of 56 patients dispensed ipilimumab for malignant melanoma¹, eight were admitted to hospital for severe, steroid refractory colitis and two of these patients received a colectomy after another biologic, infliximab failed to resolve the colitis. In practice the rate of colitis was 3 times higher than in clinical trials and the estimated cost to manage the adverse events in these patients was over \$400,000. Efalizumab, for treatment of psoriasis, was withdrawn 6 years post approval after three cases of progressive multifocal leukoencephalopathy (PML) were detected². PML has also been identified post-market with natalizumab³, for treatment of multiple sclerosis, which resulted in a temporary removal from the market. Risk of PML was shown to increase with duration of use of natalizumab and modified with prior use of immunosuppressants. These examples highlight the need for a rapid post-market surveillance system for biologics that not only identifies and quantifies harms, but identifies particular characteristics that make patients more vulnerable to harm. The aim of this study is to develop a comprehensive post-market surveillance program for biologics using both the Observational Health Data Sciences Informatics (OHDSI) and the Asian Pharmacoeconomics Network (AsPEN).

Methods

To describe biologic use we will use the **OHDSI ATLAS** platform to generate cohorts of patients exposed to biologics and examine trends over time in 1) uptake of biologics, 2) incident and prevalent use of biologics, 3) use of concurrent biologics for the same condition and across multiple conditions. Using the **OHDSI Treatment Pathway**

tool we will describe treatment pathways, or the ordered sequence of biologic use for a patient. Characterising treatment pathways will reveal how countries differ in their treatment approaches with biologics. Practice differences between regions will provide a mechanism to investigate potential modifying factors associated with risk. We will systematically determine the risk and quantify the harm of serious acute and long term adverse events associated with biologic medicines, including infection, anaphylaxis, and immunological side effects involving the liver (e.g. hepatitis), eyes (e.g. uveitis), gut (e.g. colitis), skin (e.g. skin eruptions), and lungs (e.g. respiratory infections) in datasets large enough to have sufficient power to detect them. **To quantify incidence and risk of severe acute and long-term adverse events with biologics we will use OHDSI SelfControlledCaseSeries and CohortMethod packages to generate possible associations between biologics and adverse events. OHDSI LAERTES Evidence Base Explorer** will be used to determine adverse events of interest for investigation. Further to determining whether biologics are associated with increased risk of harm at the population level it is important to identify the particular characteristics of patients that may make them more vulnerable to these risks. As well as the prior use of other biologics or use of multiple biologics, other factors including conventional medicine use, comorbidity, age and gender may all modify the risk of side effects with biologics. Using **OHDSI PatientLevelPrediction** package we will **develop predict patients who experience serious adverse events following treatment with biologics.** The **OHDSI FeatureExtraction** package will be used to develop prediction variables. Identifying characteristics of those who are most at risk of harm with biologics will have a significant impact on patient safety by providing knowledge for clinicians to modify practices for those most of risk.

Conclusion

This research specifically responds to the call-to-action by the European Medicines Agency to develop better strategies to identify and quantify safety problems arising with biologics. Our aim is to generate real world evidence for regulators, clinicians and patients to support decision-making.

References

1. Commonwealth of Australia. Public Summary Document - Ipilimumab Incidence and costs of treating adverse events. In: Committee PBA, ed. Canberra: Commonwealth of Australia; 2015.
2. Food & Drug Administration (FDA). FDA Statement on the Voluntary Withdrawal of Raptiva From the U.S. Market. 2009, 2017.
3. Lichtenstein GR, Hanauer SB, Sandborn WJ. Risk of Biologic Therapy-Associated Progressive Multifocal Leukoencephalopathy: Use of the JC Virus Antibody Assay in the Treatment of Moderate-to-Severe Crohn's Disease. *Gastroenterology & hepatology*. Nov 2012;8(11 Suppl 8):1-20.