Incidence of Serious Infections in Patients Receiving Biologic Anti-inflammatory Agents for Rheumatologic, Dermatologic, and Gastrointestinal Conditions – A Descriptive Analysis

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DISCLOSURE

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BACKGROUND

- Biologics bring challenges in post-approval surveillance of real world clinical use, safety, and effectiveness, different from small molecules and generic drugs.
  - Biologic molecules are much larger, with complex structures, and can't be chemically synthesized to be identical.
  - Complex manufacturer process using living cells.
  - Regulatory approval for biosimilars requires:
    - Adherence of the biosimilar to the same quality standards as the reference biologic.
    - Approved biosimilars be highly similar to the reference product in structure and function.
    - No clinically meaningful differences in safety or effectiveness.
  - In real world clinical practice when reference biologic and biosimilars are used in diverse populations and over long period of time.
    - Differences in structure or impurity profile that are thought at inital approval to be non-meaningful or changes in manufacturing process may result in increased risk of rare safety events unidentified from trials.
    - Postmarket safety events are common after FDA approval.[1]
    - The Biologics and Biosimilars Collective Intelligence Consortium (BBCIC), a non-profit public service initiative dedicated to providing scientific evidence on the use and comparative safety and effectiveness of biologics and biosimilars.
  - Brings expert participants with varying perspectives from managed care organizations, integrated delivery systems, pharmacy benefit management firms, research institutions, and pharmaceutical companies.
  - Has assembled a distributed research network (DRN) consisting of commercial health insurance providers and integrated delivery systems to conduct post-marketing surveillance in a transparent and unbiased fashion under the control of a public charter and independent scientific oversight.[2]

OBJECTIVE

- To evaluate the capability of the BBCIC DRN for post-marketing surveillance of reference biologics prior to introduction of biosimilars.
  - Sufficient (size) patient population.
  - Availability of data elements to identify and characterize patient populations, quantify exposure to reference biologics and key study outcomes.
- To build frame work for post-marketing surveillance of reference biologics and biosimilars in future comparative study.
  - A descriptive analysis of patients with autoimmune diseases treated with biologics and non-biologic agents, which have been associated with increased infection risk.

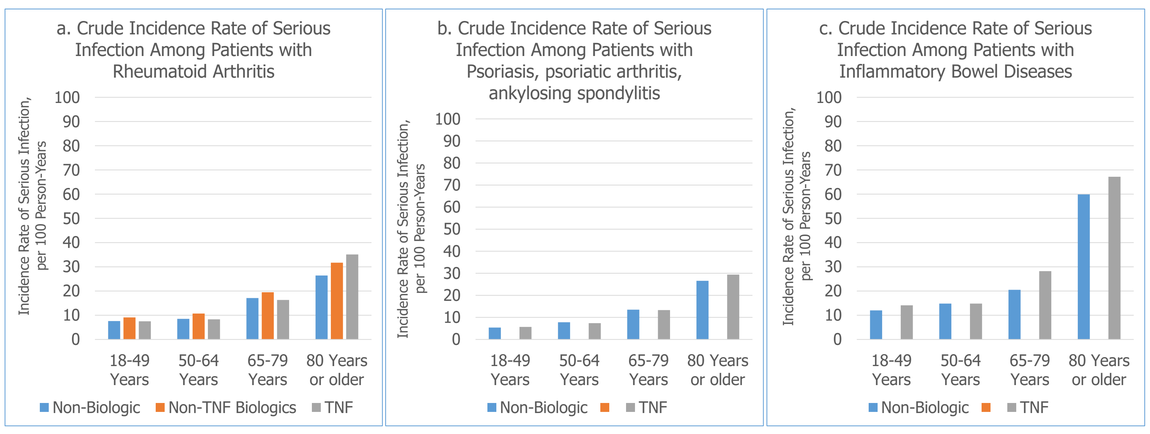
METHODS

- A retrospective cohort study among patients enrolled in one of the insurance plans that contributed data to the BBCIC DRN between 1 January 2006 to 30 September 2015.
- Eligibility Criteria:
  - Have newly initiated a disease modifying non-biologic, a tumor necrosis factor (TNF) biologic, or a non-TNF biologic agent, AND
  - Have a prior diagnosis of rheumatoid arthritis (RA), psoriasis, psoriatic arthritis, ankylosing spondylitis, (collectively referred to as "other inflammatory conditions"), or inflammatory bowel diseases (IBD), AND
  - Be at least 18 years old, AND
  - Have at least 365 days of continuous medical and pharmacy coverage prior to treatment initiation (index date).
- Follow-up started on index date and ended at the earliest of the occurrence of the outcome, treatment discontinuation or switching, death, disenrollment, or end of study period.
- Exposure Classification:
  - Mutually exclusive categories: 1) any anti-TNF biologic (regardless of non-biologic use); 2) any non-TNF antagonist biologics (regardless of non-biologic use, RA only); and 3) any non-biologic disease-modifying agents.
  - Switching: Treatment episodes were truncated when a patient switched within (from one TNF antagonist to another) or between the categories (step up from non-biologic to biologic).
- Outcomes:
  - Serious infection, defined as an emergency room visit or hospitalization with a diagnosis code for infection.
  - Pneumonia, defined similarly.
- Data Analysis:
  - The study leveraged the Sentinel infrastructure, such as the common data model (CDM) and the analytic programs, for all data management and analysis activities.
  - Descriptive statistics of patient characteristics ascertained during 183 days prior to index date.
  - Unadjusted incidence rates of outcomes during follow up were calculated, stratified by disease and treatment.

RESULTS

- The study identified 111,611 eligible patients with RA (75% female), 61,959 with psoriasis (52% female), and 30,628 with IBD (51% female).
- Anti-TNF biologics were the most commonly initiated medications, accounting for 98% of IBD, 89% of psoriasis, and 79% of RA patients.
- The overall estimated incidence rate of serious infection was 9.8 (95% CI 9.5-1.0) cases per 100 person years in RA, 7.1 (6.8-7.5) in patients with other inflammatory conditions, and 14.2 (13.6-14.8) in IBD patients.
- When stratified by treatment type, serious infection rates were lowest for patients initiating TNF agents for both RA and psoriasis and for non-biologic agents for IBD; incidence rates increased with age, monotonically (Figure 1).

Figure 1. Incidence Rates of Serious Infection among Patients with Rheumatoid Arthritis (a), Psoriasis, psoriatic arthritis, ankylosing spondylitis (b), and Inflammatory Bowel Diseases (c), by Treatment Class and Age Group



- Additional and detailed data presented in Table 1.

Table 1. Incidence Rates of Serious Infection, Overall and by Treatment Group

	Rheumatoid arthritis				Psoriasis, psoriatic arthritis, ankylosing spondylitis				Ulcerative colitis, Crohn's disease			
	# of Events	# PY	IR	95% CI	# of Events	# PYs	IR	95% CI	# of Events	# PYs	IR	95% CI
Overall	**4,649**	**47580**	**9.8**	**9.5-10.0**	**1,577**	**22076**	**7.1**	**6.8-7.5**	**2,169**	**15251**	**14.2**	**13.6-14.8**
TNF inhibitors	1,974	22057	8.9		912	13423	6.8		1,192	8000	14.9	
Non-TNF Biologics	648	5137	12.6									
Non-biologic	2,027	20386	9.9		665	8652	7.7		977	7251	13.5	

Abbreviations: Confidence interval = CI; Person-Years = PY; Incidence rate, per 100 PYs = IR

CONCLUSIONS

- BBCIC DRN is a useful source for biologic surveillance:
  - Provides sufficient sample size and follow-up time to examine relatively uncommon adverse events overall and in key subgroups (i.e., stratified by age group).
  - Contains adequately detailed data elements to characterize the study populations.
  - Produces risk estimates that were within the range of estimates previously reported.
- Methodologic challenges, lessons learned, and recommendations:
  - Significant complexity in the ascertainment of exposure to biologics.
    - Dependent on formulations available and place of service.
  - Sentinel infrastructure offered significant computational efficiency.
    - Simplified the process to conduct multi-database studies.
    - Allowed rapid, consistent and concurrent execution of validated analytic programs.
  - Recommendations:
    - In-depth understanding of the CDM and the analytic programs.
      - CDM assigns one day supply to HCPCS code by default.
      - CDM currently do not include HCPCS modifiers.
      - De novo programming may be required for select data management/analytic tasks.
    - Pilot analytic program before distributing Sentinel queries across all data sources.
      - Revisions may be needed as assumptions on data may not be true.
      - Revisions may be needed if unexpected results are observed.
    - Engagement of disease and methods experts, including Sentinel analyst.
  - Limitations:
    - Did not perform any adjusted analysis.
    - Did not include any biosimilar in the study given the study period (no biosimilar was available for the inflammatory conditions during the study period).
  - Ongoing BBCIC Work Group to address additional methodological challenges:
    - The utility of medical claim NDC codes and the use of HCPCS modifiers to ascertain biosimlar exposure.
    - How to compare treatment naive and treatment-experienced (biosimilar users who have transitioned from reference biologics).

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