An Active Safety Surveillance Using Real-World Evidence (ASSURE) Approach to Pharmacovigilance Signal Evaluation: The case of infliximab and alternative autoimmune conditions

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Background

Extensive literature exists on the topic of TNF-alpha inhibitors and the biological plausibility for risk of alternative autoimmune conditions or paradoxical reactions. Ward et. al.[1] showed that TNF-alpha inhibitors had significantly increased risk for overall immune mediated inflammatory disorders vs. azathioprine. This is contrasted with the work of Jun et. al.[2] which showed, in patients with inflammatory bowel disease, TNF-alpha inhibitors were not associated with psoriasis as an outcome.

OHDSI's standardized tools (e.g. the Strategus package[3] and the HADES modules) can be used to conduct rapid, high-throughput safety signal evaluations of marketed medical products. These tools form the foundation of the Active Safety Surveillance Using Real-World Evidence (ASSURE) team within Johnson & Johnson's Innovative Medicine Global Epidemiology Organization which supports safety signal evaluation activities identified through routine pharmacovigilance activities.

Our objective was to evaluate the association between infliximab (INF) and incident inflammatory bowel disease (IBD), rheumatoid arthritis (RA), plaque psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS) hidradenitis suppurativa (HS), dermatomyositis (DM), myositis, and autoimmune thyroiditis (AiT) among patients with prior IBD, RA, PsO, PsA, and AS, utilizing our Active Safety Surveillance Using Real-World Evidence (ASSURE) framework.

Methods

The four pillars of this analysis were defined as **Target**: INF; **Comparators:** adalimumab (ADA), vedolizumab (VEDO), abatacept (ABT), ustekinumab (UST), secukinumab (SEC), azathioprine (AZA), and methotrexate (MTX); **Indications:** IBD, RA, PsO, PsA, and AS (separately); **Outcomes:** IBD, RA, PsO, PsA, AS, HS, DM, myositis, and AiT (separately).

The index date was defined as the first observed use of either infliximab or comparator. Patients were excluded if they had a history of prior drug usage or alternative autoimmune condition under analysis. Patients were only included if they had a history of the indication under analysis. The analysis was restricted to the period after infliximab was approved (i.e., 2003-01-01 or later).

Patients were followed from the index date until the earliest of discontinuation of the index infliximab or comparator plus 31 days, switch to or addition of the comparator agent, end of observation in the database, or the occurrence of the alternative autoimmune condition under analysis for an on-treatment analysis. Patients were considered to have discontinued their index exposure at the first occurrence of a gap of > 30 days between the end of one dispensing's supply and the beginning of the next dispensing. We restricted the cohorts to patients with ≥ 365 days of prior database observation.

Comparative cohort and self-controlled case series (SCCS) designs were employed; the new-user comparative cohort design estimated adjusted hazard ratio (95% confidence interval) in an on-treatment analysis (all-time exposed) using a large-scale propensity score matching approach with 1:100 variable-

ratio matching. The SCCS design estimated an incidence rate ratio during on-treatment compared to unexposed time.

Table 1 shows the comparator selection and highlights the strengths and limitations of each comparator and seeks to aid interpretation of each causal contrast.

Table 1: Comparator Selection

	TNFα Comparator	**Non-TNFα Biologic Comparator**	**Mild Disease Comparator**
Strengths:	May reveal non-null findings if the signal is specific to infliximab	May reveal non-null findings if a class effect	Matches (potentially-poor) comparisons in literature
Limitations:	May return null findings if the signal is a class effect for all TNFα inhibitors	May not clarify whether the signal is specific to infliximab or TNFα inhibitors in general	Likely confounded by indication and/or disease severity
Indication			
IBD[†]	adalimumab	vedolizumab	azathioprine
RA	adalimumab	abatacept	methotrexate
PsO	adalimumab	ustekinumab	methotrexate
PsA	adalimumab	ustekinumab	methotrexate
AS	adalimumab	secukinumab	methotrexate

[†]Includes ulcerative colitis (UC) and Crohn's disease (CD)

A quantitative feasibility assessment identified 9 fit-for-purpose databases (6 U.S. claims, 1 U.S. EHR, 1 non-U.S. claims, and 1 non-U.S. EHR databases). We assessed pre-defined analytic diagnostics (e.g. covariate balance, power) to determine whether to unblind results from each analysis and then we pooled estimates across databases using Bayesian random effects meta-analysis.

Results

All analyses of PsO and AS as an indication and those using MTX as a comparator (RA and PsA indication) failed pre-defined analytic diagnostics. PsA as an indication had no significant meta-analysis findings across all outcomes.

In the IBD indication analysis there were significant meta-analysis findings for infliximab when compared to vedolizumab, hazard ratio of 2.14 (95% CI: 1.31-3.51) [**Figure 1**] and compared to azathioprine, hazard ratio of 2.11 (95% CI: 1.24-3.59) for the outcome of RA. Additionally, in the IBD indication analysis there were significant meta-analysis findings for infliximab when compared to azathioprine for the outcomes of PsA, PsO, and AS, 2.13 (1.24-3.66), 1.83 (1.27-2.64), 1.99 (1.03-3.63), respectively.

In the RA indication analysis, there were significant meta-analysis findings for infliximab when compared to adalimumab, hazard ratio 1.62 (95% CI: 1.04-2.53) [**Figure 2**] and compared to abatacept, hazard ratio 1.64 (95% CI: 1.09-2.46) for the outcome of IBD. Additionally, in the RA indication analysis there were significant meta-analysis findings for infliximab when compared to abatacept, hazard ratio 2.15 (1.36-3.41) for the outcome of AS.

There were no significant meta-analysis findings produced by SCCS analyses.

Figure 1: IBD Indication Infliximab vs. Vedolizumab Outcome RA

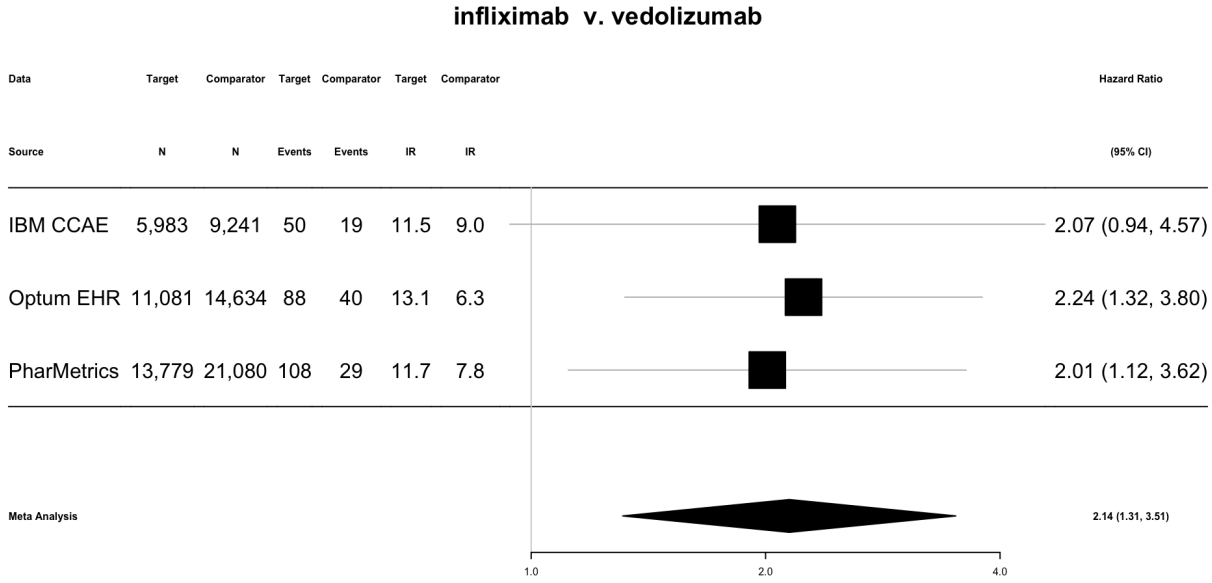
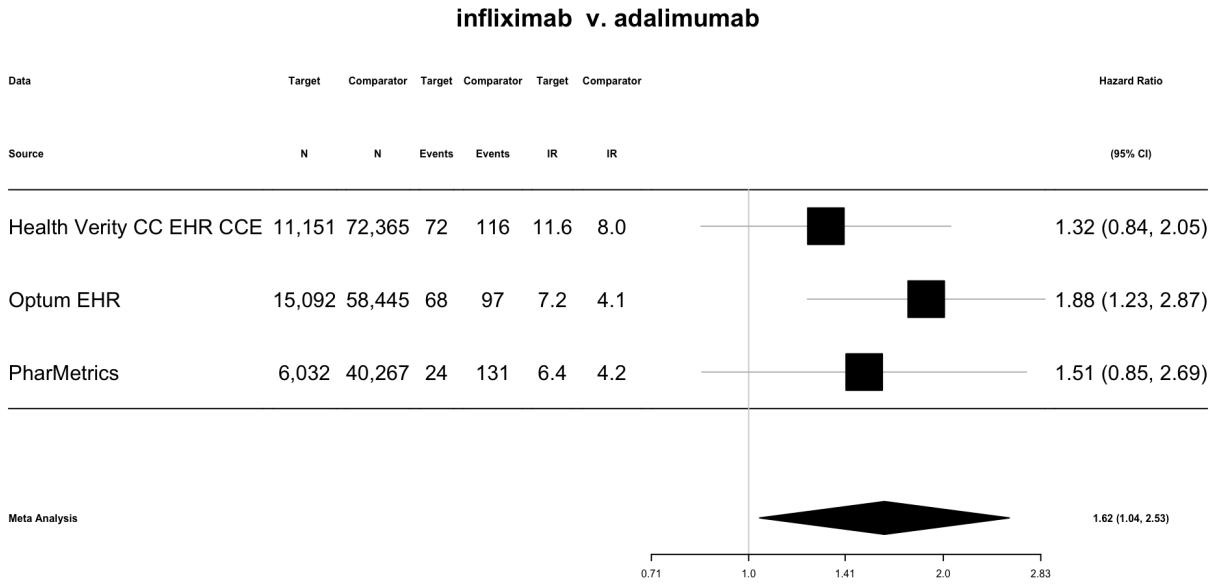


Figure 2: RA Indication Infliximab vs. Adalimumab Outcome IBD



Conclusion

Our analysis complements existing literature indicating an increased risk of alternative autoimmune conditions among infliximab treated patients compared to biologic and non-biologic therapies. Several analyses using multiple databases, indicated populations, and comparators failed to pass pre-defined diagnostics.

References

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