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Impact of Biologics on Healthcare Utilization in Patients with Rheumatoid Arthritis: An Instrumental Variable Approach

Nick Bansback[1,2,3], Eric Fu[1], Huiying Sun[1], Daphne Guh[1], Wei Zhang[1,2], Diane Lacaille[3], Aslam H. Anis[1,2,3]

1. *Centre for Health Evaluation and Outcome Sciences, 2. School of Population and Public Health, University of British Columbia, 3. Arthritis Research Centre of Canada*

CHÉOS Centre for Health Evaluation & Outcome Sciences

Background

Over 1 billion dollars were spent on TNF antagonists in 2011, predominantly for the treatment of rheumatoid arthritis (RA). Spending is justifiable based on improvements in disease activity and suppression of joint destruction leading to:

A. Anticipated long-term improvements in quality of life.
B. Future cost offsets through reduced hospitalizations, physician visits and other drug use.

While substantial evidence exists of benefits of long-term improvement in QOL (A), little evidence exists to support cost offsets (B).

Objective

To investigate the impact of biologic treatment on other health care resource utilization using a population-based cohort with administrative health data.

Methods

Data obtained from BC Linked Administrative Databases:

- Medical Services Plan (MSP) data encompasses billing data on physician visits, procedures performed and all investigations ordered from fee-for-service physicians.
- Discharge Abstracts Database (DAD) has records on hospital inpatient separation records, including resource intensity weight.
- BC PharmaNet database contains records of every prescription drug filled and cost.
- Vital Statistics data
- Data available: Jan 1, 1996 to March 31, 2010

Cohort Selection

- The RA case definition used has been previously described.[1] In this study, we further selected patients with at least 5 years of complete MSP registration after meeting the inclusion criteria so that exclusion criteria was applied on complete data.
- Patients were selected from this population-based RA cohort if:
  - They were eligible for PharmaCare coverage of a biologic in BC based on drug history from April 2003 to March 2007.
  - Received cared by a rheumatologist in the 1st year after eligibility
  - Had 3-years of follow up after eligibility

Exposure

- Treatment group: received a biologic within 365 days of eligibility
- Control group: never received a biologic within the 3 years despite being eligible

Outcomes

- Primary outcome: The cumulative direct cost of RA related hospitalizations, physician services, and prescription medications other than biologics and DMARDs incurred per patient over 3 yrs.

Analysis

Model 1: Ordinary ;east squares (OLS)

$$Cost = \beta_0 + \gamma T + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_p X_p + \varepsilon,$$

Where ***Cost*** = log(health expenditures)

- ***T*** is treatment, $\boldsymbol{X_1}$ to $\boldsymbol{X_p}$ observed confounders (age, sex, RA duration and previous health care utilization)
- ***γ*** is the cost difference due to health care utilization between treatment groups after controlling for the known confounders
- However, if ***γ*** is correlated with ***ε*** (error term), the estimate could be biased and inconsistent.

Model 2: Instrumental Variable (IV) using 2 stage lease squares (2SLS)

$$T = \alpha_0 + \eta IV + \alpha_1 X_1 + \alpha_2 X_2 + \ldots + \alpha_p X_p + \delta$$

$$Cost = \beta_0 + \gamma \hat{T} + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_p X_p + \varepsilon,$$

- IV approach can estimate treatment effects in the presence of *unmeasured confounding factors.*
- An IV needs to be 1) associated with treatment, 2) unrelated to the outcome, other than through its association with the actual treatment

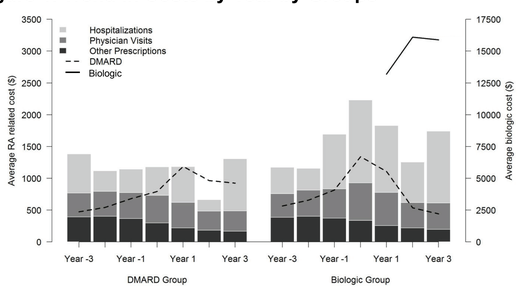
We use an IV based on physician preference for using biologic treatment in eligible patients.

1) IV associated with treatment : Patients who visit a physician with high preference of biologics will be more likely to be prescribed a biologic
2) IV unrelated with cost (the outcome), other than through treatment: Mix of severity of patients seen by each physician is unlikely to vary across physicians since long wait lists

Results

Figure 1 describes the components of (RA related) costs over time. The use of DMARDs in the biologic group decreases over time since attaining eligibility in comparison to the control arm, but the additional cost of the biologic far exceeds these costs. Interestingly, the cost of physician visits falls over time for both groups while the total frequency of surgeries is small.

Figure 1. Trend in Costs by Year by Groups



Among the 18,999 RA patients who had complete MSP registration after meeting the inclusion criteria, 1,328 became eligible for a biologic between April 2003 and March 2007. Of these, 314 patients received a biologic within 1 year of eligibility (treatment group), and 504 never received a biologic within the 3-year follow-up (control) (Table 1).

At baseline, the treatment group was more likely to have had a RA related surgery, had higher RA related and total resource utilization 1 year prior to baseline (Table 1, first 2 columns). Over the 3 years, the treatment group continued to incur higher costs.

Figure 2 demonstrates the desired heterogeneity in physician prescribing for eligible patients for use of an IV. This is captured by the IV and columns 3 and 4 of Table 1 describe characteristics of the cohort using the median of the physician preference. IV appears to work, with most characteristics between groups becoming better balanced.

Table 1. Demographics and 3 year cumulative costs by group and IV group

Variable	Treatment	Control	IV-Prefer Biologic	IV-Not Prefer Biologic
	N (%) / Median (Q1 - Q3)	N (%) / Median (Q1 - Q3)	N (%) / Median (Q1 - Q3)	N (%) / Median (Q1 - Q3)
N	314	486	392	408
Control			179 (45.7%)	307 (75.2%)
Treatment			213 (54.3%)	101 (24.8%)
Age	57.4 (48.8 - 66.1)	57.2 (46.9 - 68.8)	58 (48.9 - 68)	56.1 (46 - 67.3)
Female	242 (77.1%)	379 (78%)	301 (76.8%)	320 (78.4%)
RA disease duration	7 (3 - 9)	6 (3 - 8)	6 (3 - 9)	6 (3 - 8)
Any RA related surgeries	65 (20.7%)	81 (16.7%)	70 (17.9%)	76 (18.6%)
Health care use 1-yr prior				
RA related. all cost ($)	1654 (1228- 2705)	1241 (879 - 1713)	1419 (1020 - 1984)	1347 (920 - 1996)
Total. all cost ($)	4670 (3095 - 7414)	3566 (2384 - 5551)	3849.3 (2610 - 6428)	4046 (2674 - 6240)
No. of RA related physician visits	7 (4 - 12)	5 (3 - 9)	5.5 (3 - 10)	6 (3.5 - 11)
No. of non RA related phys. Visits	29 (19 - 43)	25 (16 - 38)	26 (17 - 41)	27 (17 - 41)
No. of physician visits	39 (26 - 55)	31 (21 - 48)	33 (23 - 51)	36 (23 - 52)
Any RA related hospitalization	28 (8.9%)	26 (5.3%)	28 (7.1%)	26 (6.4%)
Any hospitalization	92 (29.3%)	114 (23.5%)	105 (26.8%)	101 (24.8%)
Number of distinct medication taken	9 (7 - 13)	9 (6 - 11)	8 (6 - 12)	9 (6 - 12)
Continuous care by Rheumatologists during the 3-year follow-up	258 (82.2%)	306 (63%)	278 (70.9%)	286 (70.1%)
Charlson comorbidity index	1 (0 – 2)	1 (0 – 2)	1 (0 – 2)	1 (0 – 2)
RA Related Cost, 3-year cumulative				
All	1839 (1056 - 3357)	1287 (756 - 2599)	1522 (929 - 2918)	1381.3 (796 - 2892)
MSP	1065 (720 - 1644)	801 (538 - 1283)	975 (667 - 1419)	833 (541 - 1377)
Medications	299 (70 - 936)	188 (51 - 685)	222 (53 - 814)	231 (69 - 709)

Figure 2. Distribution of proportion of eligible patients receiving biologics among rheumatologists in 2003/04 - 2006/07

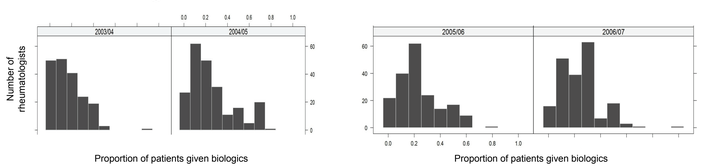


Table 2. Regression results (RA-related costs)

	OLS			2SLS		
	Estimate (SE)	% Increase/decrease wrt. Control group (95% CI)	p-value	Estimate (SE)	% Increase/decrease wrt. Control group (95% CI)	p-value
All	0.163 (0.080)	17.7% (0.6%–37.7%)	0.042	0.473 (0.257)	60.4% (-3.0%–165.3%)	0.066
MSP	0.153 (0.059)	16.6% (3.8%–31.0%)	0.010	0.394 (0.191)	48.3% (2.0%–115.6%)	0.039
Medication	0.031 (0.172)	3.2% (-26.4%–44.5%)	0.857	-0.395 (0.549)	-32.7% (-77.0%–97.4%)	0.471

Results from the OLS analysis showed that being in the biologics group was associated with 17.7% higher costs in RA related resources over the 3-year follow-up since eligibility (Table 2).

Unexpectedly, results from the IV estimation showed that costs increased rather than decreased when attempting to address unobserved confounding (60.4% and 28.6% more in RA related expenditures over 3 and 2-yr follow-up respectively).

Conclusion

This study finds no signal after 3 years that biologic therapies in patients with RA have led to overall cost offsets from RA-related treatment costs. Although costs of RA-related medications were reduced, increases in more expensive resources, such as physician visits, led to higher overall costs.

Possible explanations are:

- Falling resource utilization in both groups, potentially due to more aggressive use of conventional DMARDs in the control group, made it more difficult to demonstrate an impact of biologics on cost savings
- The association observed does not imply that biologics are causally associated with greater resource utilization, and may be due to residual confounding by indication, despite attempts to control for it with IV
- That cost offsets occur beyond 3 years
- The model is mis-specified and estimates remain biased

Given large budgets allocated to biologics, payers are increasingly scrutinising their associated costs and benefits .The message for the rheumatology community is that perceived cost savings due to biologics are not necessarily being realized. Measuring these savings is challenging – administrative databases are likely the only feasible method, but challenges remain in methodology

Future studies addressing this important question are a priority.

Acknowledgements

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[1] *Lacaille D, Anis AH, Guh DP, Esdaile JM. Gaps in care for rheumatoid arthritis: a population study. Arthritis Rheum. 2005 Apr 15;53(2):241-8.*