

Canadian Variation by Province in Rheumatoid Arthritis Initiating Anti-Tumor Necrosis Factor Therapy: Results from the Optimization of Adalimumab Trial

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ABSTRACT. Objective. We compared variations among Canadian provinces in rheumatoid arthritis (RA) initiating anti-tumor necrosis factor (TNF) therapy.

Methods. Data were obtained from the Optimization of Humira trial (OH) and from the Ontario Biologics Research Initiative (OBRI). Baseline characteristics were compared between regions: Ontario (ON), Quebec (QC), and other provinces (OTH). We compared Ontario OH to OBRI patients who were initiating anti-TNF therapy.

Results. In 300 OH patients, mean age was 54.8 years (13.3). There were 151 (50.3%) ON patients, 57 from QC (19%), and 92 from OTH (30.7%). Regional differences were seen in the number of disease-modifying antirheumatic drugs (DMARD) ever taken (ON: 3.8 ± 1.4 , QC: 3.1 ± 1.1 , OTH: 3.3 ± 1.4 ; $p < 0.001$); swollen joint count (SJC; ON: 10.9 ± 5.9 , QC: 9.0 ± 4.4 , OTH: 11.3 ± 5.6 ; $p = 0.033$); tender joint count (TJC; ON: 12.2 ± 7.5 , QC: 10.3 ± 5.7 , OTH: 14.4 ± 7.6 ; $p = 0.003$); 28-joint Disease Activity Score (DAS28; ON: 5.8 ± 1.2 , QC: 5.6 ± 1.0 , OTH: 6.0 ± 1.1 ; $p = 0.076$); and Health Assessment Questionnaire (ON: 1.4 ± 0.7 , QC: 1.7 ± 0.7 , OTH: 1.5 ± 0.7 ; $p = 0.060$). DMARD-ever use differed: methotrexate (ON: 94.7%, QC: 93%, OTH: 84.8%; $p = 0.025$); leflunomide (ON: 74.8%, QC: 21.1%, OTH: 51.1%; $p < 0.001$); sulfasalazine (ON: 51%, QC: 38.6%, OTH: 25%; $p < 0.001$); myochrysine (ON: 9.3%, QC: 0%, OTH: 15.2%; $p = 0.008$); and hydroxychloroquine (ON: 67.5%, QC: 86%, OTH: 66.3%; $p = 0.018$). In comparison to ON OH patients, 95 OBRI patients initiating first anti-TNF had lower SJC ($p = 0.017$), TJC ($p = 0.008$), and DAS28 ($p = 0.05$). **Conclusion.** In Quebec, where access to anti-TNF is less restrictive, patients had lower SJC and TJC. ON used more DMARD, especially leflunomide, as mandated by the provincial government. Both provincial funding criteria and prescribing habits may contribute to differences. Canadian rheumatologists may vary in treatment decisions, but patients generally have similar DAS28 when initiating anti-TNF therapy. (First Release Sept 15 2010; J Rheumatol 2010;37:2469–74; doi:10.3899/jrheum.091447)

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Anti-tumor necrosis factor- α (anti-TNF) therapies, which include infliximab, etanercept, adalimumab, and the recently approved golimumab and certolizumab, have proven to be effective in reducing joint pain and inflammation, slowing disease progression, and improving function and quality of life in patients with rheumatoid arthritis (RA)^{1,2,3,4,5,6,7,8}. However, anti-TNF agents are far more expensive than conventional disease-modifying antirheumatic drugs (DMARD) and this may limit patient access to anti-TNF agents. Despite Canada's ostensibly comprehensive health-care system, reimbursement of anti-TNF agents varies provincially and is supplemented by private insurance for some patients. The use of anti-TNF treatment in RA is far lower in Canada than in the United States, although it may be slightly above the European average⁹.

There is evidence of regional variation in prescribing practices for some conventional DMARD within Canada¹⁰.

However, published data comparing patients with RA initiating anti-TNF treatment in Canada are limited. Our aims were to compare regional variation in prescribing anti-TNF in RA among patients enrolled in the Optimization of Humira (OH) trial, to compare provincial formulary coverage for anti-TNF prescribing in RA, and to validate the Ontario findings from the OH patients using data from the Ontario Biologics Research Initiative (OBRI).

MATERIALS AND METHODS

Data for this study were taken from the Optimization of Humira trial and patients with RA initiating anti-TNF therapies from the OBRI. The OH trial is a multicenter, randomized, controlled, parallel-group, single-blind trial with a total of 32 sites across Canada. The OH trial was undertaken to determine the effect of treatment targets on the outcomes of patients receiving adalimumab (Humira) through usual care. Physicians and their patients were randomized to one of the following groups: treating to 0 swollen joint count (SJC), treating to Disease Activity Score (DAS) < 3.2, or routine care. Patients had to have active RA, access to reimbursable standard care (private and provincial insurance), and a rheumatologist who wished to prescribe adalimumab. Thus, drugs were obtained through usual care. Further, patients had to be ≥ 18 years old and naive to adalimumab therapy, although up to a total of 20% registered patients were permitted to have had previous exposure to other biologic therapy. Any other care was allowed. As part of the OH trial, a database of 300 well characterized patients with active RA was developed. In our study the baseline characteristics of these patients upon entry into the trial were analyzed.

Data were collected and compared according to province and included age, sex, previous biologic use, number and types of DMARD used, SJC (out of 28), number of tender joints (TJC, out of 28), 28-joint Disease Activity Score (DAS28, based on C-reactive protein), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Health Assessment Questionnaire Disability Index (HAQ-DI), and patient assessment of overall health on a visual analog scale (VAS; 0 to 100 mm).

The OBRI is a voluntary registry for patients with RA starting anti-TNF or other biologic therapies and control patients who are changing, adding, or increasing DMARD treatment because of increased disease activity. The control patients were not used in our analysis. For the anti-TNF arm, patients had to have active RA, be able to give informed consent, be initiating their first biologic, and have obtained anti-TNF through usual care. The OBRI collects data from participating physicians every 6 months (DAS, HAQ, adverse events, and global assessments) and from patients by telephone at 3 and 9 months after enrollment. The OH trial patients were recruited before the OBRI was in a pilot phase and there was no overlap in patients between the OH and OBRI patients. All provincial formulary guidelines for anti-TNF therapy coverage in RA were sought from provincial health ministry websites and by asking RA experts in each province.

Patient characteristics in the OH trial were organized into 3 groups according to region (Ontario, Quebec, and all other provinces). Groups were compared by using chi-squared tests for categorical variables and ANOVA for continuous variables. Patients with RA at anti-TNF initiation from the OBRI were compared to biologic-naïve Ontario patients from the OH trial using 2-tailed t-tests. At baseline (randomization visit) patients were asked to assess satisfaction with their current RA treatment. Very well satisfied and well satisfied were combined as "satisfied," and moderately satisfied, a little satisfied, and not satisfied were combined with dissatisfied.

RESULTS

Demographic, disease, and treatment characteristics of 300 patients in the OH trial interim analysis are presented in Table 1. Statistically significant regional differences in dis-

ease characteristics were observed for TJC ($p = 0.003$) and SJC ($p = 0.033$), with lowest values in Quebec and highest in the other provinces group. The number of DMARD used varied regionally ($p < 0.001$), with the highest value in Ontario. Regions also differed significantly in the percentage of patients who received each type of DMARD (Figure 1). More patients in Ontario used leflunomide compared to patients in other provinces. Hydroxychloroquine usage was highest in Quebec. Although methotrexate use differed significantly among regions ($p = 0.025$), in each region over 84% of patients were taking it. A majority of patients, consistently across the regions, were dissatisfied with their current RA treatment.

Table 2 shows the provincial guidelines for anti-TNF therapy coverage in RA. All provinces require intolerance or inadequate response to 2 or more DMARD including methotrexate, and 8 of 10 provinces require a trial of some form of DMARD combination. Seven provinces require a trial of leflunomide. Saskatchewan seems to have the most generous reimbursement criteria among provinces. Quebec has criteria similar to Saskatchewan, although it has more stringent requirements regarding disease activity. Interestingly, Quebec had the lowest mean previous DMARD usage, TJC, SJC, DAS28, and ESR among the 3 regions analyzed (although not all of these differences were significant). Not all patients who initiated anti-TNF treatment met the provincial guidelines and these patients presumably had other private coverage. This highlights the 2-tier system that exists for biologic drugs. Although only 2 provinces (British Columbia and Alberta) require severely active disease for anti-TNF therapy coverage, the mean DAS28 scores in all provinces was above 5.1, a commonly accepted threshold for severe RA.

Table 3 compares the baseline characteristics from the OBRI patients with RA initiating anti-TNF treatment to the subset of Ontario patients from the OH trial who were initiating their first biologic. Biologic-naïve OH patients had higher mean SJC, TJC, and DAS28 scores (2-tailed t tests, $p < 0.05$ in all cases), but no significant differences were found in demographic characteristics or ESR (2-tailed t tests, $p > 0.05$ in all cases). The differences may be related to the timing of data collection. The OH data were collected over the 2 years preceding data collection for the OBRI. Several national databases of biologic use in patients with RA have shown a decline in disease severity measures over time^{21,22,23,24,25}. This decline may be due to increasingly generous coverage criteria and/or increasing physician familiarity with anti-TNF therapies. It is important to note that the provincial coverage criteria did not change over that time interval. Also, the OBRI is still piloting sites, so it may be that physicians who are frequent biologic prescribers are the main participants in the OBRI currently. Thus it could be that low prescribers start treatment with anti-TNF agents at higher disease activity and are underrepresented in the

Table 1. Demographic, disease, and treatment characteristics by province. P values are from one-way ANOVA for means and chi-squared tests for percentage values.

Characteristics	ON	QC	OTH	p
N (%)	151 (50.3)	57 (19)	92 (30.7)	—
Age, yrs (SD)	55.1 (13.3)	54.2 (12.6)	54.6 (13.7)	0.886
Women, %	83.4	70.2	83.7	0.069
Previous biologic use, %	19.9	22.8	21.7	0.878
No. of DMARD (SD)	3.8 (1.4)	3.1 (1.1)	3.3 (1.4)	< 0.001
TJC, 0–28 (SD)	12.2 (7.5)	10.3 (5.7)	14.4 (7.6)	0.003
SJC, 0–28 (SD)	10.9 (5.9)	9.0 (4.4)	11.3 (5.6)	0.033
Patient global assessment, 0–100 mm VAS (SD)	63.9 (27.0)	64.4 (22.0)	62.0 (28.1)	0.820
DAS28 (SD)	5.8 (1.2)	5.6 (1.0)	6.0 (1.1)	0.076
ESR, mm/h (SD)	31.0 (20.4)	26.3 (17.1)	29.2 (23.0)	0.333
CRP, mg/l (SD)	14.7 (17.3)	23.2 (28.6)	19.8 (26.9)	0.062
HAQ-DI (SD)	1.4 (0.7)	1.7 (0.7)	1.5 (0.7)	0.060

OTH: British Columbia (n = 8), Alberta (n = 25), Saskatchewan (n = 17), New Brunswick (n = 8), Nova Scotia (n = 7), and Newfoundland (n = 27). ON: Ontario; QC: Quebec. DMARD: disease-modifying antirheumatic drug; TJC: tender joint count; SJC: swollen joint count; VAS: visual analog scale; DAS28: 28-joint Disease Activity Score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire-Disability Index.

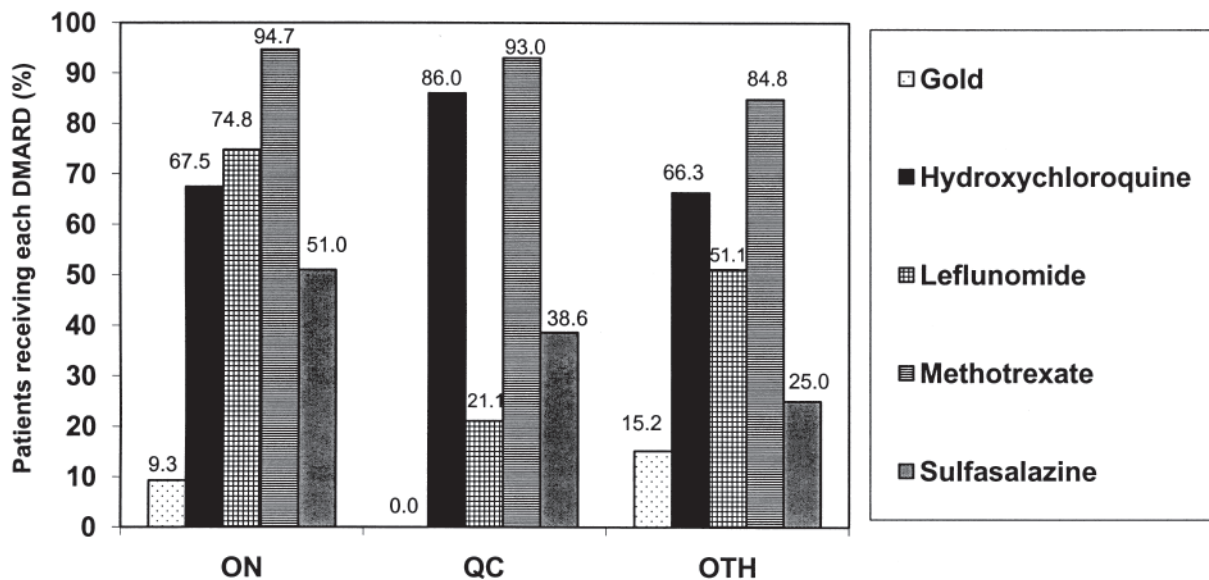


Figure 1. Provinces differ in the percentage of patients who receive each type of DMARD ($p < 0.05$, all comparisons; ON: Ontario; QC: Quebec; OTH: all other provinces). P values for group differences from chi-squared tests: gold, $p = 0.008$; hydroxychloroquine, $p = 0.018$; leflunomide, $p < 0.001$; methotrexate, $p = 0.025$; and sulfasalazine, $p < 0.001$.

OBRI, which could account for the lower mean DAS28 found among OBRI patients.

DISCUSSION

Regional variations were observed in some disease characteristics, such as TJC and SJC, and the number and type of DMARD treatments for patients with RA. Methotrexate use was consistently high across provinces in our study, in keeping with its high use in other countries²⁶ and results from previous studies of DMARD use in Canada¹⁰. The pattern of

leflunomide use (high in Ontario, low in Quebec, moderate in others) can largely be explained by variations in requirements for a leflunomide trial prior to initiation of anti-TNF coverage (e.g., required in Ontario but not in Quebec). Ontario had the highest average use of DMARD prior to anti-TNF therapy initiation. This may reflect the requirement for trials of multiple drugs plus combination therapy before provincial funding of anti-TNF agents.

Variations among provinces in TJC and SJC at initiation of anti-TNF therapy suggest that rheumatologists may vary

Table 2. Criteria for reimbursement for anti-TNF agents among adults (≥ 18 years old) with rheumatoid arthritis in the 10 Canadian provinces.

Province	Required Disease Activity	DMARD Trial (duration of trial*)	Response Required for Continued Coverage (time given)
British Columbia ¹¹	Severely active RA	(1) Parenteral MTX (min 8 wks) AND ≥ 2 of LFL (10 wks), gold (20 wks), sulfasalazine (3 mo), or azathioprine (3 mo) AND (2) At least 1 combination involving MTX plus cyclosporine (4 mo); sulfasalazine and hydroxychloroquine (4 mo); gold (20 wks); OR LFL (10 wks)	Improvement in 68-joint count, SJC, TJC, ESR, CRP, and/or duration of morning stiffness (1 yr)
Alberta ¹²	Severely active RA (DAS28 > 5.1)	(1) Oral then parenteral MTX (12 wks) AND (2) Combination of MTX plus other DMARD (4 mo) AND (3) LFL (10 wks)	ACR20 OR \downarrow DAS28 of 1.2 AND HAQ \downarrow by 0.22 (5 doses)
Saskatchewan ¹³	Active RA	(1) MTX AND LFL	—
Manitoba ¹⁴	Moderate to severe RA	≥ 3 DMARD including MTX or LFL and 1 combination	—
Ontario ¹⁵	Synovitis of ≥ 5 joints and RF+ or joint erosion	(1) MTX (3 mo) AND LFL (3 mo) AND 1 combination of DMARD (3 mo), OR (2) MTX (3 mo) and MTX plus LFL combination (3 mo)	$\downarrow 20\%$ in SJC and improvement in ≥ 2 joints
Quebec ¹⁶	Synovitis of ≥ 8 joints and 1 of RF+, HAQ > 1 , \uparrow CRP, \uparrow ESR, joint erosions	(1) 2 DMARD (3 mo each) including MTX joints AND 1 of: \downarrow	20% \downarrow in inflamed $\geq 20\%$ CRP, or ESR; HAQ $\uparrow \geq 0.2$, or return to work (5 mo)
New Brunswick ¹⁷	Moderate to severe RA	(1) ≥ 2 DMARD (including MTX and LFL) AND (2) Combination including MTX OR 1 additional DMARD	—
Prince Edward Island ¹⁸	Active RA	(1) LFL (3 mo) AND (2) Combination of MTX PLUS ≥ 1 of gold (5 mo), sulfasalazine (3 mo), hydroxychloroquine (4 mo), azathioprine (3 mo), chloroquine (3 mo), or penicillamine (4 mo) OR 2 of above if MTX intolerant OR sequential MTX plus 2 of above DMARD if combination contraindicated	Must reapply as new after 6 mo
Nova Scotia ¹⁹	Active RA	(1) Combination of ≥ 2 DMARD (including MTX and LFL) OR (2) ≥ 3 DMARD in sequence (including MTX and LFL)	$\downarrow 20\%$ in symptoms (6 mo)
Newfoundland ²⁰ and Labrador	Active RA	(1) Combination of ≥ 2 DMARD (including MTX and LFL) OR (2) ≥ 3 DMARD in sequence (including MTX and LFL)	—

* Unless drug not tolerated or contraindicated. TNF: tumor necrosis factor; RA: rheumatoid arthritis; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; LFL: leflunomide; SJC: swollen joint count; TJC: tender joint count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ACR: American College of Rheumatology; DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire; RF: rheumatoid factor.

Table 3. Characteristics of biologic-naïve Ontario patients from the OH and OBRI databases. P values are for comparison using t-tests for means and chi-squared tests for percentage values.

Characteristics	OH	OBRI	p
Period of patient enrollment	Nov 2006 to Apr 2008	Jan 2008 to July 2009	—
No.	120	95	—
Age, yrs, SD	55 (14)	54 (14)	0.568
Women, %	84	85	0.825
Disease duration, yrs	—	11.1	—
DAS28, mean (SD)	5.8 (1.2)	5.3 (1.4)	0.005
SJC, 0–28; mean (SD)	10.7 (6.2)	8.7 (5.9)	0.017
TJC, 0–28; mean (SD)	12 (7.5)	9.3 (7.1)	0.008
ESR, mm/h; mean (SD)	30.5 (20.0)	33.2 (22.5)	0.355

OH: Optimization of Humira trial; OBRI: Ontario Biologics Research Initiative; DAS28: 28-joint Disease Activity Score; SJC: swollen joint count; TJC: tender joint count; ESR: erythrocyte sedimentation rate.

in the specific measures used to make decisions regarding anti-TNF therapy. Along with funding guidelines, factors such as guideline recognition, physician's familiarity and comfort with traditional DMARD and anti-TNF agents, and

the presence of specialized rheumatologic care might give rise to these dissimilarities among provinces²⁷. However, patient profiles among Canadian provinces are similar. No Canadian province has coverage criteria in line with current

North American guidelines for the use of anti-TNF therapy in RA. All provinces require more DMARD trials than current recommendations. A position paper from the Canadian Rheumatology Association recommends that biologic therapy be initiated in patients with active RA after failure of a full trial of a single traditional DMARD (e.g., methotrexate)²⁸. Similarly, the American College of Rheumatology recommends the use of anti-TNF agents after failure of a trial of methotrexate in patients who have established RA (> 6 months' duration) and either high disease activity or moderate disease activity plus poor prognostic features²⁹. Also, anti-TNF agents are recommended without a DMARD trial in patients with early RA (duration < 6 months) if disease activity is high for either 3–6 months or < 3 months if there are poor prognostic factors and no barriers to access²⁹.

Disease duration is not currently considered in provincial coverage criteria. However, in most provinces, the number and duration of required DMARD trials would preclude patients with a disease duration < 6 months from receiving anti-TNF therapy coverage and in most cases disease duration prior to coverage is likely to be considerably longer (e.g., disease duration at anti-TNF therapy initiation was 11.1 years in the OBRI database). This is particularly important given the evidence of the benefit of early aggressive treatment of RA^{30,31} and the effectiveness of anti-TNF agents in early RA^{2,3,4,5}. Given this, an expedited approval process in cases of rapidly progressive disease may be beneficial. Anti-TNF therapy has been associated with a reduction in the rate of radiographic progression of joint damage compared to conventional DMARD in a number of clinical trials^{7,32,33,34}. This suggests that even in established RA, delays in initiation of anti-TNF agents may lead to worsening of joint damage in the long term. Provincial agencies should thus seek to avoid unnecessary delays in the approval of funding for anti-TNF agents for eligible patients.

Many provinces fail to clearly define the response required for continuing anti-TNF therapy coverage, often leading to uncertainty regarding continuing treatment. Providing such definitions, along with greater uniformity among provincial coverage criteria, would mean simpler and more equitable care across Canada.

It was assumed that patients receiving adalimumab therapy were similar to those receiving other anti-TNF treatment in the real world. In the OH trial, the drug had to be available by usual means, so it is likely that these patients are similar to other patients starting other anti-TNF therapies in the many practices that were studied. Further, meta-analyses of clinical trials have shown infliximab, adalimumab, and etanercept to be similar in efficacy^{1,35,36} and there is no evidence to our knowledge of systematic differences between Canadian patient populations prescribed different anti-TNF therapies. However, such evidence does exist for US patients, but this is likely related to unique aspects of American public health insurance programs and is

not generalizable to Canadian patients³⁷. Caution should be used in generalizing results from patients in provinces other than Ontario and Quebec because of the small sample sizes involved.

Canadian provinces are largely similar in prescribing practices, suggesting that anti-TNF agents are being used in a similar range of patients. However, it seems that the prospects for patients with RA are at least partially influenced by their geographic location, likely as a result of variations in criteria for provincial coverage of anti-TNF therapies.

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