Comparison of Anti-TNF Treatment Initiation in Rheumatoid Arthritis Databases Demonstrates Wide Country Variability in Patient Parameters at Initiation of Anti-TNF Therapy

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Objective: Characteristics of Canadian RA patients started on anti-tumor necrosis factor (TNF) treatment were compared with 12 other countries.

Methods: Data from the Optimization of HUMIRA trial (OH) were compared with Canadian real world studies [Ontario Biologics Research Initiative (OBRI) and the Real-Life Evaluation of Rheumatoid Arthritis in Canadians Receiving HUMIRA (REACH)], and to data from American, Australian, British, Czech, Danish, Dutch, Finnish, German, Italian, Norwegian, Spanish, and Swedish RA databases. Patient characteristics and temporal trends at initiation of anti-TNF therapy were compared between countries.

Results: Baseline Disease Activity Scores (DAS28) varied from 5.3 to 6.6. Lower disease severity was noted in databases from countries with less restrictive anti-TNF coverage: Dutch [based on previous disease-modifying antirheumatic drugs (DMARD) use, DAS28, swollen joint count (SJC), tender joint count (TJC), Health Assessment Questionnaire Disability Index (HAQ-DI), Danish (previous DMARD use, DAS28), Norwegian (DAS28, SJC, TJC, visual analog scale (VAS) of global health), and Swedish (DAS28, SJC, TJC, HAQ-DI)]. RA databases showed lower disease scores than did OH ($P < 0.05$). The US databases also showed lower disease severity (CORRONA: previous DMARD use, SJC, TJC; National Data Bank for Rheumatic Diseases: HAQ, $P < 0.001$). The UK and Czech Republic had restrictive coverage and higher mean baseline DAS28 than OH ($P < 0.001$). Baseline DAS28 in the registries with published data lowered over time (British, Norwegian, Danish, and Swedish) but less for the British ($P < 0.001$).

Conclusions: These results confirm that regional variation exists between the 13 countries analyzed in the initiation of treatment with anti-TNF agents among RA patients and suggest that in some cases this variation may be increasing. In some countries the mean baseline disease severity declined

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over time and regional reimbursement policies and differences in physician preferences may be influencing initiation of anti-TNF therapy in RA.

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The development of tumor necrosis factor-alpha (TNF) antagonists since the late 1990s has greatly improved the treatment of rheumatoid arthritis (RA). Anti-TNF therapy has been shown to be effective in reducing joint pain and inflammation, slowing disease progression, and improving function and quality of life in RA (1-5). However, recent evidence suggests that patient response to anti-TNF agents may be less dramatic in "real-life" patient populations compared with RCTs (6-8). Three anti-TNF therapies are currently widely available for the treatment of RA. Etanercept is a soluble TNF receptor, while adalimumab and infliximab are both monoclonal antibodies. Despite differences in their mechanisms of action, all 3 of these agents seem to have similar efficacy (9,10). Golimumab and certolizumab are also approved in many countries.

Anti-TNF agents are substantially more expensive than conventional disease-modifying antirheumatic drugs (DMARDs). As a result, guidelines have been produced by national health governing bodies to aid physicians in their appropriate use. Although all of these guidelines attempt to ensure appropriate access, they vary between countries and jurisdictions within countries such as Canadian provinces (11). Further, variation in the use of anti-TNF therapy may also result from regional variation in access to care, reimbursement policies, and physician preference. Many countries have established registries of RA patients to track the use of biologic therapies, including anti-TNF agents.

To quantitatively assess variation in the use of anti-TNF agents, this study compared both baseline characteristics of patients initiating anti-TNFs and criteria for reimbursement in countries with published registries or databases.

METHODS

PubMed was searched for RA databases or registries of anti-TNF use. Websites of registries were sought for up-to-date data. Access guidelines within countries were sought and, if not published, authors of the registries were contacted twice by email. If no response was received,

Table 1 Baseline Characteristics of RA Patients in American (CORRONA, NDB), Australian (ARAD), British (BSRBR), Canadian (OH, OBRI, REACH), Czech (Czech), Danish (DANBIO), Dutch (DREAM), Finnish (ROB-FIN), German (RABBIT), Italian (LORHEN), Norwegian (NOR-DMARD), Spanish (BIOBADASER), and Swedish (ARTIS, SSATG) Registries Prior to Initiating Anti-TNF

Database	OH	OBRI	REACH	CORRONA (6)	NDB (12)	Czech (13)	BSRBR (14)	DREAM (15)
Period of patient enrollment	Nov 2006 to Apr 2008	Jan 2008 to July 2009	Nov 2005 to July 2009	Mar 2002 to May 2006	June 2000 to Dec 2003	—	Jan 2001 to Feb 2007	Feb 2003 to Jan 2007
No. Patients	249	95	411	465	1663	880	9826	730
Age	55 (13)	54 (14)	56 (13)	58 (14)	59 (12)	47 (—)	56 (12)	54 (—)
%Female	81	85	77	77	81	74	76	69
No. of Previous DMARDs	3.5 (1.3)	—	—	1.8 (1.2)*	—	—	—	3.0 (1.4)*
DAS28	5.8 (1.1)	5.3 (1.4)*	5.3 (1.6)*	—	—	6.6 (0.8)*	6.6 (1.0)*	5.30 (1.24)*
SJC (0 to 28)	10.7 (5.5)	8.7 (5.9)*	9.0 (5.8)*	5.9 (6.4)*	—	—	—	8.6 (5.8)*
TJC (0 to 28)	12.4 (7.4)	9.3 (7.1)*	11.0 (7.6)*	4.9 (6.3)*	—	—	—	7.7 (7.3)*
ESR mm/h	29.8 (20.3)	33.2 (22.5)	30.4 (26.6)†	—	—	—	—	—
CRP mg/L	17.4 (21.0)	—	—	—	—	—	—	—
HAQ-DI	1.5 (0.7)	1.7 (0.6)*	1.5 (0.7)†	—	1.2 (0.70)*	—	2.1 (0.5)*	1.4 (0.7)*
Patient global health (VAS in mm)	62 (26)	71 (24)*	32 (9)*	28 (23)*	—	—	—	64 (22)†

P values represent comparison with OH based on 2-tailed *t*-test.
*$P < 0.05$.
†$P > 0.05$.
[a]The DAS28 score from the DANBIO database is from a subset of 1627 patients.
[b]Based on a 54-joint count.
[c]Based on a 53-joint count.
[d]The HAQ score from the ARAD is from a subset of 552 patients.

other RA experts were contacted. Data for access to anti-TNFs in Canada were obtained from the real world Optimization of HUMIRA trial (OH), the Ontario Biologics Research Initiative (OBRI), and Real-Life Evaluation of Rheumatoid Arthritis in Canadians Receiving HUMIRA (REACH).

The OH trial is a randomized, controlled, parallel-group, single-blind trial involving 32 centers across Canada. It was undertaken to determine the effect of treatment targets on the outcomes of patients receiving adalimumab through usual care. Physicians and their patients were randomized to 1 of 3 arms: treating to 0 swollen joint count (SJC, out of 28), treating to Disease Activity Score (DAS28, based on C-reactive protein) <3.2, or routine care. All other care was permissible. Patients had to have active RA, access to adalimumab via private or public insurance, and a rheumatologist who wished to prescribe adalimumab. All patients were also required to be 18 or older and naïve to adalimumab therapy, although 20% were permitted to have previous exposure to other biologic therapy. However, only data from those naïve to biologic therapy were included in the present study. Data collected included age, sex, previous biologic use, number of DMARDs used, SJC, number of tender joints (TJC, out of 28), DAS28, erythrocyte sedimentation rate, C-reactive protein, Health Assessment Questionnaire Disability Index (HAQ-DI), and patient assessment of their overall health on a visual analog scale (VAS, 0 to 100 mm).

OBRI is a clinical registry of RA patients in the Canadian province of Ontario who are starting biologic therapy and control patients who are changing DMARD treatment due to increased disease activity. As with all studies in this analysis, only data from patients initiating anti-TNFs were used in this analysis. These patients had to have active RA, be capable of giving informed consent, be initiating their first biologic, and have obtained anti-TNF via usual care. Patients are followed prospectively to assess adverse events and changes in drug use and disease severity.

REACH is an ongoing observational study of adalimumab use in routine clinical care. The study will include 1000 patients with moderate to severe RA from approximately 150 sites across Canada. It includes only patients with moderate to severely active RA who are naïve to adalimumab therapy or have been receiving adalimumab therapy for less than 4 months. In addition patients must be 18 or older, have had an inadequate response to 1 or more DMARDs, received provincial or private approval for adalimumab, and be capable of informed consent. Patients were excluded if they had a contraindication to adalimumab therapy, were receiving free adalimumab as part of a compassionate or early access program, or had a significant condition that could interfere with survey outcomes or their ability to complete survey procedures (eg, language difficulty).

All comparisons made were between biologic-naïve RA patients at initiation of their first anti-TNF agent. Char-

Table 1 Continued

DANBIO (16)	NOR-DMARD (17)	ARTIS (18)	SSATG (19)	ROB-FIN (20)	LORHEN (21)	RABBIT (22)	BIOBADASER (23)	ARAD (24)
Oct 2000 to Dec 2005	Jan 2001 to Dec 2004	Jan 1998 to July 2006	Mar 1999 to Dec 2006	—	—	May 2001 to Dec 2006	Feb 2000 to Jan 2002	Jan 2006 to Aug 2006
1813	622	6604	1839	297	1114	3266	67	563
57 (13)	—	55 (13)	56 (13)	51 (11)	56 (13)	53 (13)	53 (13)	58 (13)
73	—	75	78	69	83	78	81	71
3.3 (1.6)†	—	—	3.3 (1.9)†	—	—	—	—	—
5.4 (1.1)*[a]	5.5 (1.2)*	5.5 (1.3)*	5.6 (1.2)*	—	5.9 (1.0)†	5.8 (1.3)†	6.1 (1.2)†	—
—	9.1 (5.9)*	9.5 (6.1)*	9.7 (5.8)*	13 (7)*[b]	10.0 (5.3)†	—	—	—
—	10.0 (7.2)*	8.7 (6.7)*	9.0 (6.5)*	13 (10)†[c]	11.3 (6.4)*	—	—	—
—	33.6 (24.7)*	37 (25)*	36 (25)*	41 (28)*	40 (22)*	—	—	—
—	32.1 (35.7)*	—	31 (33)*	43 (34)*	101.8 (96.9)*	17 (22.2)†	—	—
—	—	1.4 (0.6)*	1.4 (0.6)*	1.3 (0.8)*	1.5 (0.6)*	—	—	1.6 (0.7)†[d]
—	58 (6)†	—	62 (22)†	61 (22)†	61 (18)†	—	—	—

acteristics of OH patients were compared with those of RA patients in the OBRI and REACH registries and in published American, Czech, British, Dutch, Danish, Norwegian, Swedish, Finnish, Italian, German, Spanish and Australian databases. The databases were the Consortium of Rheumatology Researchers of North America (CORRONA) (6), National Data Bank for Rheumatic Diseases (NDB) (12), Czech National Registry (13), British Society for Rheumatology Biologics Registry (BSRBR) (14), Dutch Rheumatoid Arthritis Monitoring (DREAM) (15), Danish Registry of Biological Therapies (DANBIO) (16), Norwegian Disease Modifying Anti-Rheumatic Drug (NOR-DMARD) (17), Anti-Rheumatic Therapies in Sweden (ARTIS) (18), South Swedish Arthritis Treatment Group (SSATG) (19), The Register of Biological Treatment in Finland (ROB-FIN) (20), Lombardy Rheumatology Network registry (LORHEN) (21), German Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) (22), Spanish Registry of Adverse Events of Biological Therapies in Rheumatic Diseases (BIOBADASER) (23), and Australian Rheumatology Association (ARAD) (24) databases. The NDB and CORRONA registries contained data from American patients only. ROB-FIN data included only patients initiating infliximab. Data from BIOBADASER represent a subsample of patients for whom complete data were available.

Patient, disease, and treatment characteristics at initiation of anti-TNF were summarized descriptively by country. Where necessary, means and standard deviations for subcategories were pooled or standard deviations were estimated using the protocol outlined in the Cochrane Handbook for Systematic Reviews of Interventions (25). Two-tailed *t*-tests were used to compare characteristics of OH patients to those from other databases. Statistical analyses were performed using SPSS.

RESULTS

Of 300 patients enrolled in the OH trial, the 249 (83.0%) who were naïve to anti-TNF therapy at enrollment were included in this analysis. Baseline characteristics of these patients and those of patients in the OBRI and REACH registries and American, Czech, British, Dutch, Danish, Norwegian, Swedish, Finnish, Italian, German, Spanish and Australian databases are summarized in Table 1. The majority of baseline data were collected during the early to mid-2000s (Table 1).

Sweden, the United States, and Canada were the only countries to contribute more than 1 database to this study. Mean values from the 2 Swedish registries [ARTIS and SSATG (a subset of ARTIS patients)] had percentage differences less than 4% for all data presented. The few overlapping variables from the 2 American databases (NDB and CORRONA) each differed by less than 6%. However, mean values from the 3 Canadian databases (OH, OBRI, and REACH) varied substantially with a 9% difference in mean DAS28 scores and differences of

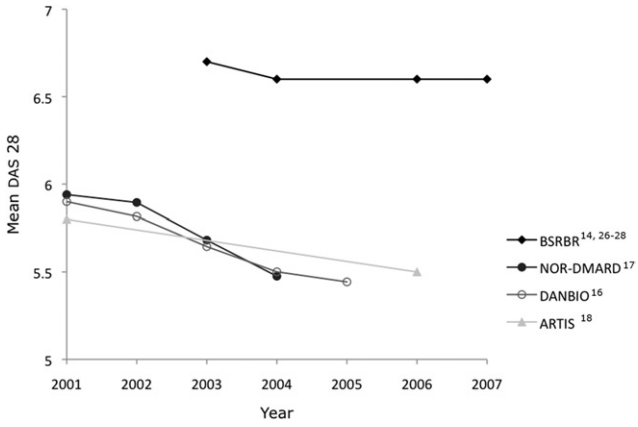

Figure 1 Change in mean baseline DAS28 scores over time in 4 databases. Data are cumulative. Average yearly change was lower in BSRBR than other databases (2-tailed *t*-test, $P < 0.001$ in all cases) (26-28).

over 20% in SJC, TJC, and VAS with most measures of disease severity higher in the OH database. This may be the result of variation in enrollment criteria. DAS28 scores among Canadian provinces did not differ significantly in the OH trial (ANOVA, $P = 0.076$).

Values from the 2 American databases (CORRONA and NDB) showed less severe disease than those in the 16 other databases (Table 1). Interestingly, however, mean HAQ score among the subgroup of patients in the NDB with public insurance was 1.47 compared with the mean of 1.5 in the OH data ($P = 0.47$). In contrast, mean DAS28 scores were highest in the Czech and BSRBR databases (Table 1), suggesting that British and Czech patients had the highest average disease severity on anti-TNF initiation among all 13 countries analyzed. In between these extremes was a broad group of databases with the OH trial database approximately in the middle. Scandinavian and Dutch databases generally showed less severe disease at anti-TNF initiation, while indicators of baseline disease severity from Spain, Italy, and Germany were somewhat higher.

Figure 1 compares temporal changes in mean baseline DAS28 scores in the British (BSRBR), Danish (DANBIO), Norwegian (NOR-DMARD) and Swedish (ARTIS) databases. DAS28 scores declined over time in each of these databases, suggesting improvements in access to anti-TNF therapy. Improved access may be the result of changes in reimbursement criteria and/or changes in physician preferences (eg, a move to earlier, more aggressive treatment strategies) and familiarity with anti-TNFs. Although the years for which data were available were not identical, average yearly decline was greater in NOR-DMARD, DANBIO, and ARTIS than in the BSRBR (2-tailed *t*-tests, $P < 0.001$ in all cases). Thus, the existing gap in access to anti-TNF therapy between the UK and Scandinavian countries appears to be widening.

Table 2 Selected Countries' Criteria for Public Coverage of Anti-TNF Therapy for Patients with Rheumatoid Arthritis

Country	Required Disease Severity	DMARD Trial(s): Name of Drug (duration of trial[a])	Response Required for Continued Coverage	Other Requirements/ Additional Information
Australia (29)	1) ESR >25 mm/h or CRP >15 mg/L and 2) SJC and TJC >20 or swelling and tenderness of >4 of elbow, wrist, knee, ankle, shoulder, hip	1) MTX and 2) MTX in combination with 2 other DMARDs (3 months) and 3) cyclosporin or LFL alone or in combination with MTX (3 months)	Response within 16 weeks	—
Canada (Ontario) (30)	Synovitis of ≥5 joints	1) MTX (3 months) AND LFL (3 months) AND 1 combination of DMARDs (3 months) OR 2) MTX (3 months) and MTX plus LFL combination (3 months)	↓ 20% in SJC and improvement in ≥2 joints	RF+ or joint erosion
Canada (Quebec) (31)	Synovitis of ≥8 joints	1) 2 DMARDs (3 months each) including MTX	↓ 20% in inflamed joints AND 1 of: ↓ ≥20% CRP, or ESR; HAQ ↓ ≥0.2, or return to work (5 months)	1 of RF+, HAQ >1, ↑ CRP, ↑ ESR, joint erosions
Czech Republic (K. Pavelka, personal communication)	DAS28 >5.1	1)1 DMARD	—	Patient must be treated in a center approved for biologic therapy
Denmark (M.L. Hetland, personal communication)	DAS28 >3.2, progressive joint erosions	1) maximum tolerate MTX dose and 2) prednisolone ≥7.5 mg daily	—	—
Finland (32)	Severely active RA (SJC and TJC ≥6, morning stiffness ≥45 minutes, ESR ≥30 mm/h, CRP >28 mg/L)	1) DMARD combination including MTX and 2) glucocorticoid	Patient response should reach ACR50 by 3 months after initiation	—
Germany (A. Strangfeld, personal communication)	High disease activity	1) MTX (6 months) and 2) 1 other DMARD	—	Treatment coverage may begin without meeting these criteria if disease progression is very rapid
Italy (33)	DAS28 >5.1 or DAS >3.7	1) MTX (12 weeks) or other effective DMARD	DAS improvement by >1.2. Evaluation at 12 weeks then at 3-month intervals	
Netherlands (M. Boers, personal communication)	DAS28 >3.2	1) 2 DMARDs or 2) 1 DMARD plus a glucocorticoid (≥7.5 mg daily)	Improvement within 3 months	—

Table 2 Continued

Country	Required Disease Severity	DMARD Trial(s): Name of Drug (duration of trial[a])	Response Required for Continued Coverage	Other Requirements/ Additional Information
Norway (34)	Moderate disease activity	1) MTX or sulfasalazine (3 to 4 months) and 2) combination of 2 or 3 DMARDs (MTX alone if disease activity high or if poor prognostic features present)	—	Use in combination with MTX[a]
Spain (J. Gómez-Reino, personal communication)	—	—	—	Covered if prescribed by a rheumatologist at a National Health Service Hospital
Sweden (R. van Vollenhoven, personal communication)	—	—	—	Etanercept and adalimumab covered with physician prescription; infliximab coverage varies by local hospital unit
United Kingdom (35)	DAS28 >5.1 (2 times, 1 month apart)	1) MTX (6 months) and 2) 1 other DMARD (6 months)	↓ ≥1.2 DAS in 6 months	Use in combination with MTX[a]

MTX, methotrexate; LFL, leflunomide; RF+, rheumatoid factor positive.
[a]Unless intolerant or contraindicated.

There is substantial variability among the countries in this comparison in the criteria used to determine government reimbursement of anti-TNF agents (Table 2).

The number of criteria required for coverage was not significantly related to mean DAS28 (Spearman's rho, $P = 0.75$). However, other than Spain, those countries that did not require high disease severity for government coverage of anti-TNF therapy (Denmark, Sweden, Norway, and the Netherlands) had the lowest baseline DAS28 scores. Interestingly, however, in each of these countries, mean baseline DAS28 nonetheless indicated high disease severity (DAS28 >5.1), suggesting that disease severity requirements were not the sole barrier to anti-TNF therapy in these countries. In Canada, nearly all provinces require intolerance or inadequate response to 2 or more DMARDs including methotrexate and to at least 1 combination of DMARDs. Provincial guidelines from all but 2 provinces allow anti-TNF coverage for moderately severe RA, although most provinces do not provide specific criteria (eg, DAS or HAQ cutoffs) for what they consider to be moderate disease severity. In contrast to the European countries analyzed, a requirement for a trial of leflunomide is common among Canadian provinces.

DISCUSSION

Despite the effectiveness of TNF antagonists, wide variability exists between countries in the severity of RA on initiation of these therapies. Thirteen of the 17 databases in this comparison reported baseline DAS28 scores at anti-TNF initiation. All of these were between 5.3 and 6.6, indicating high disease severity in each of these databases. The distribution of mean DAS28 scores among databases was essentially linear, with most databases falling between 5.3 and 5.9 (Fig. 2).

In the United States, access to anti-TNF therapy differs between privately and publicly insured patients. Medicare Part D is a national public drug insurance program established in 2006. Although the complexity of this program leads to high variability in costs, a recent study found patient out-of-pocket annual costs for etanercept and adalimumab to be over $4000 US dollars for all scenarios examined (36). Further, an analysis of American RA patients in the NDB by DeWitt and colleagues found that those in the subgroup of patients with public coverage had greater disease severity at initiation of anti-TNF therapy than those with private coverage (12). The mean HAQ score of 1.47 among this publicly insured subset was similar to that from most other databases in the present study. However, that from the entire group analyzed by DeWitt (which included both publicly and privately insured patients) was 1.2, substantially lower than most other databases. This suggests that the preponderance of private insurance in the United States may be an important factor in the markedly lower baseline disability in noted Amer-

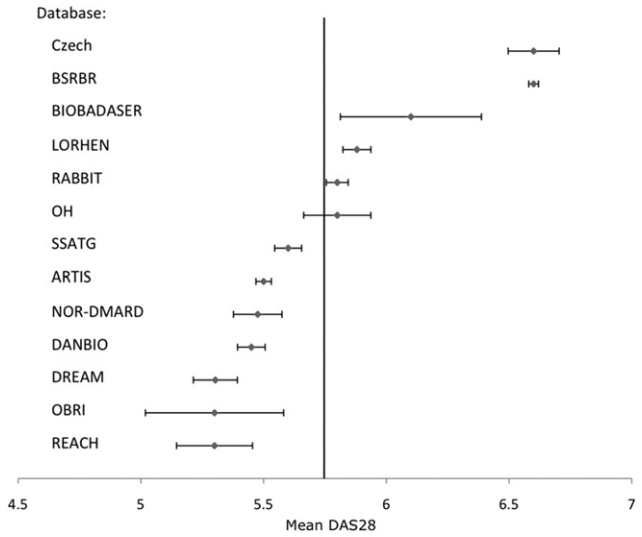

Figure 2 Mean baseline DAS28 scores with 95% confidence intervals from the Canadian (OH, OBRI, REACH) and 10 European RA registries. Vertical line represents global mean.

ican patients. Interestingly, the generous anti-TNF coverage criteria in Sweden have not resulted in a baseline disease as low as that found in the United States, despite similar clinical guidelines in these countries (37,38). This may be the result of differences in physician preferences for the use of anti-TNF therapy. A recent analysis of data from the CORRONA database found physician preference independently predicted the likelihood of anti-TNF prescription (39).

The BSRBR and Czech registries had the highest baseline disease severity in this comparison. British and Czech anti-TNF coverage criteria are both relatively stringent. Both require a DAS28 score >5.1 and the UK requires two 6-month DMARD trials (35). While German, Italian, and British anti-TNF coverage criteria are seemingly similar (Table 2), UK criteria lack the flexibility of expediting treatment in cases where disease progression is rapid. The comparatively high disease severity found in British patients is consistent with previous findings that suggest relatively limited access to anti-TNF therapy in the UK compared with Denmark, Norway, and France (40,41).

An analysis of the CORRONA database found that there was a 2.8% increase in prescribing rates of anti-TNF biologics in established RA and temporal trends in prescribing at lower disease severity (42). However, the utilization of anti-TNFs in their database is higher than in any other, so it may be difficult to compare the trends they observed to other registries (43). Declines in baseline disease severity at initiation of anti-TNF therapy over time have also been noted in Danish, Norwegian, and Swedish databases (16-19). However, virtually no decline in the mean baseline DAS28 score has occurred in the BSRBR since data from it were first published. This suggests that contrary to the trend in the US and several European countries, access to anti-TNF is not improving in the UK, resulting in a widening of the already substantial gap between the UK and other countries.

Differences in baseline disease severity, both over time and between countries, may be influenced by not only criteria for reimbursement of anti-TNF therapies but also physician factors. These influences are interrelated. For example, early diagnosis and aggressive treatment of patients with traditional DMARDs could result in requirements for DMARD trials being met at an earlier, less severe, stage of the disease, thus allowing reimbursement of anti-TNF agents to occur at a lower level of disease severity. Most countries analyzed had requirements not only for DMARD trials but also for a minimum level of disease severity before reimbursement of anti-TNF agents. However, all countries for which data were available had mean disease severities notably above these minimum requirements, suggesting that the interaction of physician practices and criteria for DMARD trials may be an important influence on anti-TNF utilization.

Prescribing practices for traditional DMARDs are known to differ between countries. For example, results from the QUEST-RA project, a study of RA patient characteristics in 15 countries, indicate substantial variation in the use of traditional DMARDs across countries with variability in the type of DMARD favored as well as the duration and time to initiation of treatment (44). Interestingly, the Netherlands, which had among the lowest DAS28 at anti-TNF initiation in the present study, also had among the lowest times to DMARD initiation in QUEST-RA (5 months). Also, Spain, with a DAS28 at anti-TNF initiation among the highest in the present study, had the second longest time to DMARD initiation (14 months) in QUEST-RA (44). However, this apparent trend did not hold true for Scandinavian countries, which had low DAS28 at anti-TNF initiation but moderate to high times to DMARD initiation in QUEST-RA (10-12 months) (44).

The higher mean disease severity found in the OH trial compared with the other Canadian databases (OBRI, REACH) may result from the temporal relationship of lower disease severity over more recent years since the OBRI and REACH registries are relatively recent. In addition, the OBRI has a series of test sites to pilot the program and these may consist of rheumatologists more likely to prescribe anti-TNF treatment and thus may not be generalizable to the entire province of Ontario. The Optimization trial may thus be more reflective of countrywide prescribing of anti-TNF therapy, particularly since the anti-TNF therapy was obtained by usual means and the investigators were from many Canadian provinces.

The strengths of this study include the broad range of databases analyzed. However, the heterogeneity of different countries' databases complicated their comparison. For example, the reduction in baseline disease severity over time that has been noted in several databases suggests that differences between databases in the timing of patient

enrollment may have impacted their results. For example, the early period (2000-2002) during which patients in the BIOBADASER subsample were recruited may explain the relatively high mean DAS28 score in this group that existed despite the generous anti-TNF coverage criteria in Spain. Differences in the duration of enrollment between databases present similar difficulties in differentiating between temporal and regional variation in patient characteristics. Comparison between databases was also limited by variation in the number and types of clinical variables reported by different databases. Further, the proportion of patients receiving each anti-TNF agent also differed between databases. While anti-TNF agents do not seem to vary substantially in efficacy (9,10), there is evidence from the United States that systematic differences may exist between patients prescribed different anti-TNF agents (12). However, this is likely related to reimbursement criteria under Medicare or other prescribing biases (12). Although all databases sought to represent real-world conditions, eligibility criteria, number of patients enrolled, and recruiting methods differed. Despite the difficulties that the heterogeneity of the analyzed databases present, there currently exists no uniformly collected international dataset of baseline characteristics of RA patients initiating anti-TNF therapy. Thus, comparison between countries necessitates the use of databases that differ in many respects.

This comparison confirms the existence of variation in the baseline characteristics of RA patients initiating anti-TNF therapies between the 13 countries analyzed and suggests that variation between certain countries may be increasing over time. Differences in both reimbursement criteria and physician practices/preferences may explain both regional and temporal variation. However, biologic penetration does not vary significantly across the Canadian provinces, despite a significant variation in formulary requirements, which suggests a contribution of national or "cultural" modifiers.

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