Determining Best Practices in Early Rheumatoid Arthritis by Comparing Differences in Treatment at Sites in the Canadian Early Arthritis Cohort

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ABSTRACT. ***Objective.*** To determine site variation by comparing outcomes across sites in an early rheumatoid arthritis cohort.

Methods. Sites from the Canadian Early Arthritis Cohort database with at least 40 patients were studied. Comparisons were made among sites in change in 28-joint Disease Activity Score (DAS28), proportion of patients in DAS28 remission, and treatment strategies.

Results. The study included 1138 baseline patients at 8 sites, with baseline (SD) age 52 years (16.9); 72% women; 23% erosions; 54% ever smokers; 51% rheumatoid factor-positive; 37% anticitrullinated protein antibody-positive; disease duration 187 (203) days; DAS28 4.5 (1.4). Site had an effect on outcomes when adjusting for confounders. At 6 and 12 months, sites B and H, the 2 largest sites, had the best changes in DAS28 (–1.82 and –2.09, respectively, at 6 mos, and –2.27 for both at 12 mos; $p < 0.001$). Site H had the most patients in DAS28 remission at 6 months [64.5% compared to other sites that had from 34.1% to 51.7% ($p < 0.001$)], and at the last followup, sites B and H had the most in remission. Subcutaneous methotrexate was used more overall and earlier at sites B and H. Those sites used less steroid therapy, and site B had the second-highest use of triple disease-modifying antirheumatic drugs at any visit. Medications were increased more in 2 of the 3 smallest sites. Biologics were used by 9 months most in the smallest (50.0%) and then largest (19.6%) sites.

Conclusion. Sites in an early inflammatory arthritis cohort yielded different outcomes. Better outcomes up to 12 months may result from initial treatment with early combination therapy and/or subcutaneous methotrexate. (J Rheumatol First Release Sept 15 2013; doi:10.3899/jrheum.121316)

Key Indexing Terms:

RHEUMATOID ARTHRITIS	REMISSION	DISEASE PROGRESSION
TREATMENT OUTCOME	OUTCOME ASSESSMENT	PROFESSIONAL PRACTICE

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by joint swelling, pain, and progressive destruction of synovial joints[1,2,3] that leads to functional impairment and disability, deterioration of quality of life, and premature mortality compared to the general population[1,2,3,4,5]. Many reports support the use of early, aggressive, tightly controlled, goal-targeted treatments with disease-modifying antirheumatic drugs

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(DMARD) to inhibit disease progression and promote optimal outcomes, thus making remission a realistic treatment goal, especially for early rheumatoid arthritis (ERA)[3,6,7,8,9,10,11]. Despite this general consensus, there currently is a lack of agreement on the best DMARD or DMARD combination, dose, or route to use and the best time to adjust treatment. Initially, most patients with RA are prescribed conventional nonbiologic DMARD such as methotrexate (MTX), and may later add combination DMARD or biologics such as tumor necrosis factor antagonists[12]. There is also variation in how treatments are administered; for example, MTX can be given orally or parenterally (subcutaneously or intramuscularly). Further, there are many DMARD combinations and various treatment strategies, including initial combination DMARD, bridging with steroids, sequential monotherapy, step-up, and step-down approaches. Several different targets may be used, but often remission is the target. Particularly in early disease, remission has various definitions[13,14]. Treatment may be affected by comorbidities, patient factors such as reluctance to change therapy, and drug access. Consequently, specific treatment is left to the discretion of each rheumatologist, leading to patients potentially receiving variable treatment at different sites.

Using data from the Canadian Early Arthritis Cohort (CATCH), we studied size and treatment variability of sites and how those factors could affect outcomes in ERA such as change in 28-joint Disease Activity Score (DAS28) and proportion of patients with RA in remission by 12 months. We anticipated that sites with larger improvements and remission would have different treatment strategies. The most effective treatment strategies could then be disseminated to the all sites to motivate adoption of these best practices and ultimately improve disease outcomes in ERA.

MATERIALS AND METHODS

The CATCH database. The CATCH is a prospective cohort that began in January 2007 with the objective of gathering longterm data to demonstrate treatment effectiveness in patients referred to Early Inflammatory Arthritis Programs at 17 sites across Canada[15]. As of March 2011, there were 1450 patients enrolled. To be enrolled in CATCH, patients must meet these inclusion criteria: age > 16 years at time of referral, joint symptoms for ≥ 6 weeks and ≤ 12 months and at least 1 of 2 or more swollen joints OR 1 swollen metacarpophalangeal or proximal interphalangeal joint. Patients must also have 1 of these: a positive rheumatoid factor (RF), positive anti-citrullinated protein antibody (ACPA), morning stiffness ≥ 45 min, a response to nonsteroidal antiinflammatory drugs, or a positive metatarsophalangeal squeeze test. After providing informed consent, each patient is followed with data collection every 3 months for the first year. All patients at all sites signed a letter of information to give consent for data to be collected and all sites have ethics approval (IRB approval).

Because CATCH is an inception cohort, there is not the bias of including only patients who have been treated already for a long time, and thus it truly reflects site differences. All sites complete the same baseline and followup forms for their patients.

Site inclusion. Only sites that had at least 40 patients at 6 months followup were included in our study, to ensure sufficient power for detecting site differences in outcomes. The 8 sites meeting this criterion were assigned a letter randomly (from A to H) with all the investigators blinded to site (only 1 administrator was aware of each site's identity).

Disease activity and remission. Disease activity was measured using the DAS28. For each study participant, DAS28 was calculated at baseline, 6 months, and 12 months. The changes in DAS28 from baseline to 6 months and from baseline to 12 months were used as continuous outcome variables. In addition, for study participants not in remission at baseline, the proportion who met the remission (DAS28 < 2.6) at 6 and 12 months and at their last recorded visit was used as a binary (Yes, No) outcome variable. We used DAS28 remission as opposed to the more stringent Boolean-based, Simplified Disease Activity Index (SDAI), or Clinical Disease Activity Index (CDAI) definitions of remission because DAS28 remission is more inclusive. This characteristic allows higher power for regression analyses when adjusting for different confounding factors, even though DAS28 < 2.6 may not reflect true remission in some patients but rather a low disease state[15].

Treatment. Differences in treatment strategies and outcomes at the various sites were determined (change in DAS28 and DAS28 remission) as per various medications singly or in combination, prescribed "early" (baseline and 3 mos) and "ever" (baseline to 9 mos). The following treatment measures were chosen: monotherapy with any DMARD, MTX route of administration, various combination therapies (most including MTX), biologics, and prednisone. We also examined changes and intensifications of treatments. Changes considered increases in treatment were a change from monotherapy to combination therapy, 2 DMARD to triple combination therapy, conventional DMARD combination therapy to a combination containing a biologic, oral MTX to subcutaneous MTX, and adding prednisone.

Covariates. Between-site differences in baseline characteristics known to be confounding prognostic factors for ERA were analyzed using 1-way ANOVA or Pearson chi-squared test. They included Health Assessment Questionnaire (HAQ), DAS28, RF, ACPA, erosions, cigarette smoking, age, sex, number of comorbidities, disease duration, and socioeconomic status as measured by level of education[2,9,10,16,17,18,19,20,21,22,23,24,25,26]. These factors were adjusted for in the regression analyses if $p < 0.1$.

Statistical analysis. Descriptive analyses of disease measures and treatment strategies across sites were performed. We determined whether site size had an effect on outcomes when adjusting for confounders. The frequency of various treatment strategies between sites was compared. Because patients were nested within sites, we could not assume independence among study participants within the same sites. Therefore, site was included as a random effect through the intercept in all our regression models. This allowed us to account for and quantify the between-site variation in outcome variables that could occur because of cluster sampling. Simple linear (logistic) mixed models were performed to test for associations between continuous (binary) outcome variables and each individual covariate while incorporating site as a random effect, adjusting for covariates with a $p < 0.10$ in regression models when examining treatment strategies. In multilevel regressions, the reference category for all binary variables was set to 0 or "no." Then, multiple linear (logistic) mixed models were done to test for associations between continuous (binary) outcome variables and each individual treatment comparison variable while incorporating site as a random effect, and adjusting for the covariates. Because some covariates might be correlated with one another, we removed insignificant covariates in a backward-stepwise fashion to ensure a good model fit. Finally, we split our data by site and used multiple linear (logistic) regression models to test for associations between continuous (binary) outcome variables and each individual treatment comparison variable. Here, we adjusted only for female sex, baseline HAQ score, and baseline DAS28 score because sample sizes within each site would quickly diminish if we included all covariates, and those 3 variables had the least missing data and were most significantly related to outcome variables in this dataset. This analysis was divided by site (comparing the largest and then the second largest to the

other sites) to reveal whether treatment effects on the outcomes (change in DAS28 and remission) varied from site to site in the database. SPSS 20.0 and R 2.15.2 were used to run analyses. Other exploratory outcomes such as varying the definition of remission (SDAI, CDAI, and Boolean) were done to determine site differences in size and treatment strategies.

RESULTS

Demographics. The baseline characteristics of the 8 sites (Table 1) included 1138 patients at baseline, 798 at 6 months, and 640 at 12 months. The mean age was 52 years (SD 16.9) and 72.3% were women. Twenty-three percent had erosions; the mean disease duration was 187 days (SD 203); the mean number of comorbidities was 2 (SD 2); 50.7% were RF-positive and 37.5% were ACPA-positive; slightly fewer than half had completed high school and

Table 1. Characteristics of the included sites and changes in DAS28 and remission by site (A–H, arranged left to right by site size from smallest to largest). Continuous variables are mean ± SD (available data); categorical variables are no./available data (valid %).

Characteristics	F	C	A	D	G	E	H	B	P
No. patients	58	85	92	122	144	157	224	255	
Age, yrs	57.2 ± 13.4 (58)	50.7 ± 18.4 (85)	54.3 ± 19.4 (91)	50.7 ± 17.1 (122)	51.3 ± 14.6 (143)	59.9 ± 13.8 (157)	55.0 ± 16.8 (224)	44.0 ± 15.5 (255)	≤ 0.001 (51.0–53.0)
Female	43/58 (74.1)	59/85 (69.4)	70/86 (81.4)	80/117 (68.4)	114/143 (79.7)	97/157 (61.8)	156/221 (70.6)	203/252 (80.6)	≤ 0.001
Symptom duration, days	228.3 ± 114.1 (58)	159.7 ± 97.3 (85)	226.0 ± 568.6 (91)	187.7 ± 100.0 (122)	213.6 ± 93.4 (143)	153.3 ± 93.0 (157)	181.5 ± 197.9 (224)	181.3 ± 112.1 (255)	0.044 (174.7–198.4)
No. comorbidities	3.2 ± 2.0 (58)	2.2 ± 2.2 (85)	2.5 ± 2.0 (91)	2.1 ± 2.1 (122)	2.9 ± 2.3 (143)	1.7 ± 1.6 (157)	2.9 ± 2.2 (224)	2.2 ± 1.9 (255)	≤ 0.001 (2.3–2.5)
Erosions on radiographs of hands or feet	12/39 (30.8)	50/74 (67.6)	7/51 (13.7)	20/95 (21.1)	29/140 (20.7)	52/139 (37.4)	45/169 (26.6)	46/214 (21.5)	≤ 0.001
RF+	23/33 (69.7)	40/83 (48.2)	40/68 (58.8)	83/117 (70.9)	127/139 (91.4)	50/153 (32.7)	122/202 (60.4)	92/241 (38.2)	≤ 0.001
ACPA+	22/46 (47.8)	20/61 (32.8)	28/46 (60.9)	85/105 (81.0)	83/140 (59.3)	53/113 (46.9)	19/71 (26.8)	116/213 (54.5)	≤ 0.001
Meets ACR/EULAR RA classification criteria	20/22 (90.9)	53/65 (81.5)	47/49 (95.9)	108/109 (99.1)	134/139 (96.4)	97/117 (82.9)	130/146 (89.0)	192/213 (90.1)	≤ 0.001
HAQ (0–3)	1.0 ± 0.8 (58)	0.9 ± 0.7 (85)	0.8 ± 0.7 (92)	1.0 ± 0.7 (120)	0.9 ± 0.7 (143)	0.8 ± 0.6 (157)	1.1 ± 0.7 (224)	0.9 ± 0.7 (255)	0.004 (0.9–1.0)
DAS28 baseline visit	4.6 ± 1.3 (58)	4.3 ± 1.5 (85)	4.8 ± 1.2 (92)	4.2 ± 1.3 (121)	4.0 ± 1.4 (143)	4.9 ± 1.3 (157)	4.3 ± 1.4 (224)	4.8 ± 1.4 (255)	≤ 0.001 (4.4–4.6)
Smoking status									
Never	22/58 (37.9)	38/85 (44.7)	34/86 (39.5)	31/116 (26.7)	62/143 (43.4)	56/152 (36.8)	101/221 (45.7)	150/252 (59.5)	≤ 0.001
Formerly	24/58 (41.4)	23/85 (27.1)	31/86 (36.0)	52/116 (44.8)	57/143 (39.96)	71/152 (46.7)	88/221 (39.8)	62/252 (24.6)	
Current	12/58 (20.7)	24/85 (28.2)	21/86 (24.4)	33/116 (28.4)	24/143 (16.8)	25/152 (16.4)	32/221 (14.5)	40/252 (15.9)	
Education									
High school or less	28/56 (50.0)	42/84 (50.0)	47/84 (56.0)	61/114 (53.5)	57/136 (41.9)	102/146 (69.9)	101/218 (46.3)	74/238 (31.1)	≤ 0.001
Beyond high school	28/56 (50.0)	42/84 (50.0)	37/84 (44.0)	53/114 (46.5)	79/136 (58.1)	44/146 (30.1)	117/218 (53.7)	164/238 (68.9)	
DAS28 change 0–6 mos	–1.12 ± 1.57	–1.63 ± 1.80	–1.09 ± 1.34	–1.56 ± 1.48	–1.17 ± 1.33	–1.79 ± 1.68	–2.09 ± 1.72	–1.82 ± 1.70	≤ 0.001 (–1.74– –1.52)
Proportion in DAS28 remission at 6 mos	15/44 (34.1)	31/60 (51.7)	14/57 (24.6)	53/105 (50.5)	56/115 (48.7)	34/102 (33.3)	91/141 (64.5)	68/171 (39.8)	≤ 0.001
DAS28 change 0–12 mos	–1.37 ± 1.78	–1.53 ± 1.77	–1.50 ± 1.66	–1.80 ± 1.40	–1.37 ± 1.32	–2.10 ± 1.50	–2.27 ± 1.67	–2.27 ± 1.85	≤ 0.001 (–2.02– –1.76)
Proportion in DAS28 remission at 12 mos	14/40 (35.0)	16/31 (51.6)	18/50 (36.0)	53/88 (60.2)	54/98 (55.1)	33/72 (45.8)	82/110 (74.5)	84/146 (57.5)	≤ 0.001
Proportion in DAS28 remission at last visit if not in remission at baseline visit	14/39 (35.9)	12/25 (48.0)	17/49 (34.7)	49/79 (62.0)	43/86 (50.0)	32/69 (46.4)	74/99 (74.7)	78/136 (57.4)	≤ 0.001

ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; HAQ: Health Assessment Questionnaire Disability Index; DAS28: Disease Activity Score in 28 joints; RF: rheumatoid factor; ACPA: anticitrullinated protein antibody; RA: rheumatoid arthritis.

54.5% were either current or ever cigarette smokers. Not all patients met the 2010 American College of Rheumatology/European League Against Rheumatism RA classification criteria[1], and some patients were missing ACPA data and could not be included for whether they met RA criteria. The mean DAS28 at baseline was 4.5 (SD 1.4); and 2.92 (SD 1.34) and 2.66 (SD 1.22), respectively, at 6 and 12 months. The mean change in DAS28 from baseline to 6 months was –1.63 (SD 1.63) and –1.89 (SD 1.66) from baseline to 12 months. Forty-five percent (362/795) of patients were in DAS28 remission at 6 months, while 56% (354/635) were in remission at 12 months. Continuous outcome variables were nearly normally distributed across all data and within each site.

Important covariate identification. Significant covariates for DAS28 change from baseline to 6 months (Supplementary Table 1, available from the author on request) were female sex, symptom duration, baseline HAQ, baseline DAS28, presence of erosions, and education level (high school or less). Similarly, significant covariates for DAS28 change from baseline to 12 months were female sex, symptom duration, baseline HAQ score, baseline DAS28, positive RF, and having ever been a smoker. Age, female sex, symptom duration, number of comorbidities, baseline HAQ, baseline DAS28, and education level were significant covariates for DAS28 remission at the most recent visit. Interestingly, high baseline DAS28 was associated with faster decreases in DAS28 at 6 months and 12 months but was associated with less likelihood of reaching remission than low baseline DAS28.

Treatment outcome regression analyses. In combined data analyses, the effects of treatment on outcomes were largely insignificant (Supplementary Table 2, available from the author on request). In general, combination DMARD performed better than DMARD monotherapy. Having ever taken a biologic or a steroid was predictive of poor outcome on all 3 measures. Finally, there was a negative relationship between good outcomes and medication changes and intensifications. The random effect component added to each model to account for site-to-site variation in outcome generally explained around 8–12% of the remaining variability in each model.

Outcome and treatment by site. Disease outcome measures were variable across sites (Table 1). Figure 1 shows the mean change in DAS28 at 6 and 12 months compared to baseline for the sites arranged by site size from smallest to largest. Sites B and H, the 2 largest sites, had the highest mean changes in DAS28 from baseline to 6 months, –1.82 (SD 1.70) at site B and –2.09 (SD 1.72) at site H, and from baseline to 12 months, –2.27 (SD 1.67) and –2.27 (SD 1.85), respectively. Similarly, site H had the highest proportion of patients in DAS28 remission at their last recorded visit (74.7%), while site B had the third-highest proportion in remission at last followup (57.4%).

Treatment practices varied across sites at various visits (Table 2). Changes and intensifications of medication ever after the initial visit showed a significant difference ($p < 0.001$) between sites. A total of 95.9% of patients were taking at least 1 DMARD at baseline, with no significant difference between sites. At baseline, 77.4% of all patients were prescribed MTX, with a highly significant difference

Table 2. Treatment prescribed at baseline and 6-month visit by site (A–H, arranged left to right by site size from smallest to largest). Data are frequency/available data (valid %).

	F	C	A	D	G	E	H	B	P
No. patients	58	85	92	122	143	157	224	255	
DMARD^									
Baseline	40/44 (90.9)	68/72 (94.4)	65/67 (97.0)	90/97 (92.8)	126/134 (94.0)	146/151 (96.7)	156/162 (96.3)	163/165 (98.8)	0.170
6 mos	42/42 (100)	49/56 (87.5)	59/59 (100)	87/92 (94.6)	104/111 (93.7)	123/126 (97.6)	130/135 (96.3)	157/159 (98.7)	0.002
MTX^									
Baseline	38/44 (86.4)	37/72 (51.4)	53/67 (79.1)	72/97 (74.2)	107/134 (79.9)	134/151 (88.7)	108/162 (66.7)	136/165 (82.4)	0.001
6 mos	41/42 (97.6)	33/56 (58.9)	47/59 (79.7)	71/92 (77.2)	93/111 (83.8)	114/126 (90.5)	97/135 (71.9)	137/159 (86.2)	0.001
MTX, SC^									
Baseline	3/44 (6.8)	4/72 (5.6)	8/67 (11.9)	7/97 (7.2)	7/134 (5.2)	43/151 (28.5)	101/162 (62.3)	62/165 (37.6)	0.001
6 mos	4/42 (9.5)	11/56 (19.6)	10/59 (16.9)	17/92 (18.5)	18/111 (16.2)	42/126 (33.3)	92/135 (68.1)	88/159 (55.3)	0.001
Biologic^									
Baseline	9/44 (20.5)	3/72 (4.2)	—	1/97 (1.0)	6/134 (4.5)	1/151 (0.7)	—	4/165 (2.4)	0.001
6 mos	20/42 (47.6)	6/56 (10.7)	2/59 (3.4)	7/92 (7.6)	5/111 (4.5)	11/126 (8.7)	—	25/159 (15.7)	0.001
At least 2 DMARD^									
Baseline	12/44 (27.3)	32/72 (44.4)	22/67 (32.8)	34/97 (35.1)	104/134 (77.6)	49/151 (32.5)	30/162 (18.5)	92/165 (55.8)	0.001
6 mos	17/42 (40.5)	30/56 (53.6)	40/59 (67.8)	33/92 (35.9)	88/111 (79.3)	66/126 (52.4)	33/135 (24.4)	101/159 (63.5)	0.001
Medication ever changed*	28/45 (62.2)	34/68 (50.0)	41/66 (62.1)	36/101 (35.6)	44/128 (34.4)	65/143 (45.5)	19/158 (12.0)	79/166 (47.6)	0.001
Medication ever increased*	26/45 (57.8)	24/68 (35.3)	40/66 (60.6)	26/101 (25.7)	31/128 (24.2)	57/143 (39.9)	14/158 (8.9)	67/166 (40.4)	0.001

^ Prescribed or receiving at each visit. * Across all visits. MTX: methotrexate; SC: subcutaneous; DMARD: disease-modifying antirheumatic drug.

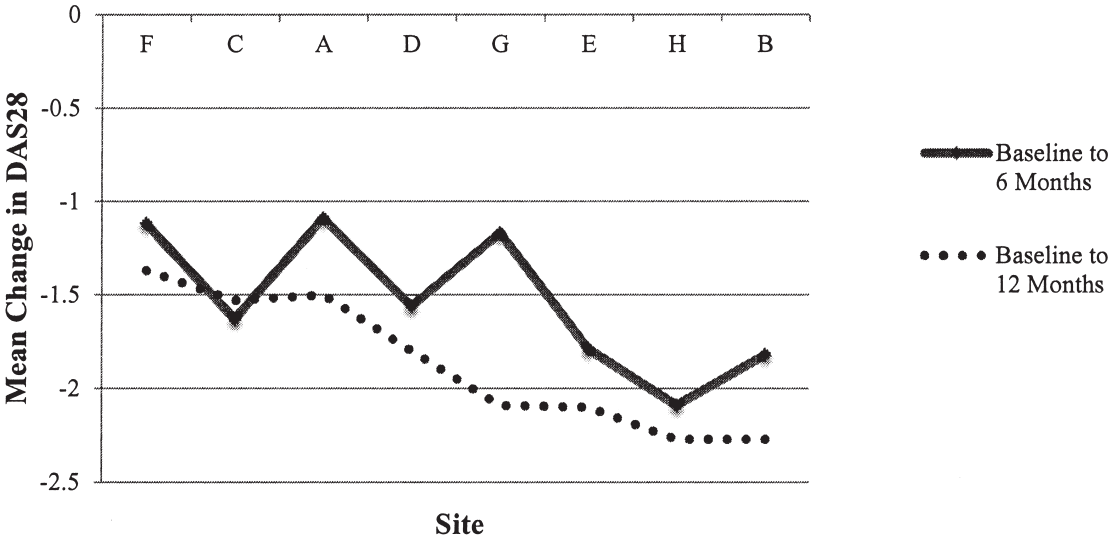

Figure 1. Mean changes in DAS28 from baseline to 6 months and 12 months by site, arranged by size from smallest to largest. F is the smallest site and B is the largest. DAS28: 28-joint Disease Activity Score.

among sites (frequencies ranging from 51.4% to 88.7%). The route of administration of MTX also varied, with a wide range in the proportion of subcutaneous MTX used across sites from 5.2% to 62.3%. There was also a significant difference ($p < 0.005$) between sites in the proportion of patients prescribed biologics as early as the baseline visit, ranging from 0% to 20.5%. In addition, there was wide disparity between sites in the proportion of patients taking DMARD monotherapy, various combination therapies, and steroids, which all differed significantly ($p < 0.001$). In general, sites with better outcomes used fewer steroids and more parenteral MTX. The use of triple therapy (3 or more DMARD) was most frequent at site G and site B.

Treatment outcome regression analyses by site. When data were divided by site, the effect of different treatment strategies on outcomes varied between sites. Treatment effects were analyzed at the 2 sites with the best disease outcomes (B and H) in an attempt to determine best practices (Table 3). The mean number of DMARD taken (ever and early) was important for the change in DAS28 at 6 months at the second-largest site compared to other sites in regression models. At site B, most strategies were not significantly different from other sites and the significant differences from site B were not the same as site H, except that medication changes had less chance of remission at 12 months. Figure 2 shows the proportion of patients taking triple DMARD treatment at baseline and also those prescribed subcutaneous MTX at baseline, across sites. Triple therapy has the second-highest proportion of patients at site B, and subcutaneous MTX is used proportionately more at sites E, H, and B, the 3 largest sites.

Other definitions of remission. Fewer patients obtained Boolean, CDAI, and SDAI remission, and there was less power to do the analyses. However, some of the findings of remission were not related to site whereas other analyses had similar conclusions to the change in DAS28 (data not shown).

DISCUSSION

As anticipated because of the absence of a standardized treatment protocol in CATCH, thus leaving treatment up to the individual rheumatologists, we found that treatment differences did occur between sites. Unexpectedly, however, we found that major differences in outcomes occurred between sites. Because such a wide disparity in treatment practices and effectiveness as measured by the change in DAS28 or remission exists between even the best sites, it is likely that there are many ways to treat patients with ERA to obtain remission. It seems that more use of initial triple DMARD or subcutaneous MTX increases the likelihood of remission, and those strategies alone or together were used at sites having the best outcomes.

There are other reasons why treatment could vary, including personal preferences, clinic resources, patient drug coverage, and access to medications. The issue of access is relevant and consistent with our finding of great diversity between sites when it came to the proportion of patients taking a biologic. The Canadian Rheumatology Association recommends that biologic therapy be initiated in patients after inadequate response to 2 DMARD in monotherapy or combination therapy after 3 months or more of a trial of DMARD, and in exceptional circumstances where there are DMARD contraindications or high disease activity and poor prognostic factors (particularly in ERA), biologics may be initiated after failure of DMARD monotherapy or even in DMARD-naive patients[27]. Provincial variations in access to and initiation of biologic therapies[28,29] affect a rheumatologist's ability to follow

Table 3. Analysis to determine treatment differences between sites (comparing the 2 largest sites with the best outcomes and other sites). Linear and logistic mixed models to test whether each treatment comparison was associated with DAS28 changes after adjusting for covariates (female sex, baseline HAQ, baseline DAS28), divided by sites with best disease outcomes (2 largest sites B and H). Regression models for treatment and outcome were significant with site having an effect.

Treatment	DAS28 Change 0–6 Months[¥] B (p value)	DAS28 Change from 0–12 Months[¥] B (p value)	DAS28 Remission at Last Visit[‡] OR (p value)
Mean no. DMARD taken			
Site B	0.0480 (0.742)	–0.2271 (0.145)	1.3747 (0.144)
Site H	0.6483 (0.003)*	0.2500 (0.238)	0.6262 (0.301)
Medication changed ever			
Site B	0.9543 (0.001)*	0.6524 (0.004)*	0.4324 (0.014)*
Site H	0.4499 (0.107)	0.7533 (0.003)*	0.4574 (0.150)
Medication increased ever			
Site B	1.0695 (0.001)*	0.6696 (0.005)*	0.3909 (0.007)*
Site H	0.7809 (0.013)*	0.9349 (0.001)*	0.2520 (0.027)*
MTX monotherapy ever^ vs MTX combined with at least 1 other DMARD or biologic ever			
Site B	0.0693 (0.818)	–0.3975 (0.229)	1.7805 (0.206)
Site H	0.7934 (0.001)*	0.2957 (0.196)	0.6463 (0.387)
MTX SC ever			
Site B	0.5212 (0.044)*	0.2789 (0.315)	1.3407 (0.448)
Site H	0.0594 (0.813)	0.0715 (0.759)	0.7875 (0.676)
Single DMARD ever^ vs combination of DMARD and/or biologics ever			
Site B	0.2362 (0.365)	–0.1956 (0.481)	1.6738 (0.188)
Site H	0.6515 (0.002)*	0.3139 (0.118)	0.6935 (0.389)
Single DMARD ever^ vs combination of DMARD ever			
Site B	–0.0662 (0.792)	–0.3676 (0.193)	2.0896 (0.071)
Site H	0.6515 (0.002)*	0.3139 (0.118)	0.6935 (0.389)

B is largest site, H is second largest. Wald test of B coefficient used in the model if significant at $p < 0.1$. [¥] Includes all study participants with measures of DAS28 at both visits. Linear mixed models. [‡] DAS28 < 2.6 = remission, includes only those study participants with baseline DAS28 > 2.6 (not in remission). Generalized linear mixed models, binary logistic with logit link. * $p < 0.05$. ^ Reference category. Ever: patient was prescribed the treatment at any visit up to the 9-month visit; B: ß coefficient; MTX: methotrexate; DMARD: disease-modifying antirheumatic drug; SC subcutaneous; DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire.

these guidelines and could account for the differences seen across sites in biologic use. Despite these differences, results in our study were mixed on the effectiveness of biologics in improving ERA outcome because there is likely confounding by indication. Biologics are used ordinarily when there is failure of traditional DMARD, so the patient's condition would be predicted to be worse if biologics were prescribed. Similarly, when more treatment changes were made, patients did worse because treatment intensification would occur in patients with active disease. The mean number of DMARD and use of combination DMARD early predicted more remission at site B compared to other centers. In randomized controlled trials in early RA, it is found that MTX monotherapy is insufficient for remission in 70% of patients, whereas early combination therapy is insufficient for remission in 30%[30,31,32]. It is important to also acknowledge the effect of other treatment variables on disease outcome, such as medication side effects, comorbid conditions, and compliance. We did not collect data to confirm compliance.

There appeared to be a relationship between the size of the site and outcomes because the 2 best sites, B and H, were the 2 largest sites. This relationship would need to be investigated in further sites to confirm whether and how site size influences ERA disease outcome. It would make sense for larger sites to have better changes in DAS28 and remission because of experience. Many other diseases and also treatments within a disease have noted better outcomes in larger sites. The more patients with ERA a rheumatologist treats, the more experience he or she has to inform treatment decision making. However, there may be other differences (use of allied health professionals, urban vs rural referrals, ethnic differences, formal ERA education programs, or factors not measured) that yielded better outcomes at those sites. The patient's highest level of completed education, RA-specific education, and attendance of educational

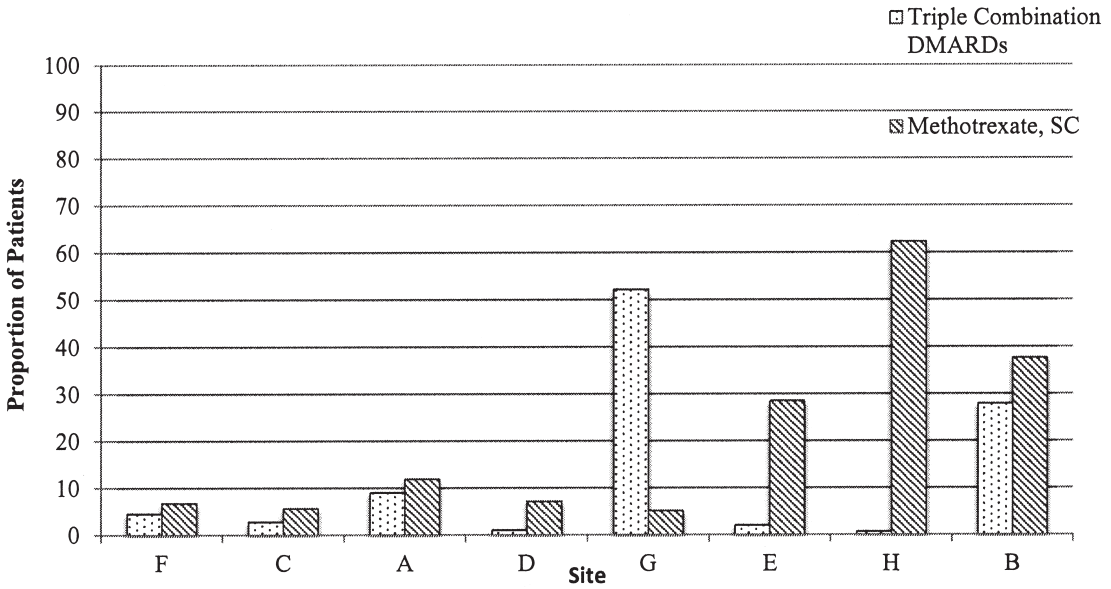

Figure 2. Proportion of patients who were prescribed triple combination DMARD therapy at baseline and the proportion of patients who were prescribed subcutaneous (SC) methotrexate at baseline, by site, arranged by size. F is the smallest site and B is the largest. P values < 0.005 for site differences for triple therapy and SC methotrexate. DMARD: disease-modifying antirheumatic drugs.

programs may improve adherence to treatment and willingness to change or intensify treatment. Most sites had only 1 main rheumatologist involved in CATCH, but within-site variability of treating rheumatologists was not studied. Although it is true that there are site-related factors that could explain site differences, further study into the treatment strategies at the 2 best sites could still be beneficial in developing best practices in ERA.

Limitations. CATCH is a "real-world" observational cohort study and thus the treatment differences that affected outcome may have other unknown biases, because this is not a randomized trial. In regression analyses where site was a factor, sample sizes would be very low for some treatment comparisons, especially those involving biologics, and we could not obtain reliable estimates for treatment effects. Some sites have patients who are involved in ERA randomized trials and also in CATCH, which could affect baseline treatment and treatment changes, but these patients likely comprise a very small percentage of the data and thus would not be a main confounder of the results. Selection bias for enrolling patients could vary between the sites. Perhaps some sites enroll patients who are more severely ill, while others avoid them. We do not know what percentage of total patients with ERA at each site is enrolled in CATCH or how many were offered but declined consent. Further, because different sites joined CATCH at different times, the number of patients enrolled may not reflect the number of patients at the site. The baseline activity scores and other confounders did vary between sites but not in an ordered way according to site size. Factors such as resources at each site and homogeneity of treatment at each site could be investigated in future studies to help determine why site size can affect outcomes. Because the CATCH database continues to grow, future studies can include more sites, which can help to further investigate the possible effects of site size on outcome.

We found that the effects of treatment on ERA outcome at 6 and 12 months varied between sites, with larger sites having better outcomes, but we cannot infer that site characteristics (such as size) are related to outcomes. The strongest treatment predictors of good outcome were early use of subcutaneous MTX, triple DMARD therapy, less use of steroids, and fewer increases in medication after the initial visit. The next steps are to disseminate results to the sites with a report card comparing each site, to encourage standardization of best practices among the sites.

APPENDIX 1.

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