Increasing Treatment in Early Rheumatoid Arthritis Is Not Determined by the Disease Activity Score But by Physician Global Assessment: Results from the CATCH Study

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ABSTRACT. ***Objective.*** To determine the factors most strongly associated with an increase in therapy of early rheumatoid arthritis (ERA).

Methods. Data from the Canadian Early Arthritis Cohort (CATCH) were included if the patient had ≥ 2 visits and baseline and 6 months data. A regression analysis was done to determine factors associated with treatment intensification.

Results. Of 1145 patients with ERA, 790 met inclusion criteria; mean age was 53.4 years (SD 14.7), mean disease duration 6.1 months (SD 2.8), 75% were female, baseline Disease Activity Score-28 (DAS28) was 4.7 (SD 1.8) and 2.9 (SD 1.8) at 6 months for included patients. Univariate factors for intensifying treatment were physician global assessment (MDGA; OR 7.8 and OR 7.4 at 3 and 6 months, respectively, $p < 0.0005$), swollen joint count (SJC; OR 4.7 and OR 7.3 at 3 and 6 months, $p < 0.0005$), and DAS28 (OR 3.0 and OR 4.6 at 3 and 6 months, $p < 0.0005$). In the regression model only MDGA was strongly associated with treatment intensification (OR 1.5 and OR 1.2 at 3 and 6 months, $p < 0.0005$); DAS28 was not consistently predictive (OR 1.0, $p = 0.987$, and OR 1.2, $p = 0.023$, at 3 and 6 months). DAS28 was the reason for treatment intensification 2.3% of the time, compared to 51.7% for SJC, 49.9% for tender joint count, and 23.8% for MDGA. For the same SJC, larger joint involvement was more likely to influence treatment than small joints at 3 months (OR 1.4, $p = 0.027$).

Conclusion. MDGA was strongly associated with an increase in treatment at 3 and 6 months in ERA, whereas DAS28 was not. Physicians rarely stated that DAS28 was the reason for increasing treatment. (J Rheumatol First Release Sept 1 2012; doi:10.3899/jrheum.120520)

Key Indexing Terms:

EARLY RHEUMATOID ARTHRITIS PREDICTORS OF INCREASING TREATMENT
DISEASE-MODIFYING ANTIRHEUMATIC DRUGS PHYSICIAN GLOBAL
DISEASE ACTIVITY SCORE SWOLLEN JOINT COUNT CATCH COHORT

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune condition characterized by swollen and tender synovial joints that can result in significant joint destruction and disability[1]. Early treatment with disease-modifying antirheumatic drugs (DMARD) and/or biologics has been shown to decrease signs and symptoms, disease progression, and associated morbidity[2,3,4,5,6]. This is particularly true in early RA (ERA) before irreversible damage has

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The CATCH study was supported initially by Amgen Canada Inc. and Pfizer Canada Inc. through an unrestricted research grant, and by Hoffmann-La Roche Ltd., United Chemicals of Belgium Canada Inc., Bristol-Myers Squibb Canada Co., Abbott Laboratories Ltd., and Janssen Biotech Inc. (a wholly owned subsidiary of Johnson & Johnson Inc.). Lonnie Pyne received the Canadian Rheumatology Association Roche Summer Studentship and JuMP (Joint Motion Program) trainee summer studentship (Canadian Institutes of Health Research NET training grant).

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Accepted for publication June 28, 2012.

occurred. Targeting therapy to a predefined goal, such as remission or low disease activity states, has been shown to result in a greater proportion of patients achieving these goals than with routine care[6,7,8,9,10]. Despite these facts the actual tool and specific target used for changing treatment in daily practice has not been standardized or universally adopted.

One measure commonly used to determine disease activity, guide therapy, and assess response to therapy is the Disease Activity Score (DAS). The DAS contains the measures swollen joint count (SJC), tender joint count (TJC), erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), and patient global assessment (PGA). The DAS was developed in Europe in the 1980s and 1990s and was based on the clinical judgment of the time. Briefly, the decision to start DMARD therapy was defined as a period of high disease activity and the decision to discontinue or not increase therapy for 1 year was defined as a period of low disease activity. Statistical analysis was used to determine those factors that best discriminated between the high and low disease activity groups and to generate the DAS[11,12]. There have been significant changes in the approach to and treatment of RA since then. Criticisms have arisen as a result of these changes and other inherent characteristics of the DAS. PGA is a measure used in calculation of the DAS. PGA has been shown to have a poor correlation with the physician global assessment (MDGA) and have a lower test-retest reliability than the MDGA[13]. The DAS formula places a greater value on tender in contrast to swollen joints (and the former correlates less well with radiographic progression), which can lead to an overestimation of disease activity in patients with concomitant fibromyalgia, which represents 10%–20% of patients with RA[14]. Patients with a low DAS can still have several swollen joints. Additionally, the DAS formula can be problematic if used for monitoring response to therapy in patients whose ESR falls within the normal range, leading to a lower score that is incongruent with both the patient and the physician assessment[15]. Many patients with a moderate/high DAS do not have their treatment altered[8,16] and the majority of rheumatologists in one survey did not calculate a DAS routinely in practice[17]. Given these shortcomings it is unlikely that the DAS is what is driving therapeutic decisions in ERA in Canada.

Given the treat-to-target concept and lack of a standard for assessing disease activity, our goal was to determine the reasons for increasing therapy in ERA. We addressed this using data from the Canadian Early Arthritis Cohort (CATCH) database.

MATERIALS AND METHODS

Subjects. Data were collected from patients (n = 1145) enrolled into the CATCH study. CATCH is an observational, prospective "real-world" cohort of patients with early inflammatory arthritis recruited at 15 sites since July 2007. Patient inclusion criteria were age > 16 years, with between 6 weeks and 12 months of persistent synovitis at time of entry to the study, and ≥ 2 swollen joints or 1 swollen metacarpophalangeal or proximal interphalangeal joint. In addition, patients had to have ≥ 1 of the following: positive rheumatoid factor (RF), positive anticitrullinated protein antibodies (ACPA), morning stiffness > 45 min, response to nonsteroidal antiinflammatory drugs, or painful metatarsophalangeal squeeze test. The majority of CATCH patients were recruited from provinces with a larger population, especially Ontario and Quebec. At each visit a worksheet is completed that collects global assessments, joint counts, and inflammatory markers, but no DAS or composite score is mandated. Reasons for changing therapies are recorded at each visit. The physician is asked: "What made you change your treatment?" and he/she may record any or all of: SJC, TJC, global assessment (unspecified whether this was PGA, MDGA, or both), Health Assessment Questionnaire-Damage Index (HAQ-DI), DAS28, abnormal radiograph results, abnormal laboratory results, ultrasound of joints, magnetic resonance imaging result, patient preference, side effects, and other reason(s). When treatment was increased at a visit, the question above was linked to the treatment change. However, when treatment was intensified between visits (which occurred only rarely), the reason for intensification of treatment was taken from the previous visit, unless an increase in treatment also occurred at the next visit, and then the question was linked to that therapeutic intensification.

Patients were evaluated at baseline and at subsequent visits (every 3 months in the first year and every 6 months thereafter) according to a standard protocol. Treatment was left to the discretion of the treating physician, and included monotherapy or combinations of DMARD therapy and biologics, as well as the option of oral, intramuscular, or intraarticular glucocorticoid bridging. Adding or increasing the dose of any DMARD, biologic, or oral steroid was considered intensifying treatment, which was labeled the "strict definition" of intensifying treatment. If therapy was switched to a stronger drug and it was not due to side effects, then this was considered intensifying therapy. The analyses were redone adding intraarticular and intramuscular steroids to determine if results were similar with this more liberal definition of increase in treatment.

Statistical analysis. Patients had to have visits recorded at 0, 3, and 6 months. An increase in therapy was examined between 0–3 and 3–6 months. Factors included in the univariate correlational analyses with increase in treatment (yes vs no) were age, sex, RF, and ACPA status as well as TJC, SJC, ESR, CRP, MDGA, PGA, DAS28 score, pain, and HAQ-DI. Correlations between the variables were performed using Pearson's correlation. To generate OR, continuous variables were divided into less than or equal to their mean and greater than their mean. Logistic regression was used to determine the combination of factors that best predicted an increase in therapy. Univariate analyses were included into a regression model when $p < 0.1$, whereas $p < 0.05$ was considered statistically significant in the regression model. Physician-reported reasons for intensifying treatment were analyzed. In addition to the number of joints for SJC, we examined by a logistic regression model what pattern of specific joint involvement was most strongly associated with an increase in therapy, such as large or small joint involvement and total SJC and number of small and large joints involved. Statistical analyses were performed using SPSS software, version 19.

RESULTS

Of the 1145 patients, 790 were eligible, having had visits at 0, 3, and 6 months (n = 777) or just 0 and 6 months (n = 13 extra patients). Reason for ineligibility was lack of followup visit at 6 months (n = 355). Additional patients were removed because of the inability to determine whether therapy had been increased at 3 months or 6 months. This loss was due to forms not being completed (n = 77 and n = 126 at 3 and 6 months, respectively) and ambiguous comments made concerning therapy changes (n = 10 and n = 8 at 3 and 6 months). The mean age was 53.4 years (SD 14.7), with

75.0% females, and a mean disease duration of 6.1 months (SD 2.8). The mean DAS at baseline was 4.7 (SD 1.9) and at 6 months 2.9 (SD 1.8; Table 1). A substantial number of treatment increases were made during these visits. At 3 months, 35.8% of visits resulted in an increase in therapy and at 6 months, 23.6%. The factors associated with intensifying treatment in univariate analyses ($p < 0.1$) were age (only at 3 months), TJC, SJC, ESR, CRP, PGA, HAQ-DI, pain today, MDGA, DAS28 score, and ACPA status (only at 6 months; Table 1). Correlations between the variables at 3 and 6 months are shown in Tables 2 and 3, respectively. Many items were weakly to moderately correlated.

In the logistic regression model the variables independently associated with treatment intensification ($p < 0.05$) were MDGA at both 3 and 6 months, HAQ-DI only at 3 months, and SJC, PGA, and DAS28 only at 6 months (Table 4). When the simplified Disease Activity Index (SDAI) or clinical DAI (CDAI) was also added to the logistic regression model, neither was significant ($p < 0.05$) at 3 or 6 months.

Similar results were found using the "liberal definition" of increased therapy, where intraarticular or intramuscular steroids were also included as intensifying treatment (data not shown). Similar results were also found when substituting TJC28 and SJC28 for TJC and SJC, respectively (data not shown).

The top 3 physician-stated reasons for treatment intensification were SJC (53.2%, 49.3%), TJC (49.8%, 50.0%), and global assessment (24.1%, 23.3%) at 3 and 6 months, respectively. Other options were selected as the reason for treatment intensification in fewer than 10% of cases. This includes the DAS28, which was the stated reason 1.7% of the time at 3 months and 3.3% at 6 months.

At 3 months, when SJC, SJC-large, and SJC-small were entered into a logistic regression model to predict an increase in treatment intensity, SJC-large was the only significant variable in the model (OR 1.4, $p = 0.027$). With the same analysis at 6 months, none of the variables was significant ($p < 0.05$; Table 5).

DISCUSSION

It is well established that early and aggressive therapy that is targeted to a goal, such as low disease activity or remission, leads to better outcomes in ERA[2,3,4,5,6,7,8,9]. However, there is currently no consensus among Canadian rheumatologists for which outcome measure to use in judging disease activity or response to therapy and consequently for determining whether to increase treatment. Our goal was to determine factors most strongly associated with an increase in therapy in ERA.

Physician global assessment was consistently found to be the single factor most strongly associated with an increase in therapy at 3 and 6 months. MDGA had the largest OR at both 3 and 6 months (data not shown), was the strongest independent predictor of increase in therapy in the logistic regression model at 3 and 6 months, and was the only factor that was statistically significant in the logistic regression models at both 3 and 6 months. It is notable that in fewer than 25% of cases was global assessment (unspecified whether it was PGA, MDGA, or both) one of the physician-

Table 1. Baseline characteristics of the CATCH cohort and factors associated with an increase in treatment by univariate correlations at 3 and 6 months (using the strict definition of increase in therapy). Variables with p value < 0.1 using Student's t test were included in the logistic regression model. Data were similar with a more liberal definition of increase in treatment (data not shown).

N = 790	Age, years	Swollen Joint Count (SJC) (0–28)	Tender Joint Count (TJC) (0–28)	ESR, mm/h	CRP, mg/l	Patient Global (0–100)	HAQ-DI (0–3)	Pain Today (0–10)	Physician Global Assessment (0–10)	DAS28
Mean at baseline (SD)	53.3 (15.0)	9.5 (8.1)	13.0 (10.0)	26.6 (23.9)	12.7 (17.9)	55.9 (30.8)	1.0 (0.7)	4.8 (3.0)	4.5 (2.9)	4.7 (1.8)
Yes increase in therapy, mean (SD) at 3 mo	52.0 (14.8)	7.1 (5.8)	11.0 (9.4)	18.9 (20.0)	6.5 (11.9)	48.2 (28.4)	0.7 (0.7)	4.3 (2.8)	4.2 (2.7)	3.7 (2.2)
No increase in therapy, mean (SD) at 3 mo	54.4 (14.9)	3.0 (4.2)	4.7 (6.3)	13.8 (14.9)	4.3 (9.0)	31.8 (27.6)	0.5 (0.6)	2.7 (2.4)	1.5 (1.9)	2.6 (1.6)
Mean difference (95% CI) at 3 mo	–2.4 (–4.7, –0.1)	4.1 (3.3, 4.8)	6.3 (5.1, 7.5)	5.1 (2.4, 7.7)	2.2 (0.6, 3.7)	16.4 (12.0, 20.8)	0.2 (0.1, 0.3)	1.6 (1.2, 2.0)	2.7 (2.4, 3.0)	1.1 (0.8, 1.4)
p, 3 months	0.041	< 0.0005	< 0.0005	< 0.0005	0.008	< 0.0005	< 0.0005	< 0.0005	< 0.0005	< 0.0005
Yes increase in therapy, mean (SD) at 6 mo	52.6 (13.9)	7.9 (7.2)	11.1 (9.4)	17.2 (18.9)	5.8 (11.4)	49.4 (27.7)	0.7 (0.6)	4.2 (2.7)	3.8 (2.5)	3.9 (2.0)
No increase in therapy, mean (SD) at 6 mo	53.4 (14.7)	2.5 (3.8)	4.3 (6.5)	14.2 (14.7)	4.4 (8.0)	27.5 (26.7)	0.4 (0.6)	2.5 (2.5)	1.5 (1.9)	2.5 (1.7)
Mean difference (95% CI) at 6 mo	–0.7 (–3.3, 1.8)	5.4 (4.5, 6.2)	6.9 (5.5, 8.2)	3.0 (0.2, 5.9)	1.4 (–0.2, 3.1)	21.9 (17.0, 26.7)	0.3 (0.2, 0.4)	1.7 (1.3, 2.2)	2.3 (2.0, 2.7)	1.4 (1.0, 1.7)
p, 6 months	0.568	< 0.0005	< 0.0005	0.039	0.146	< 0.0005	< 0.0005	< 0.0005	< 0.0005	< 0.0005

CATCH: Canadian Early Arthritis Cohort; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire-Damage Index; DAS: Disease Activity Score.

Table 2. Pearson correlations of the variables studied for intensification of treatment at 3 months.

	Age	TJC	SJC	ESR	CRP	Patient Global Assessment	HAQ-DI	Pain Today	Physician Global Assessment	DAS28
Age	—	–0.077	0.035	0.135	0.059	–0.023	0.028	0.000	–0.075	–0.020
TJC	–0.077	—	0.642	0.153	0.159	0.341	0.409	0.410	0.600	0.402
SJC	0.035	0.642	—	0.165	0.150	0.292	0.241	0.317	0.604	0.389
ESR	0.135	0.153	0.165	—	0.453	0.178	0.346	0.203	0.248	0.652
CRP	0.059	0.159	0.150	0.453	—	0.154	0.249	0.143	0.123	0.339
Patient global assessment	–0.023	0.341	0.292	0.178	0.154	—	0.493	0.769	0.352	0.412
HAQ-DI	0.028	0.409	0.241	0.346	0.249	0.493	—	0.533	0.407	0.439
Pain today	0.000	0.410	0.371	0.203	0.143	0.769	0.533	—	0.362	0.333
Physician global assessment	–0.075	0.600	0.604	0.248	0.123	0.352	0.407	0.362	—	0.467
DAS28	–0.020	0.402	0.389	0.652	0.339	0.412	0.439	0.333	0.467	—

TJC: tender joint count; SJC: swollen joint count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire-Damage Index; DAS28: Diseaes Activity Score.

Table 3. Pearson correlation of the variables studied for intensification of treatment at 6 months.

	TJC	SJC	ESR	Patient Global Assessment	HAQ-DI	Pain Today	Physician Global Assessment	DAS28
TJC	—	0.660	0.133	0.429	0.421	0.422	0.624	0.519
SJC	0.660	—	0.176	0.316	0.260	0.324	0.676	0.444
ESR	0.133	0.176	—	0.145	0.240	0.239	0.219	0.609
Patient global assessment	0.429	0.316	0.145	—	0.497	0.748	0.385	0.515
HAQ-DI	0.421	0.260	0.240	0.497	—	0.561	0.387	0.402
Pain today	0.422	0.324	0.239	0.748	0.561	—	0.405	0.452
Physician global assessment	0.624	0.676	0.219	0.385	0.387	0.405	—	0.468
DAS28	0.519	0.444	0.609	0.515	0.402	0.452	0.468	—

For definitions seee Table 2.

stated reasons for increasing therapy, so there is a discrepancy of what the physicians said and the major reason for intensifying treatment. However, some items of course influence the MDGA and may vary between physicians and between patients. For instance, a swollen joint count of 2 with no tender small joints may be interpreted far differently than 2 knee joints involved with warmth, effusions, and tenderness. The OR was highest for the MDGA but it was chosen less frequently than some other reasons.

The DAS28 was found to be an independent predictor of increasing therapy at 6 but not 3 months. However, if ESR or pain alone were removed from the model at 6 months, DAS28 was no longer statistically significant and the percentage correct classification of the model decreased by only 0.1% for removing ESR and 0.4% for removing pain. These changes did not alter the association of MDGA with increasing therapy. Consequently, DAS28 did not appear to be a very robust predictor of increasing therapy at 6 months, as these minor alterations to the model resulted in DAS28 no longer being statistically significantly associated with increasing therapy. In a Canadian treat-to-target study of established RA (OPTIMIZATION trial) there was a clear advantage in terms of achieving good clinical response and retaining patients in the study when a DAS28 evaluation was required for treatment decisions or a swollen joint count target compared to usual standard of care[16].

The PGA is one of the variables used in the calculation of the DAS. The single factor that was consistently the strongest predictor of treatment intensification was MDGA, which has been shown to not correlate well with the PGA and to have higher test-retest reliability than the PGA[13]. If the DAS is high but the MDGA and SJC are not high (i.e., patient pain could be high for reasons unrelated to joint activity), then it is not likely that intensification of DMARD will be recommended.

If evaluating a treat-to-target approach, there were intensifications of treatment at 3 months in 35% of patients; this may indeed confirm that there was a target in mind because of the many changes made.

We found that, on average, physicians in this study listed

Table 4. Summary of variables in the logistic regression model for "increase in therapy" (strict definition) at 3 and 6 months. Model had correct classification of 76.2% ($p < 0.0005$) at 3 months and 79.3% ($p < 0.0005$) at 6 months. Anticitrullinated protein antibody status was not included in the model at 6 months as it greatly increased the number of excluded cases due to missing data.

	Age	TJC	SJC	ESR	CRP	Patient Global Assessment	HAQ-DI	Pain Today	Physician Global Assessment	DAS28
Exp(B) (95% CI), 3 months	0.989 (0.975, 1.002)	1.019 (0.985, 1.055)	1.050 (0.998, 1.105)	1.008 (0.991, 1.024)	1.005 (0.984, 1.026)	1.007 (0.996, 1.017)	0.541 (0.357, 0.820)	1.116 (0.995, 1.251)	1.460 (1.316, 1.620)	0.999 (0.855, 1.167)
p	0.089	0.273	0.061	0.372	0.638	0.229	0.004	0.060	< 0.0005	0.987
Exp(B) (95% CI), 6 months	*	0.997 (0.962, 1.033)	1.098 (1.040, 1.160)	0.985 (0.968, 1.002)	**	1.015 (1.004, 1.027)	0.872 (0.569, 1.336)	0.996 (0.885, 1.122)	1.249 (1.106, 1.412)	1.235 (1.029, 1.481)
p	—	0.868	0.001	0.083	—	0.007	0.529	0.952	< 0.0005	0.023

* Age did not reach the p value < 0.1 cutoff point at 6 months. ** CRP did not reach the p value < 0.1 cutoff point at 6 months. For definitions see Table 2.

Table 5. Logistic regression model showing association of small and large swollen joint involvement with increasing treatment intensity.

	SJC-Large	SJC-Small	SJC-Total
Exp(B) (95% CI), 3 months	1.4 (1.0, 1.9)	1.1 (0.8, 1.4)	1.1 (0.8, 1.4)
p	0.027	0.623	0.533
Exp(B) (95% CI), 6 months	1.0 (0.7, 1.3)	1.1 (0.9, 1.2)	1.2 (1.0, 1.4)
p	0.767	0.535	0.068

SJC: swollen joint count.

the DAS as their reason for increasing treatment intensity only 2.3% of the time. Of note, the calculation of the DAS or any other composite score (CDAI, SDAI) was not mandated by the CATCH data collection. One might speculate that if they were required to be calculated they would have been stated more frequently as a reason for increasing therapy. This is supported in the literature; many patients with DAS > 3.2 do not have their treatment modified[8,16], and in a recent survey of rheumatologists in Ontario, the majority did not calculate a DAS[17]. However, if the DAS truly is a reflection of disease activity one would expect it to influence therapy decisions significantly, regardless of whether it was measured.

The rheumatologists said they changed treatment mostly as a result of the SJC, but it was actually the MDGA in the data analysis. The global assessment performed by the rheumatologist appears to be the primary factor driving the decision to increase therapy, and this is not surprising. It is unlikely that a physician will give any measure primacy over his or her own clinical judgment, which itself is likely a systematic assessment involving many different variables. It is unlikely that any measure can adequately encapsulate the integration of factors on which clinical judgment is based. Even traditional measures of disease activity such as the SJC and TJC were not as strongly or consistently associated with increasing therapy as the MDGA; but physicians said the SJC was the most common reason for intensifying treatment. Grading the activity of each joint is not commonly done and this is perhaps where the MDGA helps to differentiate patients at similar joint counts. The likely reason that measures such as these were strongly associated with increasing therapy in univariate analyses, but not independently associated in the logistic regression model, is that they were taken into account in the formulation of the MDGA and contribute to the calculation of the DAS28. Both SJC and TJC were highly correlated with MDGA and DAS28 (Tables 2 and 3).

The small influence of the DAS28 on the decision to increase treatment and the physician-stated reasons for increasing treatment are at odds with other studies. Others have found that, contrary to our results, physicians report that the DAS contributes a great deal to their decision to intensify treatment[18]. The main difference is that in our study, it was not mandated that DAS28 be calculated (it is not scored on the standardized forms that are completed, but scored within the database), and since the majority of Canadian rheumatologists have not adopted this practice it is reflected in our findings that very few physicians listed the DAS28 as a reason for increasing therapy. Others have shown that "evaluator global assessment" has a strong association with radiographic progression and affirms the use of evaluator global assessment as the gold standard of disease activity[19].

These results should not deter the use of or search for

objective measures of disease activity to guide therapeutic decisions. However, they do show that currently no measure, individual or composite, has overtaken physician clinical judgment as the primary determining factor in therapeutic decisions. This conclusion is important because it implies that the subjective feelings of the doctor with respect to such aspects as pain and patient's assessment of disease activity influence decisions concerning intensifying treatment, possibly influencing the outcome for the patient, or it may imply that the SJC and physician interpretation of the location and severity/activity of the joints involved are linked to the decision to intensify treatment. These issues could be the subject of further investigation.

OR were used instead of an analysis of covariance (despite loss of data by dividing in the former approach) so that the results could be interpreted from a clinical perspective.

The CATCH database is an observational multicenter cohort of patients with ERA that has no standardized care, so treatment choices are left up to the individual physician, which is a strength if trying to determine why doctors make decisions to intensify treatment. However, it is not known which of these factors were collected in routine practice so our observations are limited to practices where the data are recorded. It was also not known whether physicians were treating to a target such as CDAI or SDAI, etc. We relied primarily upon physician comments to determine when the decision was made to increase therapy. It is possible that some physicians did not diligently provide comments regarding change of medications in the survey. To be as conservative as possible with our conclusions, when no physician comments were made regarding a change in medication, the cases were coded as "no increase in therapy." However, we also studied all medications at each visit for DMARD, steroids, and injections, and if we ignore the treatment intensification question, the results are the same. Indeed, there were very few missing data regarding reasons for medication changes, as queries are sent to pursue missing data. It is also reassuring that the number of cases excluded because of unclear responses whether therapy was increased was quite low (n = 18). The resistance of patients to change of therapy was not determined either. Notably, even though all centers had the data to collect the DAS, it was not used (and likely usually not calculated during the patient encounter). We cannot comment on specific thresholds (i.e., would a change always be made at a certain high score on any of the activity items collected?), because the items were collected and evaluated simultaneously during a patient visit. It is clear that Canadian physicians within the CATCH cohort rely on the MDGA rather than a composite index.

Another limitation in our study is the selection bias that may be introduced as the physician answers the question, "What made you change your treatment?" Moreover, some doctors may have been unable to answer all questions in the interest of time, but missing data were few for these variables. Also, the question about reason(s) for change in therapy was at the end of the physician form, and so was unlikely to bias the reason(s) for change, because in general a treatment decision would already have been made. There may be a discrepancy between the outcomes of the regression analysis and the answers provided by doctors, as most physicians said it was SJC (and TJC) that caused them to change treatment, but the most robust association was the MDGA. In addition, although components of the DAS were collected, it was not necessarily calculated at each visit.

The single factor consistently and most strongly associated with an increase in therapy in early RA was the physician global assessment. DAS28 was not consistently a strong independent predictor of intensification of treatment in ERA.

APPENDIX 1

List of study collaborators. The CATCH (Canadian Early Arthritis Cohort) investigators: Vandana Ahluwalia, Pooneh Akhavan, Hector Arbillaga, Murray Baron, Mary Bell, William Bensen, Gilles Boire, Vivian Bykerk, Alf Cividino, Ines Colmegna, Paul Haraoui, Carol Hitchon, Shahin Jamal, Ed Keystone, Alice Kinkhoff, Majed Kraishi, Maggie Larche, Chris Lyddell, Henri Menard, Dianne Mosher, Bindu Nair, Erin Norris, Chris Penney, Janet Pope, Laurence Rubin, Emily Shaw, Evelyn Sutton, Carter Thorne, and Michel Zummer.

REFERENCES

1. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81.
2. Van der Heide A, Jacobs JW, Bijlsma JW, Heurkens AH, van Booma-Frankfort C, van der Veen MJ, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs: A randomized, controlled trial. Ann Intern Med 1996;124:699–707.
3. Breedveld F. The value of early intervention in RA — A window of opportunity. Clin Rheumatol 2011;30:S33-9.
4. Rantalaiho V, Korpela M, Laasonen L, Kautiainen H, Järvenpää S, Hannonen P, et al. Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic outcome in patients with early rheumatoid arthritis: The 11-year results of the Finnish Rheumatoid Arthritis Combination Therapy Trial. Arthritis Res Ther 2010;12:R122.
5. Rantalaiho V, Korpela M, Hannonen P, Kautiainen H, Järvenpää S, Leirisalo-Repo M, et al. The good initial response to therapy with a combination of traditional disease-modifying antirheumatic drugs is sustained over time: The eleven-year results of the Finnish Rheumatoid Arthritis Combination Therapy Trial. Arthritis Rheum 2009;60:1222-31.
6. Haraoui B, Pope J. Treatment of early rheumatoid arthritis: Concepts in management. Semin Arthritis Rheum 2011;40:371-88.
7. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): A single-blind randomised controlled trial. Lancet 2004;364:263-9.
8. Verstappen SM, Jacobs JW, van der Veen MJ, Heurkens AH, Schenk Y, ter Borg EJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: Aiming for remission. Computer

Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis 2007;66:1443-9.
9. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. Arthritis Rheum 2005;52:3381-90.
10. Smolen JS, Aletaha D, Bijlsma JWJ, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: Recommendations of an international task force. Ann Rheum Dis 2010;69:631-7.
11. van der Heijde DMFM, van 't Hof MA, van Riel PLCM, Theunisse HAM, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: First step in the development of a disease activity score. Ann Rheum Dis 1990;49:916-20.
12. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;39:44-8.
13. Rohekar G, Pope J. Test-retest reliability of patient global assessment and physician global assessment in rheumatoid arthritis. J Rheumatol 2009;36:2178-82.
14. Pollard LC, Kingsley GH, Choy EH, Scott DL. Fibromyalgic rheumatoid arthritis and disease assessment. Rheumatology 2010;49:924-8.
15. Gardiner PV, Bell AL, Taggart AJ, Wright G, Kee F, Smyth A, et al. A potential pitfall in the use of the Disease Activity Score (DAS28) as the main response criterion in treatment guidelines for patients with rheumatoid arthritis. Ann Rheum Dis 2005;64:506-7.
16. Pope J, Thorne C, Haraoui BP, Sampalis JS. Treating to target with TNFi in active established RA results in longer drug survival than routine care with TNFi: Results from the Optimization of Humira RCT [abstract]. Arthritis Rheum 2010; 62 Suppl: S144.
17. Pope J, Thorne C, Cividino A, Lucas K. A randomized controlled trial of rheumatologist education impacting on systematic measurements and treatment decisions in rheumatoid arthritis (RA): Results of the Metrix Study [abstract]. Arthritis Rheum 2010; 62 Suppl: S721.
18. Kievit W, Van Hulst L, Van Riel P, Fraenkel L. Factors that influence rheumatologists' decisions to escalate care in rheumatoid arthritis: Results from a choice-based conjoint analysis. Arthritis Care Res 2010;62:842-7.
19. Aletaha D, Machold KP, Nell VP, Smolen JS. The perception of rheumatoid arthritis core set measures by rheumatologists. Results of a survey. Rheumatology 2006;45:1133-9.