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A quarter of patients time their early rheumatoid arthritis onset differently than physicians

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ABSTRACT

Objective Early rheumatoid arthritis (RA) treatment requires timely recognition. This large, multicentre study compared patient-reported vs physician-reported onset of early RA.

Methods Patients from the Canadian Early ArThritis CoHort with early/suspected RA (persistent synovitis <1 year) completed questionnaires asking about the date of symptom onset; and rheumatologists date of onset for persistent synovitis. Groups with similar reported timing (patient and physician) versus differing timing of 30 days or more were compared.

Results In 2683 patients, the median patient symptom duration (IQR) was 178 days (163) and physician-reported duration was 166 (138). 1940 (72%) patients had similar patient-reported and physician-reported onset (<30 days), whereas 497 (18%) reported onset 30 or more days preceding physicians, and 246 (9%) 30 or more days after physicians. Patients reporting onset preceding physicians had lower baseline Disease Activity Score based on 28 joint count, swollen joint counts and erythrocyte sedimentation rate ($p<0.05$). Patients reporting onset after physicians were more likely to be rheumatoid factor positive ($p<0.001$) and had higher anticitrullinated protein antibody titres ($p<0.009$). Regression showed low income, smoking, fibromyalgia, osteoarthritis and baseline non-methotrexate non-biological disease-modifying antirheumatic drug use were predictors for longer patient-reported symptoms. At 12 months, patients reporting longer symptom duration than physicians had lower rates of Simplified Disease Activity Index remission and higher physician global assessments.

Conclusion Over one-fourth of patients reported differences of >1 month in symptom onset from their rheumatologist. Patients with longer symptom durations had less improvement at 1 year, which may be reflective of comorbid musculoskeletal conditions.

Key messages

What is already known about this subject?

- Early initiation of disease-modifying drugs in rheumatoid arthritis (RA) has significant prognostic benefit, as suggested by a therapeutic 'window of opportunity'.
- Definitions of disease onset in early rheumatoid arthritis (ERA) clinical studies are heterogeneous and sometimes not defined.
- It is unknown whether timing of ERA onset differs between patients and rheumatologists; how patients with discordant onsets clinically differ; nor whether who defines the beginning of the window of opportunity might impact disease outcomes.

What does this study add?

- Compared with their rheumatologist, a quarter of patients reported discordant timing of RA onset (30 days or more).
- Patients who had shorter duration compared with the physicians' report were more likely to be seropositive.
- Patients who reported longer symptom duration had lower rates of remission at 12 months compared with the agreement group.

How might this impact on clinical practice?

- Differences in patient-reported versus physician-reported symptom onset dates could have implications for defining the window of opportunity for initiating RA treatment and the likelihood of achieving treat-to-target outcomes.
- Study findings demonstrate the importance of adopting standardised definitions of onset of ERA to enable cross-study comparisons.

INTRODUCTION

Early inflammatory arthritis (EIA) is a recent-onset arthritis with one or more swollen joints that may resolve spontaneously, develop into rheumatoid arthritis (RA) or another definite arthropathy or remain undifferentiated. RA has a prevalence of about 1% causing significant morbidity. Early initiation of disease-modifying antirheumatic drugs (DMARD) therapy in patients with RA has significant prognostic benefit as measured by increased

likelihood of remission, DMARD-free remission, improved Disease Activity Score based on 28 joint count (DAS28) and reduced rates of radiologic joint destruction.[1–5] DMARD therapy should be initiated at time of RA diagnosis.[6] Recognition of the earliest clinically apparent stage of RA constitutes a significant focus of research and practice.[7 8]

Often, in RA, initial arthritis serves as disease onset and the beginning of the therapeutic window of opportunity. However, early RA clinical studies definitions of disease onset and symptom duration are heterogeneous, imprecise and sometimes not defined, making it difficult to accurately assess early therapy outcomes.[9]

Our aim was to determine if there are differences between patients and rheumatologists in reporting RA onset as the literature does not standardise which perspective we should take for the onset of RA and this could affect the window of opportunity. Previous literature does not compare patient-reported and physician-reported onsets; so, it is unclear how discordant onsets might impact disease outcomes. Based on the importance of early RA treatment initiation for achieving remission, we hypothesise that patients with discordant onsets might experience worse clinical outcomes. This study of patients with EIA from an incident cohort compared symptom onset timing as reported by patients and physicians and identified factors associated with differences in reported onset.

METHODS

Data source

The Canadian Early Arthritis Cohort (CATCH) is a prospective observational cohort of patients with EIA from 17 Canadian recruitment sites. Enrolment criteria include age over 16 years; between 6 weeks and 12 months of persistent synovitis at entry; two or more swollen joints or one swollen metacarpophalangeal or proximal interphalangeal joint and one or more of the following: positive RF, positive anticitrullinated protein antibodies (ACPA), morning stiffness of at least 45 min, response to non-steroidal anti-inflammatory drugs or painful metatarsal phalangeal (MTP) squeeze test. Only patients with suspected early rheumatoid arthritis are enrolled. Most patients are enrolled at their first visit to a rheumatologist and the history is judged by the physician to be persistent synovitis within the time frame. If arthritis has been palindromic, the date when it became persistent is recorded as the date of onset.

After signing informed consent, patients completed an initial questionnaire of baseline demographics and clinical characteristics which included questions on timing of symptom onset. Physicians or study coordinators independently asked patients about their symptom onset timing, particularly probing for persistent synovitis symptoms, especially in the joint that prompted the patient's presentation. Follow-up visits with data collection are every 3 months for the initial year and subsequently every 6 months. Patients received standard care with therapy at the discretion of the treating rheumatologists and encouragement to treat to remission. All CATCH participants signed informed consent, and the respective ethics committees of all sites approved the project. DMARDs are usually started at the first visit or shortly thereafter.

Participants

There were 2772 CATCH participants enrolled from January 2007 to March 2017. Participants were excluded if either patient-reported or physician-reported symptom onset date was missing, if reported onset date was after initial assessment date or if recorded onset was before age 16.

Variables

Baseline variables included demographics of age, sex, ethnicity, income, smoking and education; biomarkers (ACPA, RF); number of comorbidities, comorbid osteoarthritis (OA), fibromyalgia. Baseline and 12-month variables included inflammatory markers (erythrocyte sedimentation rate (ESR), C reactive protein (CRP)); erosions, 28-swollen and tender joint counts, Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), patient global score, physician global assessment and DAS28; oral or parenteral corticosteroids, and RA therapy. RA therapy at 3 months was also included. Baseline and 12-month remission rates were determined based on DAS28 ≤2.6, CDAI ≤2.8 and SDAI ≤3.3. Erosions were read by the rheumatologist or site radiologist scoring them as present or absent. The rheumatologists are asked for each patient the date of onset of symptoms of persistent synovitis (month/year) or unsure. The patients are asked to answer the question about the date when the first symptoms of inflammatory arthritis began. There was no training for patients or rheumatologists for these questions except the rheumatologists were told to choose the date of persistent synovitis onset and not palindromic rheumatism onset if that preceded persistent synovitis.

Analysis

Descriptive statistics were reported for baseline study characteristics and symptom durations as reported by physician and patient. The difference between physician-reported and patient-reported symptom onset in number of days was calculated. As there was variability in which day of the month was reported as onset date, and to decrease recall error, a cut-off of 30 days was used to differentiate agreement and disagreement timing groups.

Participants were divided into three groups: <30 days difference in reported symptom onset timing ('agreement group'); patient-reported symptom onset 30 or more days earlier than physician ('patient earlier') and patient-reported symptom onset 30 or more days after physician ('patient after physician'). The three groups were compared for baseline characteristics known to be

Table 1 Baseline characteristics by disease onset group compared using ANOVA

Variable	All patients	Concordant MD vs patient-reported RA symptom onset date (<30 days)	Discordant MD vs patient-reported symptom onset date (>30 days)		P value
			Patient onset precedes MD date	Patient onset after MD date	
N	2683	1940	497	246	
Symptom duration by MD (days), median (IQR)	166 (138)	161 (133)	163 (140)	213 (144)	<0.001
Symptom duration by patient (days), median (IQR)	178 (163)	160 (135)	373 (430)	132 (126)	<0.001
Age, years, mean (SD)	54 (15)	55 (15)	52 (16)	54 (16)	0.003
Female (%)	1911 (71)	1375 (71)	356 (72)	180 (73)	0.738
Caucasian (%)	2179 (81)	1598 (82)	391 (79)	190 (77)	0.042
Education >high school (%)	1454 (56)	1045 (56)	277 (58.1)	134 (57)	0.725
Income >US$50 000 (%)	805 (45)	559 (45)	168 (43)	174 (45)	0.755
Smoking (%)					
Never	1177 (44)	834 (43)	230 (46)	113 (46)	0.370
Past smoker	1030 (38)	755 (39)	182 (37)	93 (38)	0.594
Current smoker	465 (17)	341 (18)	84 (17)	40 (16)	0.822
# of comorbidities	2 (2)	2 (2)	2 (2)	2 (2)	0.715
Fibromyalgia (%)	57 (2)	35 (2)	17 (3)	5 (2)	0.085
Osteoarthritis (%)	314 (12)	225 (12)	61 (12)	28 (11)	0.909
2010 ACR criteria (%)	2052 (76)	1488 (77)	354 (73)	200 (81)	0.047
RF positive (%)	1402 (59)	994 (57)	259 (62)	149 (69)	0.001
ACPA positive (%)	1005 (53)	739 (52)	166 (52)	100 (60)	0.162
ACPA titre	87 (139)	82 (135)	101 (136)	110 (167)	0.009
Erosions (%)	522 (20)	376 (19)	95 (19)	51 (21)	0.851
DAS28	4.9 (1.5)	4.9 (1.5)	4.7 (1.4)	4.9 (1.4)	0.015
Swollen joint count (0–28)	7 (6)	7 (6)	6 (6)	7 (6)	0.010
Tender joint count (0–28)	8 (7)	8 (7)	8 (7)	8 (6)	0.204
HAQ-DI (0–3)	1 (1)	1 (1)	1 (1)	1 (1)	0.085
ESR	27 (22)	27 (23)	24 (20)	27 (22)	0.006
CRP	14 (18)	14 (19)	12 (16)	16 (20)	0.024
MD global score (0–10)	4.6 (2.5)	4.6 (2.5)	4.7 (2.5)	5.1 (2.5)	0.003
Patient global score (0–10)	5.7 (3.0)	5.7 (2.9)	5.6 (3.0)	5.9 (2.9)	0.398
CDAI	25 (14)	26 (14)	24 (14)	26 (14)	0.153
SDAI	27 (15)	27 (15)	26 (15)	27 (14)	0.202
Baseline oral steroid (%)	777 (29)	606 (31)	112 (22)	59 (24)	<0.001
Baseline parenteral steroid (%)	740 (28)	542 (28)	132 (27)	66 (27)	0.797
Oral steroid at 3 months (%)	633 (24)	479 (25)	102 (21)	52 (21)	0.095
Parenteral steroid at 3 months	321 (12)	220 (11)	61 (12)	40 (16)	0.079
Initial RA treatment (%)					
MTX monotherapy	725 (27)	1517 (27)	144 (29)	64 (26)	0.543
MTX combination	1062 (40)	798 (41)	162 (33)	102 (42)	**0.002**
Other DMARDs	494 (18)	355 (18)	99 (20)	40 (16)	0.466
Biologic	49 (2)	37 (2)	10 (2)	2 (1)	0.455
None of the above	353 (13)	233 (12)	82 (16)	38 (15)	**0.016**
RA treatment at 3 months (%)					

Continued

Table 1 Continued

Variable	All patients	Concordant MD vs patient-reported RA symptom onset date (<30 days)	Discordant MD vs patient-reported symptom onset date (>30 days)		P value
			Patient onset precedes MD date	Patient onset after MD date	
MTX monotherapy	608 (23)	432 (22)	128 (26)	48 (20)	0.113
MTX combination	1201 (45)	901 (46)	185 (37)	115 (47)	**0.001**
Other DMARDs	433 (16)	305 (16)	90 (18)	38 (15)	0.415
Biologic	104 (4)	77 (4)	19 (4)	8 (3)	0.858
None of the above	337 (13)	225 (12)	75 (15)	37 (15)	0.052

Results are in mean (SD) if not specified otherwise.
Statistically significant values are indicated in bold.
ACPA, anticitrullinated protein antibodies; ACR, American College of Rheumatology; ANOVA, analysis of variance; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAS28, Disease Activity Score based on 28 joint count; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; MD, medical doctor; MTX, methotrexate; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index.

prognostic factors for EIA using one-way between-groups analysis of variance (ANOVA).

As patients are often started on RA therapy after initial assessment, RA therapy at 3-month visit was compared. Twelve-month outcomes of DAS28, SDAI and CDAI remission, patient global score, physician global assessment, erosions, swollen joint count, tender joint count, erosions and RA therapy were also compared.

Univariate regression analysis was performed to identify predictors of physician-onset and patient-onset timing comparing agreement within 30 days with longer by physician and longer by patient report. Variables with p value of 0.1 or less were included in stepwise multivariate analysis for predictors of discordance, and age and sex were forced variables. Analyses were repeated omitting patients who reported symptom duration of >5 years. P values <0.05 were considered to be statistically significant and 95% CIs were used. The analysis was performed using SPSS V.25.[10]

RESULTS

Of the initial 2772 patients, 61 participants were excluded for missing physician-reported or patient-reported symptom onset dates; 16 for symptom onset prior to age 16; 12 for physician-reported or patient-reported onset after initial visit. Thus, 2683 were included in analyses. Median patient-reported symptom duration (IQR) was 178 days (163), physician-reported duration was 166 (138) days and median difference (IQR) was 0 (0). Ten per cent (n=281) of patients-reported symptom duration longer than 1 year; 1940 (72%) patients had similar patient and physician symptom onset (<30 days), whereas 743 (27%) had disagreement reported onsets of 30 days or more; 497 (18%) patients reported onset 30 or more days preceding physicians and 246 (9%) 30 or more days after physicians.

Table 1 summarises descriptive statistics for all patients and the three onset groups as well as ANOVA results. The groups significantly differed in age, ethnicity, 2010 American College of Rheumatology criteria, initial ACPA titre, RF positivity, baseline swollen joint count, ESR, CRP, DAS28, baseline physician global assessment (all p<0.05).

When there was longer patient-reported symptom duration, the outcomes at 1 year were in general not as good. The 12-month outcomes by onset group are shown in table 2. Disease activity differed at 1 year depending on concordance or discordance of RA onset, with patients reporting longer symptom duration experiencing a lower rate of SDAI remission, higher Health Assessment Questionnaire (HAQ and higher patient global assessment of disease activity than patients with agreement in onset (all p<0.05). DAS28 improvement at 12 months compared with baseline was less for patients reporting longer symptom duration than the agreement group; however, at 12 months, there were no significant differences in DAS28 or CDAI rates of remission. At 3 and 12 months, fewer patients reporting longer disease duration were on methotrexate combo therapy than the agreement group, and at 12 months more patients reporting longer disease duration were on no DMARD or biologic therapy.

In univariate linear regression analysis (table 3), non-Caucasian ethnicity, annual income <US$50 000, current smoking, comorbid OA, fibromyalgia, baseline lack of oral corticosteroid use, lack of methotrexate combination therapy and the use of non-methotrexate non-biologic DMARD were all significant predictors (p<0.1) for difference in onset towards longer patient-reported symptom duration. RF positivity, ACPA positivity and higher physician global assessment were all significant predictors (p<0.1) for difference in onset toward longer physician-reported symptom duration.

Table 2 Twelve-month outcomes and medications by disease onset group compared using ANOVA

Variable	All patients	Similar onset date	Patient onset precedes MD date	Patient onset after MD date	P value
DAS28	2.8 (1.4)	2.8 (1.4)	2.9 (1.4)	2.7 (1.3)	0.266
Change in DAS28 (0–12 months)	−2.1 (1.8)	−2.2 (1.8)	−1.9 (1.7)	−2.1 (1.5)	**0.016**
Proportion in DAS28 remission (baseline)	184 (7.3)	125 (6.8)	46 (9.8)	13 (5.6)	**0.049**
Proportion in DAS28 remission (12 months)	847 (53.3)	624 (54.1)	138 (48.6)	85 (55.6)	0.207
CDAI	8.2 (9.2)	8.0 (9.0)	9.2 (9.7)	8.0 (9.8)	0.109
Change in CDAI (0–12 months)	−17.3 (15.3)	−17.8 (15.6)	−15.6 (15.0)	−17.0 (13.8)	0.070
Proportion in CDAI remission (baseline)	36 (1.4)	26 (1.4)	9 (1.8)	1 (0.4)	0.316
Proportion in CDAI remission (12 months)	575 (32.7)	432 (34.0)	88 (27.5)	55 (32.7)	0.083
SDAI	8.9 (9.6)	8.6 (9.4)	9.9 (9.9)	8.8 (10.2)	0.136
Change in SDAI (0–12 months)	−18.3 (16.4)	−18.8 (16.7)	−16.8 (16.0)	−17.1 (14.2)	0.168
Proportion in SDAI remission (baseline)	38 (1.6)	25 (1.4)	11 (2.5)	2 (0.9)	0.204
Proportion in SDAI remission (12 months)	509 (34.3)	389 (36.2)	76 (28.4)	44 (31.9)	**0.045**
HAQ-DI (0–3)	0.5 (0.6)	0.5 (0.6)	0.6 (0.6)	0.5 (0.7)	**0.048**
Change in HAQ-DI (0–12 months)	−0.5 (0.7)	−0.5 (0.7)	−0.4 (0.7)	−0.5 (0.7)	**0.001**
Erosions (%)	323 (17.1)	237 (17.3)	59 (17.3)	27 (15.1)	0.763
Swollen joint count (0–28)	2 (3)	2 (3)	2 (3)	2 (4)	0.558
Tender joint count (0–28)	2 (4)	2 (4)	2 (4)	2 (4)	0.886
ESR	15.4 (15.5)	15.1 (15.5)	16.4 (16.1)	15.1 (13.5)	0.501
CRP	5.5 (9.5)	5.3 (9.7)	5.9 (9.6)	5.7 (7.7)	0.683
MD global assessment (0–10)	1.4 (1.9)	1.4 (1.9)	1.6 (2.0)	1.4 (2.0)	0.092
Patient global score (0–10)	2.9 (2.7)	2.8 (2.7)	3.3 (2.7)	2.8 (2.6)	**0.028**
Oral corticosteroid (%)	283 (10)	201 (10)	54 (11)	28 (11)	0.858
Parenteral corticosteroid (%)	211 (8)	157 (8)	36 (7)	18 (7)	0.777
RA therapy					
MTX monotherapy	422 (16)	302 (16)	77 (16)	43 (18)	0.731
MTX combination	953 (36)	721 (37)	148 (30)	84 (34)	**0.008**
Other DMARDs	352 (13)	253 (13)	70 (14)	29 (12)	0.671
Biologics	265 (10)	193 (10)	50 (10)	22 (9)	0.873
None of the above	691 (26)	471 (24)	152 (30)	68 (28)	**0.013**

Remission: DAS28≤2.6, CDAI≤2.8, SDAI≤3.3; results are in mean (SD) if not specified otherwise.
Statistically significant values are indicated in bold.
ANOVA, analysis of variance; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAS28, Disease Activity Score based on 28 joint count; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; MD, medical doctor; MTX, methotrexate; SDAI, Simplified Disease Activity Index.

In multivariate linear regression analysis (table 4), low income, current smoking, comorbid fibromyalgia, OA and baseline use of non-methotrexate non-biologic DMARD were significant predictors for difference in onset towards longer patient-reported symptom duration. No variables remained significant predictors for discordance towards longer physician-reported symptom duration in multivariate analysis.

When we repeated the analyses excluding patients with a patient-reported symptom duration of 5 years, the same variables had significant differences between groups except there was no significant difference in baseline CRP or parenteral steroids. There was no significant difference in 12-month outcomes of patient global assessment, HAQ or SDAI remission. Patients reporting longer symptom duration had higher baseline DAS28 remission rates, and smaller changes in DAS28 from 0 to 12 months compared with the agreement group, but no difference in DAS28 at 12 months. Univariate regression analysis identified non-Caucasian ethnicity, baseline ESR, fibromyalgia and absence of baseline oral corticosteroid use as predictors of discordance towards longer patient-reported symptom ($p<0.1$). In multivariate models, non-Caucasian ethnicity, fibromyalgia and absence of baseline oral corticosteroids were significant predictors of difference in duration towards longer patient-reported symptoms ($p<0.05$). With a 5-year patient-reported symptom duration cut-off, no additional patients were excluded

Table 3 Univariate analysis for predictors of discordance in onset comparing concordant onset with longer patient-reported and physician-reported symptom durations, respectively (days; negative towards longer patient-reported duration; bolded p<0.05)

Variable	Longer patient-reported symptom		Longer MD-reported symptom	
	Coefficient	95% CI	Coefficient	95% CI
Age	0.731	−0.741 to 2.203	−0.076	−0.163 to 0.011
Female	−5.215	−54.104 to 43.674	1.914	−0.954 to 4.782
Caucasian	**66.903**	9.710 to 124.09	0.215	−3.154 to 3.584
Education>high school	7.672	−36.236 to 51.580	0.696	−1.978 to 3.371
Income >US$50 000	**81.758**	15.658 to 147.858	0.480	−3.190 to 4.149
Smoking				
Never	10.839	−34.052 to 55.729	0.890	−1.744 to 3.523
Past smoker	28.732	−17.007 to 74.470	−0.030	−2.708 to 2.687
Current smoker	**−65.606**	−124.150 to 7.062	−1.464	−4.899 to 1.971
# of comorbidities	0.234	−11.370 to 11.839	0.149	−0.533 to 0.831
Fibromyalgia	**−328.138**	−481.394 to 174.882	−0.865	−10.586 to 8.856
Osteoarthritis	**−107.260**	−176.206 to 38.313	−0.099	−4.172 to 3.975
RF positive	−5.892	−54.126 to 42.342	**4.231**	1.448 to 7.013
ACPA positive	3.959	−47.743 to 55.661	**2.503**	−0.393 to 5.398
ACPA titre	−0.168	−0.365 to 0.029	0.005	−0.006 to 0.015
Erosions	−32.970	−89.189 to 23.248	1.047	−2.232 to 4.326
DAS28	5.372	−10.357 to 21.101	0.066	−0.842 to 0.974
Swollen joint count	1.654	−2.026 to 5.334	−0.067	−0.283 to 0.150
Tender joint count	1.458	−1.903 to 4.819	−0.053	−0.251 to 0.145
HAQ	1.666	−29.965 to 33.296	0.954	−0.904 to 2.812
ESR	0.937	−0.139 to 2.013	−0.006	−0.066 to 0.054
CRP	0.406	−0.821 to 1.633	0.028	−0.043 to 0.099
MD global score	−3.770	−12.718 to 5.178	**0.538**	0.019 to 1.058
Patient global score	−6.316	−13.947 to 1.315	0.232	−0.214 to 0.678
CDAI	0.264	−1.333 to 1.862	0	−0.093 to 0.093
SDAI	0.552	−0.984 to 2.088	0.005	−0.087 to 0.097
Oral steroid	**70.722**	22.155 to 119.288	−1.833	−4.658 to 0.992
Parenteral steroid	45.731	−3.816 to 95.278	−0.980	−3.881 to 1.922
Initial RA treatment				
MTX monotherapy	−0.346	−50.228 to 49.536	−1.529	−4.472 to 1.413
MTX combination	**57.614**	12.283 to 102.944	−0.165	−2.806 to 2.477
Other DMARDs	**−85.503**	−139.369 to 25.636	−0.853	−2.526 to 4.232
Biologic	66.117	−95.118 to 227.353	−3.026	−12.847 to 6.795
None of the above	−21.597	−87.697 to 44.503	2.440	−1.504 to 6.384

ACPA, anticitrullinated protein antibodies; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; DAS28, Disease Activity Score based on 28 joint count; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MD, medical doctor; MTX, methotrexate; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index.

from regression analysis for difference towards longer physician-reported symptoms.

DISCUSSION

In this study, a quarter of patients with RA had differing patient-reported versus physician-reported onset of 30 days or more. Of clinical importance, 12-month outcomes (SDAI remission, HAQ and patient global assessment of disease activity) differed between the onset groups. Patients who reported *earlier* symptoms compared with the rheumatologists had less remission and higher disease activity. They were younger with lower baseline DAS28

Table 4 Multivariate linear regression for predictors of longer patient-reported symptom duration (days; negative towards longer patient-reported duration)

Variable	Coefficient	95% CI
Female	29.331	−46.525 to 105.189
Age	1.426	−0.986 to 3.838
Fibromyalgia	−413.551	−627.546 to 199.555
OA	−149.903	−255.278 to 44.529
Current smoker	−99.284	−186.105 to 12.462
Income >US$50 000	73.999	6.800 t 141.198
Baseline non-MTX, non-biologic DMARD use	−90.145	−173.756 to 6.534

Ethnicity, baseline MTX combination therapy, oral corticosteroid use were not significant in final MV model.
DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; OA, osteoarthritis.

than the agreement group. Initially and at 12 months, they had lower rates of combination DMARDs, less corticosteroid usage and higher rates of no DMARD treatment started at first visit compared with the agreement group. These patients likely had pain from MSK conditions other than RA contributing to their disease activity scores. Whereas, patients who identified symptom onset *after* physicians were more likely to be rheumatoid factor positive, had higher baseline ACPA titres and higher initial physician global assessments than the agreement group, although not significant in multivariate analysis. Antibody-positive RA may present as smouldering or insidious disease that is challenging for patients to recognise[11] and is associated longer time to DMARD initiation[3 12–16]; these patients can present later (beyond the timing of the 'window of opportunity'). As a marker of poor prognosis, seropositive RA predicts higher disease activity, erosive disease, and functional disability.[17–25]

A review of RA clinical trials that included disease duration showed studies use variable definitions ranging from onset of symptoms (symptoms rarely defined), time of first reported joint swelling, fulfilment of classification criteria, time of diagnosis and sometimes omitted any clear definition.[9] Heterogeneity in definitions poses significant difficulties for ascertaining the 'window of opportunity'. EULAR proposed recommendations for prospective cohort studies to define the onset 'starting point' used for reported disease/symptom duration.[26] Previous publications described heterogeneous initial symptoms in patients with early rheumatoid arthritis, ranging from gradual, vague symptoms; transient, acute episodes (palindromic); migratory pain; to acute, severe and debilitating onset, fatigue, morning stiffness, impaired function and poor sleep.[27–32]

Nearly 10% of patients timed their symptom onset at least 30 days after physicians. Prior to diagnosis, many patients with EIA may not be able to distinguish different types of arthritis, and misattribute early symptoms.[15 28 33 34]

Lack of standardisation of how onset of symptoms and persistent synovitis timing were determined constitutes a limitation; while patient baseline surveys asked for 'date when first symptoms began', and physician baseline surveys asked for 'date of onset of symptoms', neither the patients nor rheumatologists were trained about how to answer these questions. Another limitation is that there could be concordance or discordance between the reported onset of RA and some patients would be within the 3 months optimal window for best outcomes with treatment and others far outside the window within any of the groups we defined. The 30-day difference in timing of onset between patients and their rheumatologist was chosen arbitrarily.

In multivariate analysis, OA, fibromyalgia, low annual income, active smoking and initial non-methotrexate, non-biologic DMARD use predicted discordance in reported onsets towards longer patient-reported symptom duration. OA can be associated with patients who reported RA onset prior to physicians or vice versa, but in the former group, the timing is longer. Comorbid OA and fibromyalgia as predictors of discordance reflect the difficulty in distinguishing between musculoskeletal symptoms of various aetiologies; concomitant OA or fibromyalgia predicts increased time from RA symptom onset to treatment.[35] Low socioeconomic status is associated with a longer time to rheumatologist consultation, delay in DMARD initiation and worse disease activity.[36–39]

Strengths of this study include a large number of EIA participants, multicentre design and real-world observational data and less recall bias as patients required new-onset fixed synovitis to enrol and completed questionnaires at their initial visit. Patients with high pain ratings seemed to be less accurate in their recall of initial symptom timing.[40]

Some patients enrolled in the cohort already on therapy (eg, if enrolled after their initial rheumatology visit) so they could present with lower disease activity. Since CATCH inclusion criteria limited onset of physician-reported persistent fixed synovitis to less than a year, there could be an even greater difference in onset timings between physician and patient report in a clinic setting or if longer symptom duration were examined.

CONCLUSION

Compared with their rheumatologist, a quarter of patients reported discordant timing of RA onset (30 days or more). Patients who had shorter duration compared with the physicians' report were more likely to be seropositive, so they may be serologically and clinically different. Differences in patient-reported versus physician-reported symptom onset dates could have implications for the likelihood of achieving treat-to-target outcomes, as evidenced by 12-month outcomes of lower remission among patients who reported longer symptom duration compared with the agreement group. However, the comorbid conditions of OA and fibromyalgia associated

with longer patient-reported disease duration likely influenced disease activity scores that are not related to inflammation from RA. Adopting standardised definitions of onset of early rheumatoid arthritis to enable cross-study comparisons is encouraged.

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