Dating the "Window of Therapeutic Opportunity" in Early Rheumatoid Arthritis: Accuracy of Patient Recall of Arthritis Symptom Onset

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ABSTRACT. ***Objective***. A "window of therapeutic opportunity" has been hypothesized to be present in early rheumatoid arthritis (RA). To determine the date of this window, we must know the symptom-onset date of the RA. Patients participating in an observational study of early aggressive rheumatoid factor (RF) positive RA were evaluated to assess the accuracy of their recall of symptom-onset date by comparing the onset date they reported at the first visit with that reported on subsequent 6-monthly questionnaires.

Methods. One hundred eighty-six patients with early RA (at entry: median disease duration 5.8 mo, mean RF 413.8 ± 630.7 IU/ml, 20.6 ± 10.9 swollen and 23.7 ± 13.4 tender joints) completed a self-reported mailed questionnaire every 6 months for up to 5 years. As a part of each questionnaire, patients were asked to recall their RA symptom-onset date. These dates were then compared to the dates reported on the initial questionnaire.

Results. Thirteen months after symptom onset (i.e., about 6 mo after study entry) 61% of patients recalled the symptom-onset date (within 1 mo) that they had reported at baseline; the proportion decreased to 39% at 31 months and 25% after 70 months. During this period, the proportion overestimating RA duration remained about 20%, but the proportion underestimating it increased from 23% at 13 months to 39% at 31 months, and to 50% after 56 months. Patients with longer disease duration, less disease activity, and higher pain levels tended to be less accurate.

Conclusion. Accuracy of recall of RA symptom-onset date by patients tends to decline over a period of 5 years. This should be taken into consideration when enrolling patients, when interpreting the findings of early RA clinical trials, and when attempting to ascertain the presence of a window of therapeutic opportunity. (J Rheumatol 2004;31:1686–92)

Key Indexing Terms:
PATIENT RECALL
SYMPTOM ONSET
EARLY RHEUMATOID ARTHRITIS
WINDOW OF THERAPEUTIC OPPORTUNITY

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder of unknown etiology that primarily involves the joints. It may be remitting, but if uncontrolled, may lead to deformity and destruction of joints due to erosion of cartilage and bone. This symmetrical disease often progresses from peripheral to more proximal joints and, in many patients, results in significant functional disability.

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Supported by NIH grant P60AR36834; Oregon Chapter Arthritis Foundation; Charlotte Mundt Trust; and Centocor Health Outcomes in Rheumatic Diseases Fellowship (D. Khanna).

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Submitted December 17, 2003; revision accepted June 9, 2004.

The rapidity of disease progression necessitates immediate therapeutic intervention[1]. In early RA, the presence of a "window of therapeutic opportunity" has been hypothesized[2,3]. This conceptual window occurs while early arthritis is less entrenched, has a smaller load of "disease cells," and is more responsive to treatment. According to this hypothesis, aggressive treatment during this phase is more likely to succeed than if the same treatment is applied later in the course of disease[2]. The inclusion criteria for early RA studies usually require disease duration of 1–3 years at entry into the study[4-6]. However, the duration of this window and its time relationship to the onset of RA symptoms is not known; some studies suggest that a delay of only 4 months in the initiation of certain treatments may substantially decrease the responses of early RA patients[7]. If this window is of limited duration and is related to pathophysiologic events occurring shortly after onset of RA, then it is important to be able to date the symptom-onset of RA patients. A delay of a few months from onset of symptoms to institution of therapy has been shown to decrease the ability to induce remission in early RA[7]. Early,

rather than late, institution of therapy with disease modifying antirheumatic drugs (DMARD) has also been suggested to be more effective in prevention of joint damage and maintenance of clinical benefit[6-8].

Establishing the date of onset of RA has not been a high priority in the design of RA clinical trials. "Early" RA has been defined as within one, 2, 3, or even 5 years of a variably defined onset timepoint. Sometimes duration of RA is determined from the date of diagnosis, which varies depending on the assertiveness of the patient and the skills or experience of the first attending clinicians. Sometimes the patient or a family member is asked when the RA started, but early symptoms of RA may wax and wane or be attributed to other events. It is also possible that important events in the initiation of RA occur before any noticeable symptoms. How can one initiate treatment within a discrete, limited window of therapeutic opportunity if we can't date the onset of the disease?

Our aim was to compare self-reported symptom-onset dates indicated in 6-monthly questionnaires over a period of 5 years with the onset date reported at the first visit of patients with positive rheumatoid factor (RF) and active RA, in an observational study of early RA with the initial median reported disease duration of 5.8 months. If we consider the date of symptom onset reported at the initial visit to be the gold standard, how accurately might patients recall the date of onset if they were seen one or 2 or more years later?

MATERIALS AND METHODS

Patients included in this study are a subset of a group of RA patients participating in a longterm observational study involving the Western Consortium of Practicing Rheumatologists (CPR), which is a regional consortium of rheumatology practices in the western United States and Mexico. The consortium physicians participating in this sub-study were mainly from community and university practices in California, Idaho, New Mexico, Oregon, Utah, Colorado, Washington, Wyoming, and Guadalajara, Mexico.

Since 1993, 322 patients have been enrolled into the study on a rolling basis. Inclusion criteria for the CPR cohort included a diagnosis of early RA (≤ 12 months since symptom onset), no previous DMARD treatment, RF seropositive (RF titer ≥ 1:80 or ≥ 40 IU), and ≥ 6 swollen joints and ≥ 9 tender joints[9-14]. The consortium rheumatologists assessed patient disease status at study entry (baseline), 6 months, and one year, and yearly thereafter. Using standard methods, detailed physician assessment included all core set outcome measures required to calculate the disease activity score (DAS), including complete tender and swollen joint counts and acute phase reactant measures, as well as 0–100 mm visual analog scales (VAS) for global and pain assessments. The DAS was calculated according to the published algorithm using the Ritchie index, swollen joint count of 44 joints, and Westergren erythrocyte sedimentation rate (ESR) in mm/h[15,16]. In addition, study visits included radiographs of the hands, wrists and forefeet, HLA susceptibility epitope genotyping, and assays for RF. At each scheduled physician visit, blood specimens were collected for C-reactive protein (CRP); ESR was determined, when clinically indicated, in the rheumatologist's office or local laboratory[10].

Patients were asked to complete a detailed self-report mailed questionnaire at study entry and every 6 months thereafter for the duration of the study. Included were questions about changes in demographics, health, medication and pain, as well as global VAS, the Health Assessment Questionnaire-Disability Index (HAQ-DI), and the Center for Epidemiological Studies-Depression scale (CES-D). Patients were also asked to recall their symptom-onset date — the date of first appearance of joint symptoms — on each 6-monthly questionnaire. If the month of onset was reported but the day of the month was not, by convention, onset was attributed to the midpoint, i.e., the 15th, of the month. Similarly, if only the year of symptom onset was stated, the date of onset was assigned to be July 1 of the given year. Patients were given the option to answer "same" to all or any of the questions if the answers were the same as those provided in the previous questionnaire. However, responses of "same" and corresponding patient visits were not included in this analysis. To evaluate the accuracy of recall at each time period, symptom-onset dates reported by patients were compared to date reported at baseline within one month of accuracy. The date of symptom onset reported on the baseline questionnaire was considered to be the correct date, or gold standard date, as it was closest to symptom onset. The same date (± one month) was used as the standard for symptom-onset date comparison. At each time period, patients were divided into 2 groups: (1) all patients (both those who answered "same as before" on the questionnaire and those who gave a specific symptom-onset date), and (2) patients who reported a specific date as their onset date. Patients reporting specific dates at baseline and at 6 months were included in the analysis, but were excluded for other time periods if "same" was reported in subsequent visits. For each observation point, data were analyzed only for the patients who had paired data (i.e., baseline with that observation point). Radiographs, laboratory values, and DAS were available at baseline, 6 months, and one year, and yearly thereafter from the physician assessments, whereas pain VAS, HAQ-DI, and demographics were recorded at baseline and with every 6-monthly questionnaire.

Tests of statistical significance were performed using Student's t test and chi-square tests for differences between the analyzed and excluded populations. Because patients may have multiple encounters over the duration of the study, their visits may be correlated. This was accounted for using generalized estimating equations (GEE) to model correlated response data for the patients using the logit link for binary response and by specifying an unstructured within-patient correlation structure, leading to what are essentially logistic regression models for correlated data[17]. A value of $p < 0.05$ was considered to be statistically significant. We used statistical software packages SAS System Release 8.2 (SAS Institute Inc., Cary, NC, USA) and Stata Statistical Software: Release 7.0 (Stata Corporation, College Station, TX, USA).

RESULTS

Data were analyzed for the 186 patients who had reported symptom-onset dates at baseline and at least one other study visit. These 186 patients were mainly Caucasian (75.1%) and female (75.3%) with a mean ± standard deviation (SD) age of 51.0 ± 13.1 years and 12.8 ± 3.0 years of education. The mean disease duration was 7.5 ± 7.7 months (median 5.8), but for 21 patients disease duration was > 12 months at entry (21.7 ± 15.4 mo). At baseline, patients had mean tender joint counts (0–69) of 23.7 ± 13.4, swollen joint counts (0–66) 20.6 ± 10.9, CRP of 2.7 ± 3.5 mg/dl, ESR of 41.7 ± 23.5 mm/h, RF of 413.8 ± 630.7 IU/ml, and DAS of 4.8 ± 1.2. The mean HAQ-DI (0–3.0) was 1.23 ± 0.71; the global and pain VAS were 43.7 ± 24.1 and 52.5 ± 24.5, respectively. Radiograph erosion score was 2.04 ± 3.65 at baseline, with 27.2% of patients having erosion score ≥ 2. Patients were dichotomized by erosion score (< 2 vs ≥ 2) to indicate presence of erosive damage. Mean CES-D at baseline was 15.8 ± 11.6.

Of the 186 analyzable patients with 1664 total observations, 577 patient observations with "same" reported for symptom-onset date and 201 visits with no patient questionnaire completed were excluded; 886 observations were

reported with specific dates. The analysis included 700 paired observations with specific dates reported at baseline and another timepoint.

Among the 322 CPR patients at baseline, the 186 analyzed patients and the 136 excluded patients had statistically different values for disease duration (7.45 ± 7.71 vs 10.16 ± 12.57 mo), pain VAS scores (52.5 ± 24.5 vs 45.6 ± 25.1), DAS (4.83 ± 1.21 vs 4.42 ± 1.20), number of swollen joints (20.6 ± 10.9 vs 17.7 ± 11.0), and RF (413.8 ± 630.7 vs 291.6 ± 362.3 IU/ml). All values except disease duration were higher for analyzed patients at $p < 0.05$. There were no other statistically significant differences.

Longitudinal difference in symptom-onset reporting. As time since date of onset of initial RA symptoms increased, the accuracy of recall decreased. Thirteen months after onset, about 61% recalled the onset date they had provided on the baseline questionnaire. This decreased to 39% at 31 months and to 25% after 70 months. More patients underestimated their disease duration over time (Figure 1, Table 1). For instance, 19 months after symptom onset, or about a year after entry into the study, 30% of patients underestimated, 21% overestimated, and 49% recalled their correct date of symptom onset. The proportion of patients overestimating their RA duration remained about 20% over time, but the proportion underestimating their disease duration increased from 23% at 13 months to 50% after 56 months (Table 1).

In examining all available data for the 186 patients, 64 (34%) were consistently correct within one month of their baseline reported symptom onset dates, whereas 24 (13%) always underestimated and 19 (10%) were always overestimated. (The remaining 43% of patients erred in recall of their onset dates in a random pattern.) Outliers markedly influenced the magnitudes of error for over- and underestimation, as noted in Table 1. Excluding the 10% of values that deviated most from the correct values, the overestimation of RA duration ranged from 8.0 to 57.8 months and underestimation ranged from 4.8 to 13.1 months. Most underestimates were within 6 months of the correct duration, but after 3 years, more than 25% were wrong by more than 12 months.

Factors influencing patient recall. Based on published literature[7,18-20], patient characteristics deemed important in recalling symptom-onset dates included patient depression score by CES-D, pain VAS, disease duration, and gender. To examine this, we also included patient age, years of education, and DAS in our analysis, considering these factors potentially important in correctly recalling symptom-onset dates.

In separate univariate analyses, duration, DAS, education, and pain were statistically significantly ($p < 0.05$) associated with underestimates of duration (short duration). Only patient gender, duration, and DAS significantly ($p < 0.05$) predicted overestimates of RA duration (long duration) in similar analyses. All 7 variables then were entered into GEE logistic regression models for either short duration or long duration; patients reporting the same dates as the baseline-reported dates ("correct dates") made up the reference group.

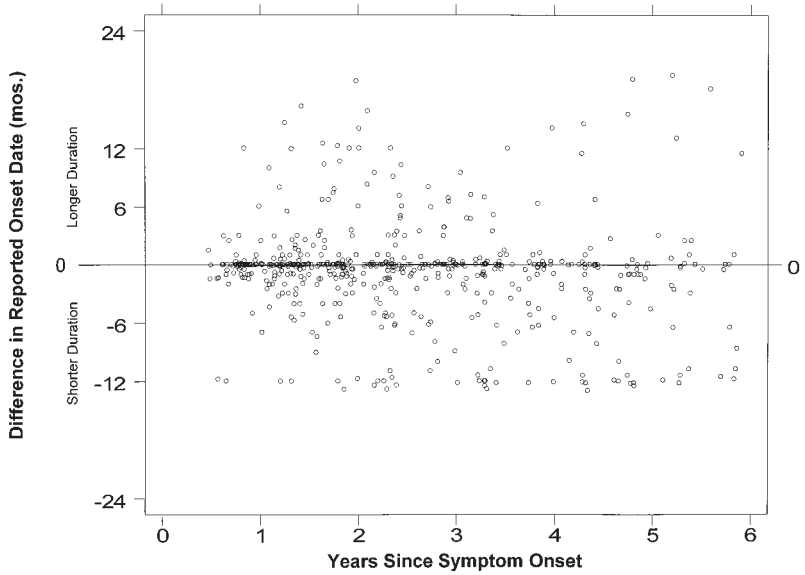

Figure 1. Accuracy of patient recall of the date of first symptoms of RA. Each point represents a patient's estimate of the number of years since symptom onset. The time of onset reported when the patient entered the study (within 12 mo of symptom onset) is accepted as correct and placed on the zero line. If a subsequent 6-monthly questionnaire reports the same date of symptom onset, it is entered on the zero line at that time after onset. If the symptom-onset date reported on the questionnaire is earlier than the date reported at entry, a corresponding point is placed above the zero line (longer duration); if it is later, it is placed below the zero line (shorter duration). A period of 6 years since symptom onset is noted. To simplify the graph, 5% of patient points from shorter duration and 5% from longer duration that were outliers have been excluded.

Table 1. Longitudinal differences in date of symptom onset reported by patients with paired data at baseline and at another visit. On each 6-month questionnaire, early RA subjects are asked the date of onset of RA symptoms. Values reflect comparison to baseline reported onset date. Dates are considered to be "correct" if they fall within 1 month of the baseline reported date. The table is divided into 3 groups: patients reporting the identical (± 1 mo) onset date as that reported at the baseline visit, patients overestimating (longer duration), and patients underestimating (shorter duration) the initially reported date of onset when responding 13 to 70 months later.

		Months from Onset*									
		13	19	26	31	38	45	50	56	63	70
	Average duration*, mo (SD)	12.67 (6.74)	19.50 (7.56)	25.76 (7.78)	31.27 (6.62)	38.18 (8.46)	44.91 (9.99)	50.33 (9.23)	56.38 (9.55)	62.65 (10.33)	69.95 (11.06)
	No. with paired data, N	139	118	96	82	62	59	42	42	32	28
Correct date within 1 mo	No. with no difference (% of N)	85 (61.2)	58 (49.2)	46 (47.9)	32 (39.0)	31 (50.0)	23 (39.0)	15 (35.7)	15 (35.7)	11 (34.4)	7 (25.0)
Longer duration	No. overestimating (% of N)	22 (15.8)	25 (21.2)	20 (20.8)	18 (22.0)	12 (19.4)	9 (15.3)	9 (21.4)	6 (14.3)	4 (12.5)	5 (17.9)
	Average mo overestimated (SD)	38.5 (98.3)	15.5 (25.2)	43.8 (125.0)	16.2 (24.4)	10.4 (9.7)	22.1 (23.8)	68.0 (112.7)	99.9 (138.3)	10.3 (9.6)	21.9 (16.7)
	Outliers excluded†: average mo overestimated (SD)	13.21 (13.20)	8.01 (6.49)	12.20 (12.52)	9.49 (9.44)	8.00 (5.29)	16.72 (18.73)	33.07 (44.26)	57.84 (103.39)	10.3 (9.6)	15.68 (10.66)
Shorter duration	No. underestimating (% of N)	32 (23.0)	35 (29.7)	30 (31.3)	32 (39.0)	19 (30.6)	27 (45.8)	18 (42.9)	21 (50.0)	17 (53.1)	16 (57.1)
	Average mo underestimated (SD)	11.7 (24.5)	17.1 (40.3)	9.6 (14.4)	9.77 (14.0)	12.6 (17.9)	13.0 (14.8)	27.3 (63.0)	23.2 (47.4)	15.4 (19.4)	18.7 (18.9)
	Outliers excluded†: average mo underestimated (SD)	4.84 (3.82)	6.80 (4.89)	6.30 (4.79)	6.57 (4.17)	7.91 (6.04)	8.87 (7.37)	10.78 (8.01)	11.33 (10.39)	9.49 (6.90)	13.08 (7.94)
	Difference ≤ 3 mo: number (% of no. underestimating)	13 (40.6)	11 (31.4)	11 (36.7)	9 (28.1)	6 (31.6)	7 (25.9)	4 (22.2)	4 (19.0)	4 (23.5)	3 (18.8)
	Difference ≤ 6 mo: number (% of no. underestimating)	20 (62.5)	17 (48.6)	16 (53.3)	15 (46.9)	8 (42.1)	12 (44.4)	6 (33.3)	6 (28.6)	6 (32.3)	3 (18.8)
	Difference ≤ 12 mo: number (% of no. underestimating)	28 (87.5)	26 (74.3)	23 (76.7)	24 (75.0)	12 (63.2)	16 (59.3)	8 (44.4)	11 (52.4)	10 (58.8)	7 (43.8)
	Difference ≤ 18 mo: number (% of no. underestimating)	29 (90.6)	30 (85.7)	28 (93.3)	30 (93.8)	16 (84.2)	21 (77.8)	13 (72.2)	17 (81.0)	14 (82.4)	11 (68.8)

* Onset is defined as the date RA symptoms started as reported by the patients at their baseline visit. The average (SD) baseline duration for the 186 patients was 7.45 (7.71) months (median 5.8). † 10% of the outlying points were excluded at each timepoint.

The GEE method for correlated data was used to model the 7 patient predictors of recall accuracy for symptom-onset dates: age at time of encounter, CES-D, DAS, disease duration from symptom onset, number of education years, gender, and pain VAS scores. Separate models were run to predict (1) short duration (underestimation) versus "correct date" and (2) long duration (overestimation) vs "correct date," with patients who correctly recalled their symptom-onset dates as the reference group. The model predicting short duration was statistically significant ($p < 0.0001$), whereas the model predicting long duration was marginally significant at $p = 0.0538$.

In addition, the GEE method requires a specified within-patient correlation structure. Because no apparent trend was observed between encounters within patients, the unstructured correlation structure was selected. This structure imposes few constraints on the model and allows correlations to vary between visits. When it is compared with the autoregressive structure (assumes high correlation at closer visits and low correlation elsewhere), the exchangeable structure (assumes equal correlation between all visits), and the independent correlation structure (assumes no correlation between visits), the selected unstructured correlation structure gave similar results in predicting short and long durations.

Short duration (underestimation). According to the GEE method modeling short duration, patients who underestimated their date of onset tended to have significantly longer disease duration [$p < 0.0001$; odds ratio (OR) = 1.059; 95% confidence interval (CI) 1.04–1.08] and lower disease activity by DAS ($p = 0.036$; OR 0.757; 95% CI 0.58–0.98) than those who correctly recalled their symptom-onset dates. This means that patients who had lower DAS scores were more likely to underestimate their disease duration than those who recalled

their correct date of symptom onset within a month, i.e., there was more disease activity in patients who correctly recalled the symptom-onset date they had given at baseline. An odds ratio of one means that the variable has no effect on the accuracy of recall. No other variables (female, CES-D, pain VAS, years of education, or age) were statistically significant ($p > 0.12$).

Long duration (overestimation). According to our model for long duration (overestimation) versus correct date, only pain VAS was statistically significant ($p = 0.012$). The odds ratio of 1.02 (95% CI 1.00–1.04) for pain VAS means that patients with higher pain scores tended to overestimate their disease duration, all else being held constant. However, no other variable was statistically significant ($p > 0.14$), and the model itself was only marginally significant ($p = 0.0538$).

DISCUSSION

Early diagnosis and early appropriate treatment of rheumatoid arthritis are thought to be key to controlling progress of disease and preventing further joint and tissue damage. Consequently, patients are enrolled in early RA clinical studies within the first 1–3 years of their disease and are treated within the first few months of symptom onset[1,4-6].

The concept of window of therapeutic opportunity exists from the notion that early institution of therapy for RA is more effective in preventing joint damage, decreasing functional disability, and inducing clinical remission[2]. As an example in support of this concept, 40% of patients with early RA (symptoms < 6 mo) have erosive disease at presentation[21], and remission is rare (< 5%)[22]. Institution of treatment with DMARD within the first year of RA symptom onset leads to a good clinical response in 53% of patients, compared to 43% with 1–2 years' duration and 38% with 5–10 years' duration[23]. Early therapy also leads to retardation of radiographic progression[24] and decreased functional disability[25]. Delay in institution of DMARD therapy in early RA (symptoms < 2 years) by as little as 8 months leads to a less favorable longterm clinical and radiological outcome[8,26]. In DMARD-naive patients with early RA (median disease duration 6 mo), multiple DMARD therapy is more successful in inducing remission than a single DMARD strategy (37% vs 18% remission at 2 years' RA duration)[24]. More important, delay of as little as 4 months in instituting either therapy was the only significant influence on the probability of disease remission at 2 years. If therapy with a single agent was started within 4 months of symptom onset, patients had a higher disease remission rate (35%) compared to patients who had the same single-agent therapy started more than 4 months after symptom onset (remission rate 11%)[7]. Thus, the literature does support the presence of a window of opportunity, where early institution of DMARD therapy can lead to favorable outcomes in RA.

Patients are qualified for early RA clinical trials based on their recall of their symptom onset. It is known from the literature that patients frequently fail to recall and therefore underreport the incidence of previous symptoms and events[18]. None of 3 early RA trials[4-6] mentioned how the disease duration was determined and confirmed.

Our study was undertaken to evaluate this question in a cohort of patients with early RA using the consortium data. RA patients were more likely to underestimate their disease duration than to overestimate it, that is, more patients reported shorter disease duration. This phenomenon is known as "forward telescoping," in which remote events tend to be displaced forward in time and remembered as occurring more recently than they actually did[18,27]. This leads to over-reporting of the frequency of events within a time period[18,20]. In one event-dating study, an event that actually occurred within the previous 4 months was mis-dated by as much as 3 months[20,28].

Several factors could affect the accuracy of recall. Patients' current depression and physical pain may enhance the recollection of past symptoms and events that are not recalled under normal circumstances[18]. Also, time elapsed may be related to accuracy of recall. The longer ago an event occurred, the more difficult it is to remember the time when the event occurred[20].

Our findings support the hypothesis that the accuracy of recall of past symptoms is influenced by present disease activity of RA, as measured by the DAS. For example, patients with a higher disease activity tended to be more precise in recalling their symptom-onset date. Patients with lower DAS (less severe RA) tended to underestimate their disease duration. Also, as more time passed from the initial symptom(s) onset, fewer patients were able to recall their previously reported symptom-onset date. In contrast to reports in the literature[18], patients with higher pain VAS scores were slightly more likely to overestimate their RA duration. The pain VAS scores were only marginally significant; the lower 95% CI included 1.0.

In contrast to other event dating studies[18,19], our results did not show an influence of depression or gender on recalling onset date. This could be due to sample representation bias, as most of our patients had normal baseline CES-D scores (15.8 ± 11.6) and the majority of patients were female (75%).

Another difficulty in recalling exact symptom-onset date is that the majority of RA patients have a slow and insidious onset of joint symptoms that may occur over weeks or even months[27]. A slow (insidious) onset in RA patients makes it more difficult to recall exact onset date of symptoms. Patients occasionally combine multiple, separate incidents or episodes into a single one, a process referred to as "recomposition"[18]. Incidents with similar characteristics that recur repeatedly tend to be merged into a single, generic memory for the group as a whole[18]. In the case of RA patients, these similar incidents may be a gradual or additive development of joint problems. Recomposition of these isolated occurrences of joint symptoms could lead to reporting a date different from that of actual onset. According to Fleming, *et al*, onset is considered to be the first appearance of joint symptoms[27].

Moreover, in RA early diagnosis requires specialized knowledge and a complete examination of the joints. Many patients and some physicians may be unfamiliar with certain characteristics associated with RA, such as joint pain associated with morning stiffness.

In addition there are no definitive diagnostic tests. Basic laboratory tests, such as RF, lack adequate sensitivity and specificity, and in early stages of the disease (before the occurrence of any joint erosion) are often in the normal ranges. The early stages of RA may lack disease-specific features, as the characteristics of the disease develop over time. If one relies on these tests for diagnosis of the disease, early RA may not be recognized and the true onset date may not be recorded.

Because RA is not considered life-threatening, its recognition has not led to urgent care and therapy; moreover, hospitalization for early diagnosis and treatment is rare[29]. Even if the primary care provider makes a diagnosis in the early stages, symptomatic therapy may be tried, and referral to a rheumatologist may not be a priority.

The total delay between symptom onset and initiation of DMARD treatment includes delay in initial presentation to a physician, diagnosis lag time between presentation to a physician and disease diagnosis[30], and lag time between diagnosis and the start of appropriate treatment, reflecting delay in seeing a rheumatologist.

How can one obtain a RA onset date that is most reliable? Educating patients and physicians on the importance of early diagnosis and treatment increases the chances of disease improvement and remission. Medical students, fellow residents, and nonrheumatologist physicians should be educated to recognize the importance of early treatment[29]. In general, learning about rheumatic disease should be emphasized more in medical schools[29].

Validation of a window of therapeutic opportunity and determining its time constraints should change the general indifference toward dating onset of RA. If aware that opportunity for enduring major clinical benefit can be lost when effective treatment is delayed, primary care providers as well as rheumatologists and patients will be much more attentive to dating onset of disease, i.e., opening the "window."

Early recognition of RA is possible through specialized early arthritis clinics (EAC). Van der Horst-Bruinsma, *et al* compared patients presenting to EAC with routine patient care; for patients presenting to special EAC the delay between symptom onset and the first referral to the rheumatologist was reduced by at least 3 months[31].

Errors in recall of symptom-onset dates demonstrated in our study suggest that patient recall of medication use and drug dosage, diagnostic studies, hospitalizations, and history of other chronic illnesses may also be suspect. Much of this information should be available through the medical records of the patients' physicians. Other studies suggest fairly accurate recall for prior hospitalization, surgery, and self-report of chronic illness history. Mitchell, *et al* demonstrated the importance of questionnaire design in recall of drug use[32]. They suggested that poor recall of drug use during pregnancy may actually reflect the nature of questions asked. Symptom-onset date could be better defined in our questionnaire. For instance, we might categorize different types of onset as acute versus gradual and explain what is meant by onset date in each of these onset types.

Limitations of our study. We did not ask patients about their onset type; however, questions regarding RA onset type have since been added to the patient questionnaire. Another limitation is that we compared the 6-monthly questionnaire data with onset dates obtained from the patients' self-reported data at baseline. The date thus reported at study entry itself might not reflect the true symptom-onset date of RA. Also, in these instances it is only possible to draw conclusions about accuracy of recall for patients who reported a date at baseline. Data were analyzed only for patients who gave a specific onset date at entry and who then also reported an onset date at least once during the followup questionnaires, rather than for all of participating patients. One cannot extrapolate from these investigations to the overall accuracy of recall of symptom-onset date by RA patients, which could result in a report bias. Further, based on its enrollment criteria, our study patients may differ from patients in the general population.

Our results suggest that recall of the date of RA symptom onset by patients is often inaccurate. Patients tend to underestimate disease duration, even within the first year after symptom onset. At study entry, most of our patients had aggressive disease. Because they had a relatively short duration of RA symptoms and active disease, we anticipated better patient recall of symptom-onset date. Such recall bias may compromise results expected and reported in early RA trials, and will make it difficult to determine the precise time and duration of the window of therapeutic opportunity.

APPENDIX

The Western Consortium of Practicing Rheumatologists: Robert Shapiro, Maria W. Greenwald, H. Walter Emori, Fredrica E. Smith, Craig W. Wiesenhutter, Charles Boniske, Max Lundberg, Anne MacGuire, Jeffry Carlin, Robert Ettlinger, Michael H. Weisman, Elizabeth Tindall, Karen Kolba, George Krick, Melvin Britton, Rudy Greene, Ghislaine Bernard Medina, Raymond T. Mirise, Daniel E. Furst, Kenneth B. Wiesner, Robert F. Willkens, Kenneth Wilske, Karen Basin, Robert Gerber, Gerald Schoepflin, Marcia J. Sparling, George Young, Philip J. Mease, Ina Oppliger, Douglas Roberts, J. Javier Orozco Alcala, John Seaman, Martin Berry, Ken J. Bulpitt, Grant Cannon, Gregory Gardner, Allen Sawitzke, Andrew Lun Wong, Daniel O. Clegg, Timothy Spiegel, Wayne Jack Wallis, Mark Wener, and Robert Fox.

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