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FACTORS PREDICTING RESPONSE TO TREATMENT IN RHEUMATOID ARTHRITIS

The Importance of Disease Duration

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Objective. **To use individual patient data from rheumatoid arthritis (RA) clinical trials to identify factors that affect the response to treatment as defined by the American College of Rheumatology (ACR) criteria for improvement (the "ACR response").**

Methods. **Primary trial data from 14 diverse, randomized, controlled trials of second-line drugs or devices in RA were analyzed. The trials included 11 methotrexate (MTX) trials (5 placebo controlled and 6 comparative, of which 2 were unpublished), 1 combination trial of cyclosporine plus MTX, 1 induction trial of a combination treatment in early RA (the COBRA trial), and 1 placebo-controlled trial of a new device (Prosorba). Both patient factors and disease activity measures (primarily, items from the ACR core criteria set) were available.**

Results. **A total of 1,435 patients (549 in placebo-controlled trials, 886 in comparative trials) were studied. In both active treatment and placebo groups, disease duration had a strong effect on the likelihood of patient response (e.g., with any active treatment, the response rate was 53% for patients with ≤1 year of disease, 43% for 1–2 years' disease duration, 44% for 2–5 years, 38% for 5–10 years, and 35% for >10 years; $P = 0.001$). Decreasing response with greater disease duration was seen during treatment with most of the individual active drugs, as well as with placebo. Other factors decreasing the rate of response to treatment included any prior use of a disease-modifying antirheumatic drug (DMARD), higher disease functional class (according to the Steinbrocker criteria), low disease activity (according to patient's global assessment), and female sex. Each ACR core set variable exhibited a diminished response to treatment in patients with long-standing disease. The difference between active treatment and placebo response rates was not affected by disease duration nor by other factors associated with the ACR response.**

Conclusion. **RA patients with longer disease duration do not respond as well to treatment compared with patients with early disease, and female sex, prior DMARD use, disease functional class, and disease activity also have effects on the likelihood of patient response to treatment. This has implications for trial interpretation and for the clinical expectations of RA patients.**

It is unknown why some patients with rheumatoid arthritis (RA) respond to treatment better than others. It has been suggested that patients with more severe disease may be less likely to show a response, and that patients who have previously been treated unsuccessfully with second-line drugs also may have more recalcitrant disease (1). In addition, there are indications that the biologic process of RA changes early in the disease, so that patients may be less responsive to treatment over time (2–5). The interval in early disease during which response may more readily occur is not clearly defined, so that the relationship between disease duration and response to treatment is of considerable interest. It would also appear that patients with especially active disease are more likely to respond to treatment, particularly in a clinical trial context. Better response in these patients would represent regression to the mean.

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Table 1. Trials included in the study of factors affecting response to second-line drug treatment in rheumatoid arthritis*

Trial, first author (year of publication)	Ref. no.	Number of subjects in trial	% of subjects meeting ACR20 response	Treatments in trials	Number of subjects (% meeting ACR20 response) per treatment group
Placebo-controlled trials					
Weinblatt (1985)	10	35	34	MTX vs. placebo	MTX 17 (65); placebo 18 (6)
Furst (1989)	11	59	37	MTX vs. placebo	MTX 42 (40); placebo 17 (29)
Schmid	Unpublished	11	18	MTX vs. placebo	MTX 5 (20); placebo 6 (17)
Williams (1985)	12	191	20	MTX vs. placebo	MTX 94 (34); placebo 97 (6)
Wilke	Unpublished	19	5	MTX vs. placebo	MTX 11 (9); placebo 8 (0)
Tugwell (1995)†	19	143	27	MTX + CYCLO vs. MTX	MTX + CYCLO 70 (41); placebo 73 (12)
Felson (1998)	21	91	22	Prosorba vs. placebo	Prosorba 48 (33); placebo 43 (9)
Total no. of subjects		549			
Comparative trials					
Weinblatt (1990)	13	274	46	MTX vs. AUR	MTX 135 (65); AUR 139 (28)
Williams (1992)	14	318	43	MTX/AUR vs. MTX vs. AUR	MTX 110 (43); AUR 108 (34); MTX/AUR 100 (51)
Suarez-Almazor (1988)	15	38	40	MTX vs. Gold	MTX 20 (35); Gold 18 (44)
Morassut (1989)	16	33	42	MTX vs. Gold	MTX 18 (50); Gold 15 (33)
Hamdy (1987)	17	40	38	MTX vs. AZA	MTX 21 (38); AZA 19 (37)
Bell (1988)	18	28	43	MTX vs. AZA	MTX 15 (67); AZA 13 (15)
Boers (1997)	20	155	53	MTX/SSZ/Pred vs. SSZ	MTX/SSZ/Pred 76 (72); SSZ 79 (32)
Total no. of subjects		886			

* ACR20 = American College of Rheumatology 20% improvement criteria (6); MTX = methotrexate; CYCLO = cyclosporine; AUR = auranofin; Gold = sodium aurothiomalate; AZA = azathioprine; SSZ = sulfasalazine; Pred = prednisone.
† In this trial, all patients were being treated with methotrexate before the trial began, so it is included here as a placebo-controlled trial of cyclosporine.

An understanding of which types of patients with RA are most likely to respond to treatment has implications for the aggressiveness of treatment of individual patients. In addition, there may be implications for the design of clinical trials, in that the anticipated power of a trial may be a function of the particular mix of patients who participate in the trial. To address these questions, we have made use of patient data from a variety of clinical trials of second-line drugs and devices in RA that have been conducted since the early 1980s. We selected only trials in which patient response, as defined by the American College of Rheumatology (ACR) criteria for improvement (6) (referred to herein as the "ACR response"), could be determined, and in which individual patient and disease factors were available.

PATIENTS AND METHODS

We analyzed primary trial data from randomized, controlled trials of second-line drugs or devices in RA. Criteria for selection of the trials included treatment with second-line drugs and the availability of individual patient data on baseline and outcome variables, so that the response rate (according to the ACR 20% improvement criteria [6]) could be calculated. The ACR improvement criteria require that a patient improve by at least 20% in each of his or her tender joint count and swollen joint count during a clinical trial, and also improve by at least 20% in at least 3 of the other 5 core set measures (patient's assessments of pain and physical function, patient's and physician's global assessments, and an acute-phase reactant measure).

We evaluated whether each subject met the ACR criteria for improvement at the end of the trial by an intent-to-treat approach using the last observation carried forward. We did not otherwise make use of any intermediate assessments in assessing whether a patient satisfied the ACR response criteria. In the 3 most recent trials, the Health Assessment Questionnaire (HAQ) (7) disability score was the physical function measure used in the calculation of improvement, while in the earlier trials, grip strength was available as the physical function measure for this calculation. We have previously shown a moderate correlation between change in grip strength and change in self-reported functional status (6).

We used logistic regression to analyze the factors affecting the likelihood of patient response, with initial tests performed on each of the candidate factors separately. These factors fell into 2 groups: patient factors (age, sex, disease duration, Steinbrocker functional class [8], any prior use of second-line drugs, and any prednisone use during the trial) and disease activity factors (each of the ACR core set items evaluated at baseline). In all logistic regression analyses, we controlled for treatment, with an indicator variable for each non-placebo treatment. We did not include the trial, or "study," as an effect in these analyses because some active treatments were studied in only 1 trial. It was therefore not possible to control for both study and treatment. We retained, for subsequent multivariate analyses, any patient or disease

Table 2. Patient factors and disease activity measures across the 14 trials*

	Overall mean	Range of means	No. of trials missing
Patient factors			
Age, years	53	50–60	0
Female, %	69	55–91	0
Disease duration, years	7.8	0.5–17.7	0
Steinbrocker class III, %	20	12–47	4
Prior use of DMARDs, %	45	10–100	1
Prednisone use, %	31	3–82	1
Disease activity measures			
Pain assessment (0–10 scale)	5.3	4.3–7.6	0
Swollen joint count (of 66 joints)	22.5	14.8–30.3	0
Tender joint count (of 68 joints)	29.7	19.5–37.4	0
ESR, mm/hour	44	34–67	0
Grip strength, mm Hg	94	52–140	3
HAQ score (0–3 scale)	1.5	1.4–1.9	11
Physician's global assessment (0–10 scale)	5.6	4.9–7.5	3
Patient's global assessment (0–10 scale)	5.8	4.7–8.0	3

* DMARDs = disease-modifying antirheumatic drugs; ESR = erythrocyte sedimentation rate; HAQ = Health Assessment Questionnaire.

activity factor with a *P* value less than 0.15 in its statistical association with the ACR response.

Because of missing data on several items in some trials, we constructed 2 data sets for the multivariate analyses. These were an "all variable" data set, consisting of the trials in which all retained candidate variables were available, and an "all trial" data set, from which some of the retained variables were missing and therefore not analyzable. In the multivariate analyses, we assessed the simultaneous associations of candidate factors with response. Data on the strength of the association identified in the multivariate logistic regressions are expressed as an adjusted odds ratio (OR_{adj}) that represents the odds ratio per unit increase in a variable when other variables are also in the model.

For factors found to have an association with response to treatment, we looked for possible effects on the statistical power of trials. We used logistic regression to test the interaction of active treatment versus placebo with the factor to determine whether the difference in response between active treatment and placebo varied with factor level. In further logistic regressions, we also examined the association between the response (≥20% improve-

Table 3. Association of patient and disease activity factors with the likelihood of patient improvement*

	Univariate analyses		Multivariate models: "All variable" data set of 10 trials (n = 985)		Multivariate models: "All trial" data set of 14 trials (n = 1,404)	
	OR_{adj}	*P*	OR_{adj}	*P*	OR_{adj}	*P*
Patient factors						
Age (per year)	0.99	0.341				
Sex (F)	0.79	0.053	0.72	0.040	0.81	0.095
Disease duration (per year)	0.97	0.001	0.98	0.028	0.97	0.001
Steinbrocker functional class (per 1)	0.66	0.007	0.60	0.004		
Any prior DMARDs (yes)	0.59	0.001	0.62	0.008		
Any prednisone during trial (yes)	0.98	0.871				
Baseline disease activity measures						
ESR (per mm/hour)	1.00	0.512				
Pain assessment (0–10 scale) (per unit)	1.05	0.085	1.02	0.590	1.00	0.931
Tender joint count (0–68) (per unit)	1.00	0.813				
Swollen joint count (0–66) (per unit)	1.01	0.064	1.01	0.356	1.10	0.172
Grip strength (per mm Hg)	1.00	0.419				
HAQ (0–3 scale) (per unit)	0.77	0.145				
Patient's global assessment (0–10 scale) (per unit)	1.10	0.001	1.11	0.027	1.10	0.010
Physician's global assessment (0–10 scale) (per unit)	1.08	0.030	1.09	0.148		

* All analyses adjusted for treatment. OR_{adj} = adjusted odds ratio (see Table 2 for other definitions).

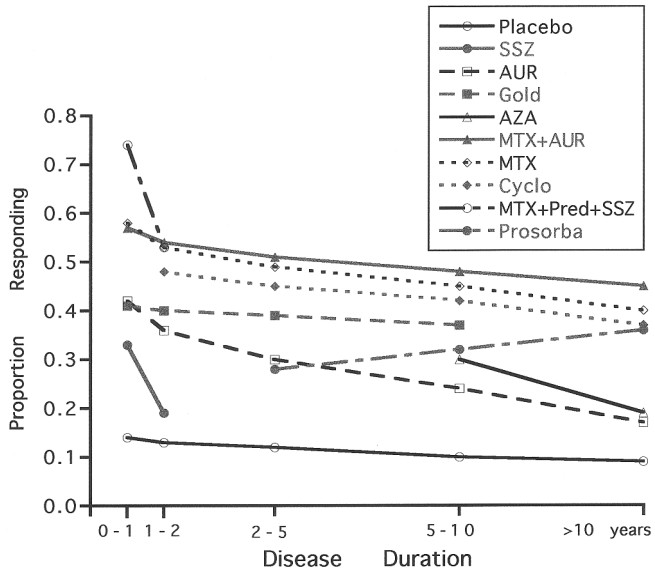

Figure 1. Proportion of patients in 14 trials having a response satisfying the American College of Rheumatology 20% improvement criteria (see ref. 6), within each combination of treatment and disease duration category. Treatments are placebo, sulfasalazine (SSZ), auranofin (AUR), sodium aurothiomalate (Gold), azathioprine (AZA), combination of methotrexate and auranofin (MTX+AUR), methotrexate (MTX), cyclosporine (Cyclo), combination of methotrexate, sulfasalazine, and step-down prednisolone (MTX+Pred+SSZ), and an immunoadsorption column, apheresis-based treatment containing *Staphylococcal* protein A (Prosorba). Disease duration categories are ≤1 year (0–1), >1 and ≤2 years (1–2), >2 and ≤5 years (2–5), >5 and ≤10 years (5–10), and >10 years.

ment) in individual ACR core set items and these same factors.

RESULTS

We analyzed data from 14 RA trials. These included 11 methotrexate (MTX) trials (5 placebo controlled and 6 comparative, of which 2 were unpublished) that were conducted in the 1980s and assembled into an archive (9–18 and unpublished observations from Schmid FR and from Wilke WS). Three additional trials from the 1990s were also studied: 1 combination trial of cyclosporine plus MTX (19), 1 induction trial of a combination treatment in early RA (referred to as the COBRA trial) (20), and 1 placebo-controlled trial of a new device (Prosorba) (21). Table 1 lists the 14 trials with their publication dates and treatments, as well as the sizes and ACR response rates for each treatment group. The treatments included MTX, auranofin (AUR), the combination of MTX and AUR, sodium aurothiomalate (injectable gold), azathioprine (AZA), cyclosporine, sulfasalazine (SSZ), the combination of MTX, SSZ, and prednisolone, and Prosorba.

We studied 1,435 patients (549 participating in the placebo-controlled trials, 886 in the comparative trials). Overall response rates were higher in the comparative trials (ranging from 38% to 53%) than in the placebo-controlled trials (5% to 37%).

Table 2 shows the mean values and range of means for the patient factors and disease activity measures in the 14 trials. In some respects, the trials were similar, in that each had a majority of female patients and the average age of the patients ranged from 50 years to 60 years. The trials varied considerably, however, in average disease duration, which ranged from 0.5 years in the COBRA trial (20) to 15.5 years in the Prosorba trial (21) to 17.7 years in 1 of the small trials of MTX versus placebo (Schmidt FR: unpublished observations). The trials also varied in the distribution of patients according to Steinbrocker functional class (12–47% of patients in class III per trial), the extent of prior use of disease-modifying antirheumatic drugs (DMARDs) (10–100% of patients per trial), and the baseline disease activity (for example, the average number of swollen joints ranged from 15 to 30 across the 14 trials).

The "all variable" data set did not include 4 comparative trials because 1 or more of the variables of prior DMARD use, physician's global assessment, or Steinbrocker functional class was either not assessed or not recorded in these 4 trials. The largest of these trials was the COBRA trial, in which only the Steinbrocker functional class was not available for our analyses.

As shown in Table 3, the univariate analyses identified 4 patient factors associated with a reduced likelihood of treatment response: female sex, longer disease duration, higher Steinbrocker functional class, and prior DMARD use. The univariate effects persisted in the multivariate analyses. In multivariate analyses using the "all variable" data set, the odds of response to treatment for women were 0.72 times those for men. Similarly, the odds of response were only 0.60 for patients in Steinbrocker functional class III versus those in functional class II, and prior DMARD use was associated with a similar reduction in the odds of response, to 0.62. The disease duration effect on odds of response was 0.74 when expressed per 15-year increase in disease duration (0.98 per extra year of disease duration). Despite the possibility of strong correlations between these patient factors, particularly between prior DMARD use and disease duration, each maintained an independent effect in the multivariate analysis.

Among the disease activity measures associated

Table 4. American College of Rheumatology (ACR) response rates for active treatment and placebo-treated patients within the strata of factors related to response

	Active treatment		Placebo treated		
	No.	ACR response, %	No.	ACR response, %	Active–placebo difference, %
Overall	1,178	43	262	10	33
By sex					
Male	371	46	72	15	31
Female	807	41	190	8	33
By baseline patient global assessment					
<5	222	39	42	5	34
≥5	943	44	212	11	33
By Steinbrocker functional class					
I or II	710	43	166	13	30
III	194	38	96	4	34
By disease duration					
≤1 year	312	52	10	20	32
>1, ≤2 years	148	43	9	22	21
>2, ≤5 years	245	44	36	14	30
>5, ≤10 years	213	39	72	7	32
>10 years	260	35	135	9	26

with response were the patient's assessment of pain and the swollen joint count, as well as the patient's and the physician's global assessments. Each of these factors increased the likelihood of response, while the opposite trend occurred for physical function as measured by the HAQ score. In the univariate analyses, the effect of the HAQ score appeared substantial, at 0.77 per unit on the 0–3 scale used for the HAQ. The test of significance had low power, however, with $P = 0.15$, because HAQ assessments were available in only 3 of the trials. In the multivariate analysis of the "all variable" data set, the patient's global assessment was the sole significant disease activity variable affecting the likelihood of response.

In the final multivariate analysis, summarized in Table 3, among the variables in the "all trial" data set, the results for the variables in common were similar to those for the variables in the "all variable" data set, except that the effect of sex was less strong (OR_{adj} 0.81 versus 0.72) and the disease duration effect was stronger (OR_{adj} 0.97 per year, which translates into 0.63 per 15 years, versus an OR_{adj} of 0.98 per year, corresponding to 0.74 per 15 years).

The strong effect of disease duration on response to treatment for most of the different treatments can be seen in Figure 1. Among the patients receiving active treatment, there was a response rate of 53% for those with a disease duration under 1 year, 43% for a disease duration between 1 year and 2 years, 44% for 2–5 years' disease duration, 38% for 5–10 years' disease duration, and 35% for patients with a disease duration exceeding 10 years. The pattern of response was similar for the different DMARD treatments, particularly for the treatments in the COBRA trial, in which all but 10% of participants had <1 year of disease. Because there were only 9 subjects treated with Prosorba who had a disease duration under 5 years, the response rate estimate of 22% (2 of 9 subjects) for that range was unstable, but the response was steady at 33% and 35%, respectively, in the longer ranges of disease duration.

The difference between active treatment and placebo response rates was not affected by disease duration or the other factors. Table 4 shows response rates for active treatment and placebo-treated patients in all of the trials by categories of disease duration, Steinbrocker functional class, sex, and patient global assessment. The differences in response were generally ~30% regardless of category, and did not vary significantly across the strata ($P > 0.05$ in each case). Too few placebo-treated subjects had not had prior DMARD use (n = 6) to evaluate the response rates for this factor.

We examined the response by disease duration for each of the core set components separately. For each core set measure, we found lower proportions of patients who improved by at least 20% with longer disease duration. The response in tender joint count and swollen

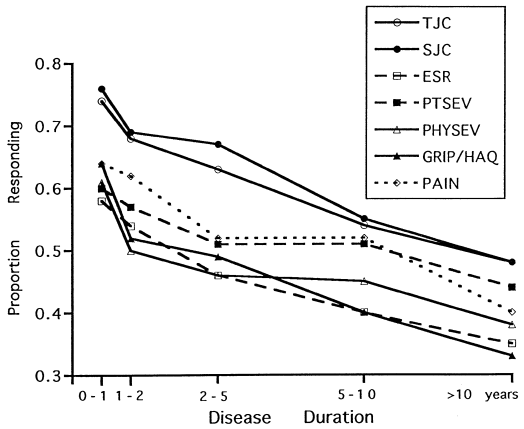

Figure 2. Proportion of patients in 14 trials improving by at least 20% in each of 7 American College of Rheumatology (ACR) core set items, within each disease duration category. ACR core set items are tender joint count (TJC), swollen joint count (SJC), erythrocyte sedimentation rate (ESR), patient assessment of disease severity (PTSEV), physician assessment of disease severity (PHYSEV), grip strength (in 11 trials) or Health Assessment Questionnaire score (in 3 trials) (GRIP/HAQ), and patient assessment of pain (PAIN). Disease duration categories are ≤1 year (0–1), >1 and ≤2 years (1–2), >2 and ≤5 years (2–5), >5 and ≤10 years (5–10), and >10 years.

joint count dropped off more steeply than did the response in other core set items (Figure 2), yet these 2 items, both of which must improve by at least 20% for the ACR improvement criteria to be satisfied, remained more likely to improve than did any of the other 5 items in each of the 5 intervals of disease duration. The drop-off in response with disease duration was fairly uniform across all components of the ACR core set.

DISCUSSION

The major findings of our analyses are that disease duration has a considerable impact on response to treatment, as do the Steinbrocker functional class and previous DMARD use. Understanding the magnitude of these effects and of the difference in response for male and female patients can be useful to both patients and physicians in anticipating the likelihood of response to treatment with any of these DMARDs. In these trials, we saw a net 5% greater response probability for male versus female patients and between Steinbrocker functional class II and functional class III patients, as well as a 10% greater response probability among patients who had not previously been treated with DMARDs.

Some effect of disease activity is to be expected in patients entering a clinical trial. We found a 5% difference in response for patients with high versus low baseline disease activity levels as measured using the patient global assessment. In part, this may represent regression to the mean, since the usual requirement of a certain level of disease activity for patients entering a clinical trial generally results in some improvement in disease activity during the trial, independent of any effects of medication. However, the effect of disease activity seen in these data was substantial, as large as the difference seen between male and female patients and between the 2 levels of disease severity.

A limitation of this study was the absence, from the trial data available to us, of information on rheumatoid factor, which may affect response to treatment (22,23). In addition, only 3 trials had HAQ data available as a measure of physical function, with the remainder of trials providing grip strength data. It is possible that we could have found stronger results for the independent effects of physical function on response to treatment if a more comprehensive measure had been available in a greater number of trials.

A lesser limitation is that 3 of the trials whose data were included did not have 1 of the ACR core set measures available, specifically, the physician's global assessment. This meant that it was slightly more difficult for the patients in these trials to achieve the ACR response compared with patients in other trials. To satisfy the response criteria, the patients in these trials were required to improve by at least 20% in 3 of 4 items rather than 3 of the 5 available to a patient in whom all core set items had been measured. The trials affected were both of the MTX versus injectable gold trials and the larger of the 2 MTX versus AZA trials. The effects may be seen in Figure 1, where the response to injectable gold was consistently less than the response to cyclosporine or to MTX for each disease duration category. Similarly, the AZA response in these data was relatively low, being only slightly higher than that of patients with similar disease duration who were treated with AUR.

The disease duration effect was strongest in patients with a shorter disease duration. When the COBRA trial, with its very short disease duration, was not included in the multivariate analysis (using the 10-trial "all variable" data set), the disease duration effect, though still statistically significant, was attenuated (OR_{adj} 0.74 per 15 years versus OR_{adj} 0.63 in the "all trial" data set). Also, there was no disease duration trend for the small number of Prosorba-treated participants, of whom more than 80% (39 of 48) had substantial disease duration of ≥5 years.

The most widely used treatments for RA are

represented in our data, but we did not have trial data on major new agents for RA, especially those targeting tumor necrosis factor α. It is not clear whether response rates also diminish with longer disease duration when these agents are used.

We found an ~30% difference between active and placebo treatment response that varied little across the strata of disease duration, Steinbrocker functional class, disease activity, and sex. An implication of this finding is that the distribution of patients in a trial with respect to levels of these factors should have little effect on the statistical power of the trial. Nevertheless, the interpretability of trial results in general would be enhanced by the explicit use of disease duration strata in particular. Many trials have already planned to include or exclude patients on the basis of disease duration, prior DMARD use, Steinbrocker functional class, or sex. When trials include patients in multiple strata, the presentation of trial results by these strata would facilitate comparisons of results across trials.

A problem with the interpretation of our finding of a reduced likelihood of response to treatment with greater duration of disease would arise if the disease duration effect were an artifact of the way response is measured. It could be that some components of the core set are less responsive than others for patients with greater disease duration, and thus arguably unsuited for use as part of a response criterion in longer-standing disease. In particular, it might be expected that the presence of fixed residual swelling of joints would reduce responsiveness of the swollen joint count, and that physical function might also be intrinsically less responsive in patients with longer-standing and more advanced disease. Our examination of the relationship between disease duration and response for each separate ACR core set item showed a fairly uniform drop-off in response with increasing disease duration. This suggests that there is a real decline in disease responsiveness with greater duration of disease, and that the decrease is not an artifact of measurement.

Patients with longer disease duration who enter clinical trials are likely to have prior DMARD exposure, and these DMARDs may not have worked well for them, otherwise it is unlikely that they would be participating in a clinical trial. Our data show independent effects of disease duration, disease severity, and prior DMARD exposure with respect to ACR response, which suggests that the patients who are least likely to respond are those who have long-standing, refractory disease.

In summary, we have found, from an analysis of patient-level data in a set of 14 clinical trials in RA, that patients with longer disease duration do not respond as well to treatment in RA as do those with earlier disease, and that female sex, prior DMARD use, and worse functional class also, simultaneously, reduce the likelihood of patient response. There is no evidence that the ACR improvement criteria are less valid in longer-standing disease, nor should the power of trials be adversely affected by any particular distribution of patients across the various strata of factors related to response. The implications for trial interpretation and for clinical expectations of patients, however, are that the response can be expected to vary according to which group a patient is in with respect to each of the variables of disease duration, sex, prior DMARD use, and disease severity. In particular, there is a window of opportunity for effective treatment of RA during the early stages of the disease.

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