Association of Anemia and Physical Disability Among Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To evaluate the relationship between hemoglobin concentration and physical disability in patients with rheumatoid arthritis (RA).

Methods. Data were derived from 2495 patients with RA enrolled in 3 clinical trials (ATTRACT, ASPIRE, and START) and treated with infliximab (3 to 10 mg/kg) plus methotrexate (MTX), or MTX plus placebo. The association of hemoglobin and the Health Assessment Questionnaire (HAQ) score was assessed at baseline (n = 2471) and Week 22 (n = 2458) by Spearman correlation, and multivariate linear regression models were employed to control for confounding effects from demographic and other clinical variables. A logistic regression model was used to estimate the odds ratio (OR) for a clinically meaningful improvement (≥ 0.25 point increase) in HAQ associated with a ≥ 1 g/dl improvement in hemoglobin from baseline at Week 22.

Results. About 37% of patients with RA had anemia based on World Health Organization criteria: hemoglobin < 12 g/dl in women (39%) and < 13 g/dl in men (32%). Low hemoglobin level was significantly associated with more severe physical disability at baseline ($p < 0.001$), and both male and female patients with anemia had more severe disability at baseline. Improvement in hemoglobin after treatment at Week 22 was an independent contributor to improvement in HAQ, and a ≥ 1 g/dl improvement in hemoglobin after treatment was associated with a clinically meaningful improvement in the HAQ score at Week 22 (OR 1.43, 95% CI 1.10–1.86; $p < 0.01$).

Conclusion. Anemia is one of the independent factors contributing to physical disability in patients with RA. Improvement in anemia following effective RA treatment may play an independent role in improving physical function. (First Release Oct 15 2007; J Rheumatol 2007;34:2177–82)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ANEMIA PHYSICAL FUNCTION

Loss of physical function is a common outcome of rheumatoid arthritis (RA). Unfortunately, physical function deteriorates so aggressively in patients with RA that roughly half of these patients experience work disability within 10 years of disease onset[1]. Notably, the overall indirect costs resulting from this loss of productivity may exceed the direct heathcare costs of RA, especially in patients with more established disease[2,3]. As well, in an analysis of patients with longstanding RA, patients who achieved a clinically important improvement in physical function, as measured by the Health Assessment Questionnaire (HAQ), had significant improvements in their employability, time lost from work, total and direct medical costs, and quality of life[4].

Disability in RA is multifactorial. Factors influencing disability can include both disease-specific factors (disease duration, inflammatory status, erythrocyte sedimentation rate, articular signs and symptoms, and performance-based functional limitations) and external/contextual factors (age and sex, formal education, psychosocial status, and depression)[5].

Although anemia is the most common hematological problem in patients with RA, occurring in about 50% of these patients[6,7], the association between anemia and disability in RA patients has not been well studied[8]. Interestingly, in an evaluation of the influence of varying hemoglobin levels on mortality, function, and cognition in a representative non-RA population of older persons (≥ 71 yrs), anemia was strongly associated with poorer physical function and cognitive function, and predicted decreases in both of these outcomes over a 4-year period[9].

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Since little is known about the role of anemia in the physical function of patients with RA, we evaluated the association between anemia and physical disability, as measured by HAQ, among RA patients who participated in 3 large multicenter clinical studies, i.e., the ATTRACT[10-12], ASPIRE[13], and START[14] studies.

MATERIALS AND METHODS

Patients. ATTRACT, ASPIRE, and START were phase 3, randomized, double-blind, placebo-controlled studies. In all studies, patients with RA were randomly allocated to receive treatment with infliximab (doses ranging from 3 to 10 mg/kg) plus methotrexate (MTX) or placebo plus MTX. Details of the designs and treatment assignments for these studies have been published[10-14].

Measures and analyses. Clinical and laboratory assessments in the 3 studies, including joint counts, pain scores, C-reactive protein (CRP) level, and hemoglobin level, were collected at baseline and during followup visits that occurred from Weeks 2 through 22 in START and from Weeks 2 through 54 in ATTRACT and ASPIRE. For the purpose of maintaining consistency of available data across the trials in this analysis, only data through Week 22 were included.

In all 3 studies, physical function was measured using the HAQ score at baseline and Week 22. The HAQ is a validated self-administered questionnaire that assesses functional ability in a variety of areas, including the ability to dress, arise, eat, walk, maintain personal hygiene, reach, and grip, on a scale ranging from 0 (no difficulty) to 3 (unable to perform the activity)[15,16]. Hemoglobin levels were assessed at baseline and Week 22 in all 3 trials. Anemia was defined based on World Health Organization (WHO) criteria as hemoglobin < 12 g/dl in women and < 13 g/dl in men[17].

Missing values for clinical measurements during followup were replaced using last observation carried forward methodology. However, patients with missing values at baseline and patients with missing values at all followup visits prior to Week 22 were excluded from the Week 22 analyses. In general, simple descriptive statistics, including the mean and standard deviation (SD) for continuous variables and counts and percentages for discrete variables, were used to summarize data. The association of hemoglobin and HAQ was assessed at baseline (n = 2471) and Week 22 (n = 2458) in all 3 studies. The association of hemoglobin and HAQ was assessed by Spearman correlation, and multivariate linear regression models were employed to control for confounding effects from demographic variables (age, sex, disease duration) and disease activity as assessed by the Disease Activity Score using 28 joint assessments and CRP (DAS28)[18]. A logistic regression model was used to estimate the odds ratio (OR) and 95% confidence interval (CI) for a clinically meaningful improvement in HAQ, defined as a ≥ 0.25-point decrease in HAQ, among patients who achieved at least 20% improvement in individual clinical measures or patients who achieved at least a 1 g/dl improvement in hemoglobin.

RESULTS

Patient characteristics. Patient characteristics are summarized in Table 1. The majority of patients in the 3 RA studies were women, consistent with the overall distribution of RA between men and women in the general population. Overall, the mean baseline HAQ score and hemoglobin levels were 1.5 and 12.5 g/dl, respectively. Major differences in the patient populations among the 3 studies included disease duration and prior exposure to MTX, as mandated by the study protocols. Patients enrolled in ASPIRE had early RA (mean disease duration 0.9 yrs) and were MTX-naive. Patients enrolled in ATTRACT and START had longer mean disease duration at baseline (10.5 and 10 years, respectively) and had previously received MTX (data not shown). In addition, patients in ATTRACT had more severe disease activity, as evidenced by a higher HAQ score (1.7), lower hemoglobin (12.2 g/dl), and severity of joint damage (data not shown) at baseline compared with the other trials. At baseline, 37.1% of patients had anemia based on the WHO criteria: 32.3% in men and 38.6% in women.

Correlation of baseline HAQ and hemoglobin. Hemoglobin and HAQ were significantly correlated ($p < 0.001$) at baseline in all 3 trials (Table 1). Compared with patients who had baseline hemoglobin levels > 14 g/dl, those with moderate (hemoglobin 10 to < 12 g/dl) or severe (hemoglobin < 10 g/dl) anemia, or even with mild anemia (12 to ≤ 14 g/dl), had more severe baseline disability, for both male and female patients (Figure 1). Multivariate analyses were used to adjust for

Table 1. Baseline characteristics of patients with RA. Data presented are mean (standard deviation) unless otherwise specified.

	ASPIRE	ATTRACT	START	All Trials
Patients randomized	1004	428	1063	2495
Patients evaluated	993	424	1054	2471
Age, yrs	50.3 (12.5)	52.6 (11.7)	52 (12.6)	51.4 (12.4)
Female gender, %	71.0	77.4	80.6	76.2
Disease duration, yrs	0.9 (0.7)	10.5 (8.6)	10 (9.1)	6.4 (8.3)
HAQ score, 0–3	1.5 (0.6)	1.7 (0.6)	1.4 (0.7)	1.5 (0.6)
Hemoglobin, g/dl	12.7 (1.5)	12.2 (1.4)	12.5 (1.4)	12.5 (1.4)
Hematocrit, %	38.4 (4.22)	36.9 (3.86)	38.1 (3.92)	38.0 (4.07)
Patients with anemia, %				
All	34.6	47.6	35.2	37.1
Male	29.5	50.0	27.8	32.3
Female	36.7	46.9	37.0	38.6
Correlation of HAQ vs hemoglobin, r (p value)*	–0.32 (< 0.001)	–0.21 (< 0.001)	–0.14 (< 0.001)	–0.23 (< 0.001)

* For the correlation between baseline HAQ and baseline hemoglobin, the data are presented as Spearman's correlation coefficient (p value).

demographic variables (age, sex, disease duration) and disease activity using the DAS28. Results of these analyses indicated that the baseline hemoglobin level was associated with HAQ scores at baseline in all patients ($p < 0.001$), as well as in each of the individual studies (Table 2).

Association of improvement in hemoglobin and improvement in HAQ. We performed a multivariate linear regression analysis to determine the relationship between improvement in hemoglobin levels and improvement in physical function, as assessed by the HAQ (Table 3). After adjustment for demographic variables (age, sex, disease duration) and improvement in disease activity (DAS28), we found that greater improvement in hemoglobin from baseline to Week 22 was associated with a greater improvement in physical function ($p < 0.001$; Table 3). However, in the regression models, the correlation between improvement in hemoglobin and improvement in HAQ after adjustment for improvement in disease activity was more striking among patients with early RA and who were MTX-naive (ASPIRE: ß = 0.09, $p < 0.001$) than in patients with longstanding RA who had previously been treated with traditional disease modifying antirheumatic drugs (DMARD) in ATTRACT (ß = 0.04, $p = 0.11$) or START (ß = 0.04, $p = 0.03$).

Among the subgroups of patients with varying degrees of anemia at baseline, patients who had a ≥ 1 g/dl increase in hemoglobin from baseline to Week 22 had a higher probability of achieving a significant improvement in their HAQ scores (with p values ranging from < 0.01 to < 0.05) compared with patients who had no improvement in hemoglobin levels. However, among patients with normal baseline hemoglobin, i.e., > 14 g/dl, the improvement in physical function at Week 22 was not significantly associated with a change in hemoglobin (Figure 2).

To assess the individual contribution that changes in different clinical variables made to observed changes in HAQ scores, a logistic regression model was employed. As illustrated in Figure 3, clinically significant improvement in hemoglobin (> 1 g/dl) was independently associated with a clinically significant improvement in HAQ (≥ 0.25) at Week 22 (OR 1.43, 95% CI 1.10–1.86).

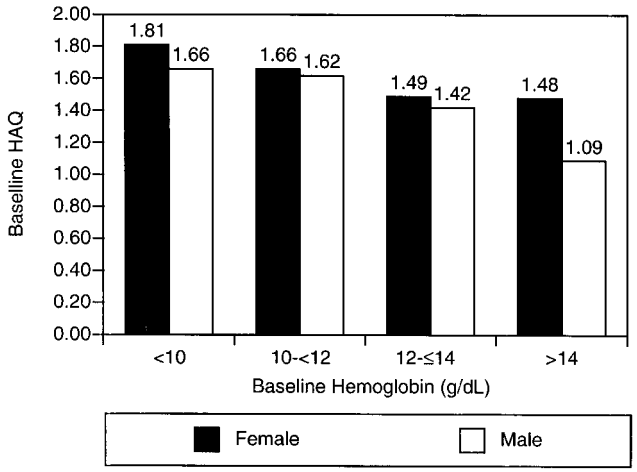

Figure 1. Baseline HAQ scores across all trials by baseline hemoglobin levels.

DISCUSSION

Loss of physical function has long been recognized in RA. In previous studies, severe declines in functional and work abilities have been documented[19,20]. Patients with RA become disabled due to the combined effect of pain, inflammation, joint damage and deformities, extraarticular disease, and other manifestations, together with external factors such as age, sex, psychosocial background, and comorbidity. Escalante, *et al*[5] constructed a sequence of hierarchical regression models to determine the relative contributions of patient and disease variables to physical disability, as assessed by the HAQ and SF-36 physical component summary scores, in patients with RA. Results of this extensive modeling showed that RA disease manifestations (signs and symptoms and the erythrocyte sedimentation rate) and other external factors (demographic, socioeconomic, and psychological factors) accounted for only about 59% of the total variance of disability; the remaining 41% was attributed to the effect of "unmeasured patient characteristics." As documented in a 12-year prospective cohort of 132 female patients with longstanding RA, disease activity appears to be the main determinant of functional ability[21].

Anemia of chronic disease (ACD; also known as anemia of chronic inflammation) is the most common hematologic problem in patients with RA. Previously, the prevalence of anemia in RA patients has been reported to be approximately 50%[7]. In this analysis, we found that approximately 37% of RA patients had anemia (32.3% of men and 38.6% of women).

Table 2. Multivariate linear regression analyses of HAQ with adjustments for demographic features and clinical variables at baseline.

	ASPIRE		ATTRACT		START		All Trials	
	ß	P value	ß	P value	ß	P value	ß	P value
Age, yrs	0.0037	0.0089	0.0030	0.2191	0.0045	0.0037	0.0040	< 0.0001
Male	–0.2204	< 0.0001	–0.1906	0.0061	–0.1724	0.0008	–0.1946	< 0.0001
Disease duration, yrs	–0.0173	0.4867	0.0045	0.1735	0.0080	0.0002	0.0071	< 0.0001
Baseline DAS28, 1–10	0.3191	< 0.0001	0.2285	< 0.0001	0.2405	< 0.0001	0.2786	< 0.0001
Baseline hemoglobin, g/dl	–0.0746	< 0.0001	–0.0445	0.0369	–0.0346	0.0185	–0.0572	< 0.0001

ß = estimated coefficient.

Table 3. Multivariate regression analyses of improvement in HAQ and improvement in clinical variables from baseline to week 22.

	ASPIRE		ATTRACT		START		All Trials	
	ß	P value	ß	P value	ß	P value	ß	P value
Age, yrs	–0.0020	0.1706	–0.0039	0.0653	–0.0029	0.0245	–0.0024	0.0070
Male	–0.0997	0.0154	–0.0273	0.6348	–0.0157	0.6906	–0.0360	0.1658
Disease duration, yrs	–0.0529	0.0413	–0.0060	0.0368	0.0000	0.9993	–0.0096	< 0.0001
Improvement in DAS28, 1–10	0.2381	< 0.0001	0.1803	< 0.0001	0.2193	< 0.0001	0.2342	< 0.0001
Improvement in hemoglobin, g/dl	0.0916	< 0.0001	0.0388	0.1082	0.0374	0.0300	0.0582	< 0.0001

ß = estimated coefficient.

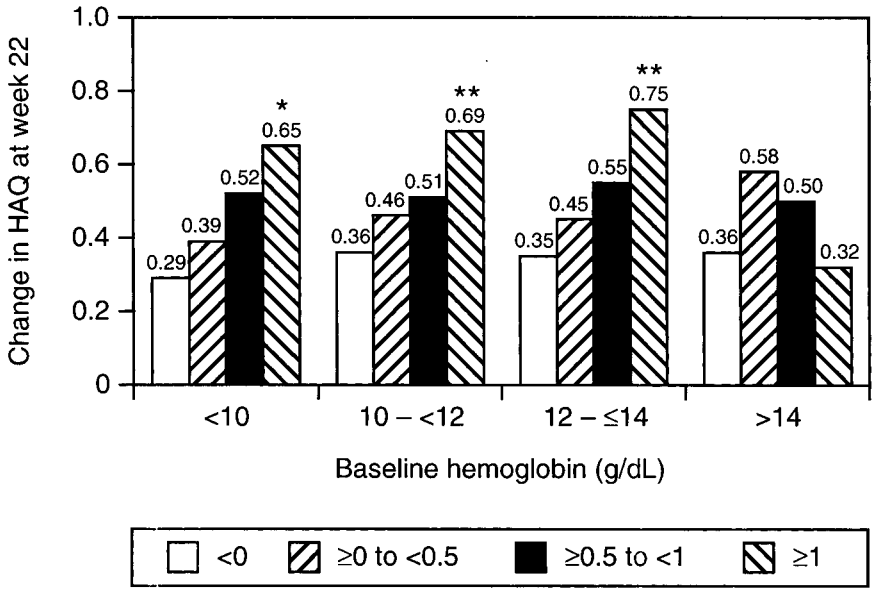

Figure 2. Change in HAQ by change in hemoglobin at Week 22 across all trials, grouped by baseline hemoglobin level. *p < 0.05, **p < 0.01 vs patients with no improvement in hemoglobin.

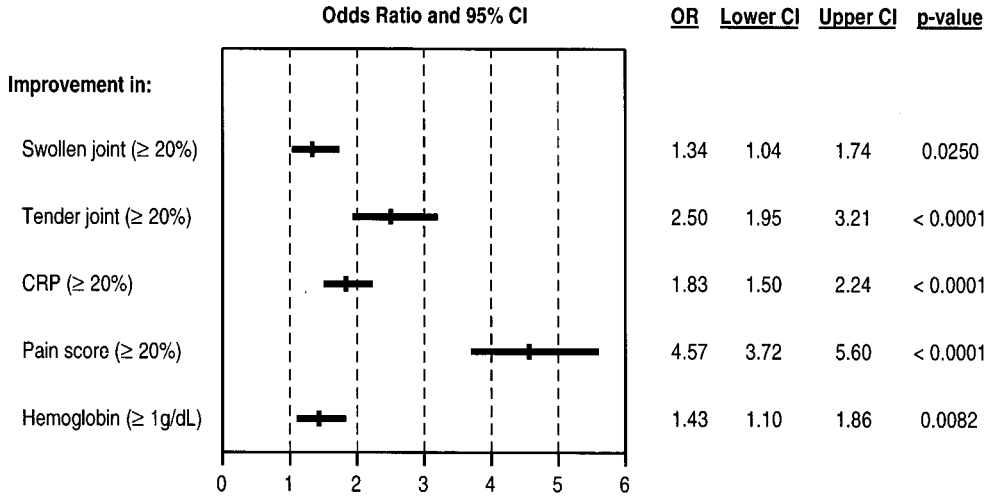

Figure 3. Odds ratios and 95% confidence intervals for a clinically meaningful improvement in HAQ, defined as a ≥ 0.25-point decrease in HAQ, among patients with an increase ≥ 1 g/dl in hemoglobin level or ≥ 20% improvement in other clinical measures after treatment at Week 22 across all trials: results from logistic regression analysis adjusted for age, sex, and disease duration.

Although the influence of anemia on the physical function of patients with RA has not been well studied, evidence continues to indicate that anemia has an independent effect on physical function and quality of life. Evidence supporting an association of anemia and physical function in patients with RA comes from epidemiological studies, such as that by Wolfe, *et al*[22], who analyzed 2120 patients with RA and 7124 patients with noninflammatory disorders. Overall, 51.6% of patients with RA had hemoglobin < 12 g/dl and 13.7% had hemoglobin < 10 g/dl. Among patients with RA, a lower hemoglobin level was associated with increased disease activity as reflected by joint counts, erythrocyte sedimentation rate, CRP level, HAQ score, pain, and fatigue. Patients with hemoglobin levels < 10 g/dl had HAQ scores that, on average, were 0.18 (95% CI 0.16 to 0.21) units higher than those in patients without anemia[22].

In our analysis employing multivariate regression models to control for confounding variables that included age and other clinical features of RA, anemia was found to be one of the independent contributors to the disability seen in patients with RA. Specifically, a low hemoglobin level was significantly associated with more severe physical disability at baseline ($p < 0.001$) after adjustment for demographic variables and disease activity, as assessed by the DAS28. Moreover, we found that improvement in hemoglobin after treatment at Week 22 resulted in a clinically significant improvement in the HAQ score ($p < 0.001$) at Week 22. Of note, at least a 1 g/dl improvement in hemoglobin was associated with an OR of 1.43 at Week 22 for a ≥ 0.25-unit improvement in HAQ, which was similar to the OR that resulted from 20% improvement in CRP (1.83) or 20% improvement in swollen joint count (1.34) after adjustment of other variables. These findings emphasize the importance of anemia in physical function. Of note, change in patient pain was also a potent predictor of change in HAQ, with an OR of 4.57 (Figure 3).

While improvement in hemoglobin of ≥ 1 g/dl is clinically meaningful in terms of improving physical function, patients with normal hemoglobin levels may experience less benefit in physical function with further improvement of their hemoglobin levels. In addition, when assessed by multiple regression models, the correlation of improvement in hemoglobin and improvement in HAQ after adjustment for improvement in disease activity was more significant among patients with early RA and who were MTX-naive than in those with longstanding disease and who were previously treated with traditional DMARD. This result was consistent with our previous findings that showed disability caused by joint damage in patients with longstanding RA is less likely to be reversed even though these patients may have significant improvement in disease activity[23,24].

The pathogenesis of both RA and ACD is related to cytokine production, including proinflammatory cytokines such as interleukin 1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α)[25-28], that can enhance apoptosis of marrow erythroid progenitors, suppress erythropoietin production, and shorten red cell survival. These effects can be partially reversed by recombinant human Erythropoietin (r-h-Epo). R-h-Epo has been shown to increase baseline hemoglobin levels to normal in patients with RA in clinical studies involving small numbers of patients. Results of several studies that evaluated the use of R-h-Epo in patients with RA and ACD collectively suggest that, in some patients, improvement in anemia can lead to improvement in quality of life, particularly in fatigue and energy level measurements[29-32]. Because of the role TNF-α plays in the pathogenesis of RA as well as RA-associated anemia, and the success of anti-TNF-α therapies in treating other manifestations of the disease, the effect of TNF-α inhibition on hemoglobin levels in RA has been investigated. Papadaki and colleagues reported that repeated administration of anti-TNF-α inhibitor therapy (infliximab 3 mg/kg at Weeks 0, 2, 6, 14, 22, and 30) was effective in significantly raising hemoglobin levels in both anemic (14% increase) and nonanemic (7% increase) patients with RA ($n = 40$)[25]. A beneficial effect of infliximab in patients with RA and ACD was also demonstrated by Davis, *et al*[7] following a single infusion of infliximab (1 mg/kg or 10 mg/kg) or placebo to 73 patients with RA. Hemoglobin levels increased 0.0 to 0.2 g/dl at 2 weeks in patients treated with infliximab and decreased by 0.5 g/dl in patients receiving placebo.

Anemia in patients with RA may be underdiagnosed and/or undertreated in general medical practice, since analyses of health claims databases have indicated that only about 11.3% of patients with RA had a documented diagnosis of anemia[33]. Although we could not discern the etiology of anemia in our patient population, given the independent correlation we observed between hemoglobin and physical disability, effective treatment that can reduce inflammation and improve hemoglobin levels may provide more patient benefit in terms of overall health and physical function and may result in additional economic benefits.

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