Anemia in Early Rheumatoid Arthritis Is Associated with Interleukin 6-Mediated Bone Marrow Suppression, But Has No Effect on Disease Course or Mortality

CATHRIN NIKOLAISEN, YNGVE FIGENSCHAU, and JOHANNES C. NOSSENT

ABSTRACT. ***Objective.*** Anemia of chronic disease (ACD) is the most common extraarticular manifestation of rheumatoid arthritis (RA), but there is limited information on the cause and consequences of ACD. We investigated the prevalence, relation with proinflammatory cytokines, and effect on disease outcome of ACD in patients with RA.

Methods. The presence of anemia was analyzed in a cohort of 111 consecutive patients with early RA. Anemia was related to markers of erythropoiesis and inflammation [clinically and by levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum interleukin 1ß (IL-1ß), IL-2, IL-6, IL-8, and tumor necrosis factor-α]. The frequency of various disease outcomes during the mean followup of 74 months was compared between ACD and nonanemic patients.

Results. ACD was present in 25% during the first year of disease. ACD was associated with higher CRP (45 vs 22 g/l; p = 0.04) and ESR levels (54 vs 33 mm/h; p = 0.002). Hemoglobin levels were inversely correlated with serum erythropoietin (p = 0.003) in univariate analysis, but in multivariate analysis only ESR (p = 0.005) and IL-6 (p = 0.056) remained as independent predictors of hemoglobin levels. Presence of ACD was not associated with later development of disease manifestations or mortality.

Conclusion. While ACD affected 25% of patients with RA early in the disease course, this had no influence on disease outcome including mortality during the following 6 years. The association between IL-6 and ACD suggests that IL-6-mediated bone marrow suppression is the main mechanism for development of ACD in RA. (First Release Feb 1 2008; J Rheumatol 2008;35:380–6)

Key Indexing Terms:
ANEMIA RHEUMATOID ARTHRITIS INTERLEUKINS OUTCOME CHRONIC DISEASE

Rheumatoid arthritis (RA) is the most prevalent systemic inflammatory autoimmune disease and while its exact etiology remains obscure, it has become evident that proinflammatory cytokines drive most of the clinical symptoms[1]. While RA primarily induces synovial hyperplasia that may lead to bony joint damage, extraarticular manifestations occur quite frequently. Amyloidosis, which severely reduces life expectancy in RA, affects 2%–4% of patients with RA[2], whereas rheumatoid nodules that pose mainly cosmetic problems may affect up to 40%[3]. However, the most frequent extraarticular manifestation in RA is anemia, and although rarely acknowledged as such, it can affect 60% of all patients with RA at least once during their lifelong disease course[4]. Anemia not only contributes to fatigue and reduced quality of life in RA[5], but longstanding anemia can have deleterious cardiovascular effects and contribute to increased mortality[6].

Anemia in RA is usually anemia of chronic disease (ACD). ACD is typically characterized by a normochromic, normocytic anemia in the absence of folate and vitamin B12 deficiencies. ACD is associated with a relative iron deficiency that arises from iron storage within cells of the reticuloendothelial system, while iron concentration in the circulation is low. In addition, patients with RA are at risk for drug-induced anemia as the use of nonsteroidal antiinflammatory drugs (NSAID), corticosteroids, and cytotoxic drugs may lead to bleeding and bone marrow suppression[7]. ACD is traditionally regarded as the result of inefficient erythropoiesis in an inflammatory setting[8,9]. Tumor necrosis factor-α (TNF-α) is an important mediator of inflammation in RA and has been implicated as a cause of ACD due to its apoptotic effect on erythroid precursors[10]. In view of these findings, and given that there are no data on the longterm effect of anemia on RA outcome[11], we

From the Department of Rheumatology, Institute of Clinical Medicine, University of Tromsø; and the Departments of Medical Biochemistry and Rheumatology, University Hospital North Norway, Tromsø, Norway.

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C. Nikolaisen, MD, Department of Rheumatology, Institute of Clinical Medicine, University of Tromsø; Y. Figenschau, MD, PhD, Department of Medical Biochemistry; J.C. Nossent, MD, PhD, Professor of Medicine, Department of Rheumatology, University Hospital North Norway.

Address reprint requests to Dr. C. Nikolaisen, Department of Rheumatology, Institute of Clinical Medicine, University of Tromsø, N-9037 Tromsø, Norway. E-mail: cathrin.nikolaisen@unn.no

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investigated the prevalence of anemia during the early phase before treatment with disease modifying antirheumatic drugs (DMARD) or corticosteroids is initiated, its association with clinical and serological markers of inflammation, and its influence on disease outcome.

MATERIALS AND METHODS

Consecutive patients with RA (as defined by the 1987 American College of Rheumatology classification criteria[12]) seen at the Department of Rheumatology, University-Hospital North-Norway in 1993-2000 were included in our study. The following baseline data were recorded at the first patient visit (as described[3]): demographics, morning stiffness during the previous week, active joint count (swollen and tender joints in 56 individual joints), and routine laboratory data [hemoglobin levels, mean corpuscular volume (MCV), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP)]. Patients were followed every 3 months for the first year and biannually thereafter. At the last registered visit during 2003-2004 the cumulative use of and time spent taking DMARD, NSAID, and corticosteroid medication (minimum period for registration was 1 month of completed therapy) were calculated and outcomes were recorded by record review. Relevant outcomes were considered to be nonsurvival, ever-presence of rheumatoid nodules (clinical and/or histological diagnosis) or other extraarticular manifestations (serositis, vasculitis, amyloidosis), erosive disease (in any joint), surgical interventions, and development of comorbidity (arterial hypertension, diabetes mellitus) during the disease course.

Anemia was defined in accord with the World Health Organisation (WHO) criteria as presence of hemoglobin levels < 13.0 g/dl for men and < 12.0 g/dl for women, while severe anemia was defined as hemoglobin levels < 10 g/dl. ACD was defined as anemia in the absence of nutrient deficiencies or cytotoxic drug use[9], while iron deficiency was defined as microcytic mean corpuscular volume (MCV) < 80 fl anemia with serum ferritin level < 50 µg/l[13]. Ferritin levels were measured by a commercial immunoassay method (Elecsys® Ferritin, Roche), which is standardized against a liver ferritin preparation. The assay measures basic L-ferritin that is responsible for longterm iron storage and found mainly in the liver, spleen, and bone marrow. Ferritin measurements were performed at our clinical chemistry laboratory, which is certified by the Norwegian Accreditation Organization on this analysis with the ferritin reference interval based on data from a recent study at the National Hospital.

MCV, ferritin, vitamin B12, and folate levels were measured by routine laboratory procedures. Stored serum samples (–20°C) were available for 71 patients with RA from the time of disease presentation, and levels of the inflammatory cytokines interleukin 1ß (IL-1ß), IL-2, IL-6, IL-8, and TNF-α were measured by commercial sandwich ELISA assays (Diaclone, Besancon, France). Serum erythropoietin (EPO) was analyzed by Immunolite 2000 (DPC, Los Angeles, CA, USA). All measurements were performed in accord with the manufacturers' instructions.

For these laboratory studies, a cohort of 46 patients (mean age 54 yrs, 69% women) with musculoskeletal pain without clinical or laboratory signs of inflammation served as the control group (20 patients with fibromyalgia, 3 with osteoarthritis, and 23 with various noninflammatory disorders such as enthesiopathia, lymphoma, and lumbago).

All numbers reported are median values unless otherwise stated. Comparison of group differences was done with nonparametric test methods (Kruskal-Wallis test for continuous variables and chi-square/Fisher's exact test for categorical data). To assess the effect of ACD, patients with iron deficiency anemia were excluded from all analyses on correlations between ACD, inflammatory markers, and outcome. Analyses were then repeated with the inclusion of iron-deficient patients, and differing results are given. Correlations between variables are reported as Spearman's rank coefficients, and a multivariate regression analysis was performed to estimate the independence of each correlation ($p < 0.1$ to enter and $p < 0.05$ to stay) with hemoglobin levels. Outcomes were analyzed as dichotomous variables using odds ratios and with time-to-event analyses by Kaplan-Meyer survival estimates with comparison of subgroups by log-rank testing. All analyses were performed with statistical software (SPSS version 14.0), and resulting 2-sided p values < 0.05 were considered to indicate statistical significance.

RESULTS

Descriptors. Anemia was present in 32 patients (29%) and more frequent in women than men (35% vs 19%; $p = 0.04$). There were no differences in anemia prevalence between the various age groups ($p = 0.3$; Table 1). Vitamin B12 and folate levels were normal in all patients, while iron deficiency was present in 4 patients (4%, all women), and the remaining patients were classified as having ACD. Severe anemia was rare (3%) and due to ACD in 2 patients and iron deficiency in 1 patient.

While most demographic and clinical findings such as active joint count were similar in subjects with and without anemia (Table 2), ESR and CRP levels were significantly increased in patients with ACD compared to patients without anemia. Anemic patients had lower MCV and higher red cell distribution width and EPO levels, whereas serum ferritin levels and the presence and titers of autoantibodies were not associated with ACD. By definition, patients with iron deficiency anemia had lower MCV and ferritin levels, but apart from lower CRP levels they had similar clinical characteristics compared to patients with ACD (Table 2).

Proinflammatory cytokines in RA versus controls. Serum levels of IL-1ß, IL-6, and TNF-α were increased in patients with RA compared to controls (Table 3A), while IL-2 levels were similar and IL-8 lower than controls. Also, EPO levels were increased in patients with RA, while there were no differences in vitamin B12, folate, and ferritin levels.

Proinflammatory cytokines in RA patients with and without ACD. Serum levels of cytokines and the percentage of patients with increased levels (compared to controls) were mostly similar for RA patients with and without ACD (Table 3B). Only IL-6 levels were higher in patients with ACD and more patients with ACD had increased IL-6 levels. While TNF-α levels were higher in non-anemic patients with RA, this failed to reach statistical significance.

Correlations between measures of anemia and proinflammatory cytokines in patients with RA. Overall hemoglobin levels were inversely correlated with IL-6 levels ($Rs = -0.27$, $p = 0.05$), but no correlations were seen with levels of the other cytokines analyzed. Similarly, there was a positive correlation between EPO and IL-6 levels ($Rs = 0.39$, $p = 0.012$), but with none of the other cytokines. TNF-α levels correlated strongly with IL-2 ($Rs = 0.47$, $p < 0.001$) and IL-1ß levels ($Rs = 0.65$, $p < 0.001$; Table 4). These data were not altered by the inclusion of patients with iron deficiency anemia.

Correlations between measures of anemia and clinical signs of inflammation in patients with RA. Hemoglobin levels were inversely correlated with levels of ESR ($Rs = -0.43$, $p \leq 0.001$), CRP ($Rs = -0.30$, $p = 0.002$), and EPO ($Rs = -0.24$, p

Table 1. Prevalence of anemia and severe anemia in RA by sex and age groups. Figures indicate number of patients.

	No. with Anemia, n = 32	No. with Fe Deficiency, n = 4	No. with ACD, n = 28	p for Group Difference
Female	24	4	20	0.2
Male	8	0	8	
Age, yrs				0.3
< 40	3	1	2	
40–60	13	2	11	
> 60	16	1	15	
Severe anemia	3	1	2	
Female	1	1	0	NA
Male	2	0	2	
Age, yrs				NA
< 40	–	–	–	
40–60	1	1	–	
> 60	2	–	2	

NA: not analyzed; ACD: anemia of chronic disease.

Table 2. Characteristics of patients with rheumatoid arthritis (RA), classified by the absence or presence and type of anemia. Figures represent numbers (%) or median values (interquartile range).

	All RA, n = 111	Non-anemic, n = 79	ACD, n = 28	Iron Deficiency Anemia, n = 4	p
Female (%)	68 (61)	44 (56)	20 (71)	4 (100)	0.09
Age, yrs	61 (48–71)	60	63	45	0.5
Disease duration., mo	4.5 (0–22)	4.5	6	4	0.8
Hemoglobin, g/dl	12.9 (12–14)	13.7	11.3	11.1	0.001
MCV, fl	86 (82–90)	88.4	83.8	78.6	0.01
RDW, %	14 (13–15.6)	13.8	16.1	15.6	0.001
Platelet count (10^9/l)	350 (267–412)	321	386	347	0.07
Ferritin, µg/l	75.5 (33.3–143)	52	52	29	0.03
Vitamin B12, pmol/l	406 (334–512)	408	465	357	0.56
Folate, nmol/l	8 (7–11)	8	7	9	0.3
Erythropoietin, mIU/ml	13.1 (9.3–22.3)	12.3	22.8	22	0.001
Serum creatinine, µmol/l	70 (62–82)	71.5	70	63	0.5
Morning stiffness, min	61 (61–120)	120	80	61	0.2
Active joint count	7 (5–9)	7	7.5	5	0.4
ESR, mm/h	41 (22–67)	32.5	54	48	0.002
CRP, mg/l	24 (10–55)	21.5	45	13	0.04
Latex RF-positive	87 (78)	61 (77)	23 (82)	3 (75)	0.7
Waaler-Rose RF-positive	54 (49)	34 (43)	18 (29)	2 (50)	0.24
ANA-positive	10 (9)	6 (8)	4 (14)	0	0.4

ACD: anemia of chronic disease (see Methods for definition); MCV: mean corpuscular volume; RDW: red cell distribution width; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; ANA: antinuclear antibody.

= 0.003) and positively correlated with serum creatinine level (Rs = 0.30, p = 0.002; data not shown). No correlation existed between hemoglobin and joint counts, morning stiffness, or rheumatoid factor (RF) titers (data not shown).

Correlations between clinical signs of inflammation and proinflammatory cytokines in patients with RA. IL-6 levels were positively correlated with ESR (Rs = 0.31, p = 0.003), CRP (Rs = 0.44, p < 0.001), and duration of morning stiffness (Rs = 0.32, p = 0.015), while levels of IL-1ß, IL-2, IL-8, and TNF-α were not significantly correlated with clinical measures of inflammation or RF titers (data not shown).

Multivariate regression analysis of predictors for ACD. Given the multiple correlations observed with hemoglobin levels, multivariate linear regression analysis was performed with hemoglobin levels as the dependent variable and log-transformed values of predictors with a significant univariate correlation with hemoglobin. Only red cell distribution [ß = –3.9 (95% CI –17 to –5), p = 0.001], ESR [ß = –2.77 (95% CI –0.3

to –0.005), p = 0.005], and IL-6 [ß = –0.17 (95% CI –0.78 to 0.01), p = 0.056] remained as independent predictors of hemoglobin levels.

Anemia and disease outcome in RA. During a mean followup period of 74 months (range 13–164), 6 patients with ACD and 14 non-ACD patients died (22% and 18%, respectively; p = 0.42). Established causes of death were infectious disease (n = 4), cardiovascular events (n = 4), and malignancy (n = 1), while 11 patients died outside hospital and cause of death is unknown. Overall 5 and 10-year survival rates were 86% and 71%, respectively, and they were not influenced by the presence of anemia (p = 0.81 by log-rank test; Figure 1). Separate analyses were made in which patients with iron deficiency were included, and this gave similar results. None of the associations between ACD and various other disease outcomes was significant by dichotomous analysis (Table 5).

Table 3A. Anemia and cytokine profile in patients with rheumatoid arthritis (RA) in comparison with controls (see Methods). Figures represent mean values (range) or numbers.

	RA	Controls	p
Hemoglobin, g/dl	12.9	13.7	0.01
Vitamin B12, pmol/l	442	412	0.3
Folate, nmol/l	11	9	0.9
Ferritin, µg/l	103	126	0.15
Erythropoietin, mIU/ml	17.2	10.1	0.01
IL-1ß, pg/ml	3.2 (0.1–88.6)	0.3 (0.1–5.5)	0.021
IL-2, pg/ml	6.6 (0.1–238.0)	1.0 (0.1–38.1)	0.44
IL-6, pg/ml	11.9 (0.7–60.0)	3.1 (0.03–49.3)	0.0001
IL-8, pg/ml	1.0 (0.1–32.3)	4.9 (0.1–54.8)	0.023
TNF-α, pg/ml	17.9 (0.1–501.9)	0.4 (0.1–13.7)	0.003

TNF-α: Tumor necrosis factor-α.

Table 3B. Anemia and cytokine profile in RA patients with and without ACD. Figures represent mean values (interquartile range) or numbers.

	ACD	Non-anemic	p
Il-ß, pg/ml	1.7 (0)	4.5 (0)	0.67
Percentage with IL-1ß ≥ 7 pg/ml	4.8	8.4	0.5
IL-2, pg/ml	5.9 (80)	7.4 (0)	0.88
Percentage with IL-2 ≥ 14 pg/ml	9.5	7.1	0.6
IL-6, pg/ml	25.9 (820.2)	11.8 (11.1)	0.004
Percentage with IL-6 ≥ 2 pg/ml	95	71	0.02
IL-8, pg/ml	4.7 (0)	0.97 (0)	0.65
Percentage with IL-8 ≥ pg/ml	8.3	12.1	0.8
TNF-α, pg/ml	4.7 (8.2)	47 (5.4)	0.06
Percentage with TNF-α ≥ 8 pg/ml	27	35.5	0.7

TNF-α: tumor necrosis factor-α; Fisher's exact test used when n < 5.

DISCUSSION

Our results add new data to the relatively sparse knowledge on the presence and consequences of anemia in RA[9,11,14]. The overall prevalence of ACD was 25% in our RA cohort with short disease duration (4.5 mo) and severe anemia due to ACD was rather rare (2%). Another 4% of patients with RA were anemic due to iron deficiency. The anemia of the patients in this RA cohort was not due to side effects of treatment with DMARD or corticosteroids, as data were gathered at or close to the time of RA diagnosis. Hemoglobin levels were inversely correlated with serum EPO and IL-6 levels, which were both significantly higher in patients with ACD than in non-anemic patients with RA. Anemia during the early phase of the disease was not related to disease-specific outcomes during the followup period.

While the 25% ACD prevalence in this cohort is in the lower range according to a recent review[9], this cannot be attributed to the makeup of this cohort in terms of age and sex. The main distinctive feature was the shorter disease duration of this RA cohort compared to other studies. Using the same WHO definition, Wolfe and Michaud recently reported a lifetime prevalence of anemia of 57% in RA patients and a cross-sectional prevalence of 32% in patients after a mean disease duration of 10 years[4]. However, the authors did not distinguish between ACD and other types of anemia, but assuming a 5% prevalence of nutrient deficiency as cause of anemia, the ACD prevalence would be nearly similar to our study. Similarly,

Table 4. Spearman's rank correlations between hematological measures and inflammatory markers in all patients with RA.

	Hb, g/dl	Erythropoietin, mIU/ml	Ferritin, µg/l	CRP, mg/l	ESR, mm/h	IL-1ß, pg/ml	IL-2, pg/ml	IL-6, pg/ml	IL-8, pg/ml	TNF-α, pg/ml
Hb	1.000	–0.243*	0.229*	–0.304**	–0.431**	0.013	0.019	–0.270*	0.214	0.132
Erythropoietin		1.000	–0.083	0.334**	0.364**	0.081	0.055	0.391**	–0.039	0.041
Ferritin			1.000	0.058	0.090	–0.153	–0.152	0.085	–0.130	–0.126
CRP				1.000	0.771**	–0.027	0.071	0.439**	–0.227	–0.066
ESR					1.000	0.081	0.098	0.308**	–0.126	0.007
IL-1ß						1.000	0.255*	0.018	0.102	0.654**
IL-2							1.000	0.006	0.111	0.474**
IL-6								1.000	–0.122	–0.121
IL-8									1.000	0.288
TNF-α										1.000

* Correlation is significant at the 0.05 level (2-tailed). ** Correlation is significant at the 0.01 level (2-tailed). CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; TNF: tumor necrosis factor.

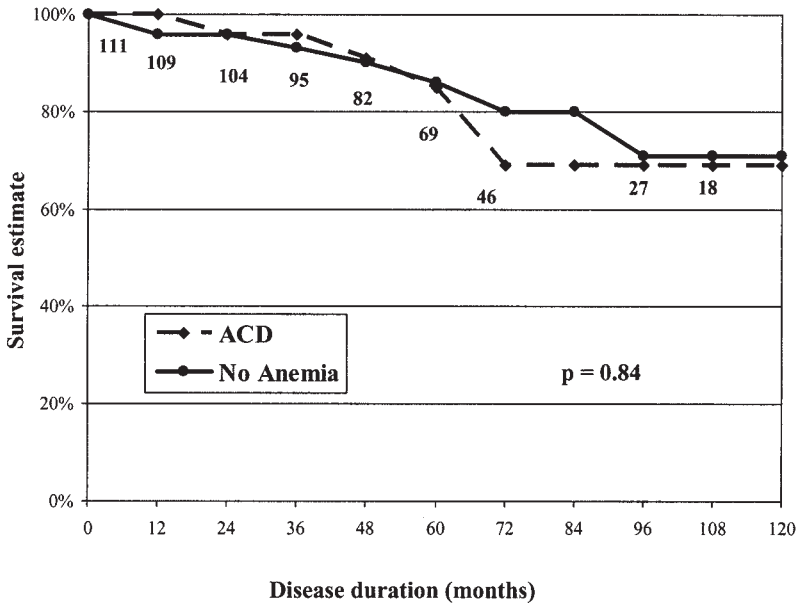

Figure 1. Overall 5 and 10-year survival rates for patients with RA with and without anemia of chronic disease (ACD).

Table 5. Associations between specified disease outcomes and presence of ACD in patients with RA. Figures refer to number of patients (%) or median value for the specified outcome in each subgroup.

	Non-anemic	ACD	p
Erosive disease	56 (71)	20 (71)	0.6
Joint surgery	26 (33)	13 (46)	0.13
No. of operations	0.3	0.5	0.17
Rheumatoid nodules	15 (19)	8 (29)	0.19
Other extraarticular manifestations	15 (19)	4 (14)	0.5
Mean no. DMARD used	2.2	2.6	0.11
DMARD use at last control	49 (62)	18 (64)	0.4
Prednisolone use at last control	34 (43)	17 (61)	0.047
Months spent on prednisolone	24.5	36.8	0.054
Diabetes mellitus	6	0	0.2
Cardiovascular event	15	1	0.11
Malignancy	6	1	0.4

DMARD: disease modifying antirheumatic drug; ACD: anemia of chronic disease; RA: rheumatoid arthritis.

Voulgari, *et al*, using only marginally different hemoglobin cutoff levels, describe an ACD prevalence of 31% in 232 consecutive RA patients with longstanding disease (> 10 yrs)[8]. Together, these prevalence rates argue against a large effect of disease duration on ACD prevalence. However, Jongen-Lavrencic, *et al* described a 49% ACD prevalence in an RA cohort with median disease duration of 24 months, during which a considerable proportion of initially non-anemic patients subsequently became anemic[15], indicating that there are as-yet undefined patient-specific dynamics in the ACD of RA. However, the authors did not exclude the RA patients with anemia due to low folic acid and vitamin B12. Segal, *et al* found decreased vitamin B12 in 25% (50/201) and decreased folic acid in 5% (11/201)[16], while there was none in our study. Iron deficiency was present in 4% in our cohort whereas other studies found it to be more frequent (23%–52%)[13,17,18]. The differences may be related to methodology, as ours was an early RA cohort, while other studies mainly included patients later in the disease course, and also used different definitions for anemia. The acute-phase response seen in RA makes it impossible to use the standard ferritin cutoff level to define iron deficiency in healthy people (< 15 µg/l). Based on earlier studies that have selected various optimal ferritin levels for detecting iron deficiency in RA[19-23], we chose 50 µg/l as the cutoff point.

The presence and severity of ACD have been related to a number of clinical markers of RA disease severity such as active joint counts, ESR and CRP levels, and the presence of erosive disease[8,13,15,18,24]. Our data, showing significantly increased CRP levels in patients with ACD, confirm an association between ACD and the magnitude of the acute-phase response. The work by Voulgari and Vreugdenhil has demonstrated an association between ACD and increased CRP and ESR[8,18,24], whereas Jongen-Lavrencic, *et al* have demonstrated association to increased ESR levels only[15]. The association between ACD and ESR levels is more complex, as ESR increases independently with falling hemoglobin levels and presence of autoantibodies[25].

There has been little doubt that ACD is to a large extent immune-mediated, although the exact interplay of immunological factors and erythropoiesis remains elusive. There was no association between ACD and the presence of RF, similar to the results by Vreugdenhil, *et al*[18,24]. The hallmark of ACD

is cytokine-induced, ferritin-mediated diversion of iron to the reticuloendothelial system, leading to the unavailability of iron for erythropoiesis and resulting in a situation of "starving in the midst of plenty"[26,27]. More specifically, cytokines affect the expression of iron transport molecules into the cells of the reticuloendothelial system[28], and also induce formation of the acute-phase protein hepcidin, which blocks iron export through ferroportin[29]. Hepcidin has recently been identified as the acute-phase protein that is central to iron diversion in ACD[30], and while we were unable to analyze hepcidin, its role in the ACD of RA clearly needs to be investigated. The inverse correlation between serum ferritin and hemoglobin levels reported here clearly reflects iron diversion in RA, but the findings that ferritin levels were similar in ACD and non-anemic patients, and the unexpected lack of correlation between ferritin levels and proinflammatory cytokines and CRP, indicate that this is not the single or sole pathway by which ACD occurs. Proinflammatory cytokines also exert effects on the bone marrow, where they inhibit the proliferation of erythroid progenitor cells partly by reducing the biological activity of erythropoietin[8,10]. Our findings support a role mainly for IL-6 in this mechanism of ACD, as IL-6 levels were significantly higher in patients with ACD than non-anemic patients with RA, correlated with EPO levels, and were the only marker of inflammation that independently and inversely correlated with hemoglobin levels. Thus one role of IL-6 in ACD is likely due to inhibition of erythropoiesis through reducing the number and activity of burst-forming erythroid colonies[8], which then leads to a secondary increase in EPO production. As IL-6 can also induce hepcidin, it seems to play a dual role in the anemia of RA by acting at the level of both the bone marrow (ineffective erythropoiesis) and the reticuloendothelial system (iron diversion).

Although blocking of TNF-α reverses ACD in many patients with RA and while TNF-α also may reduce erythroid progenitor activity, we found no direct correlation between TNF-α levels and markers for ACD in this cohort. TNF-α levels were significantly increased in all patients with RA, but levels in non-anemic patients did not differ from those in patients with ACD. This is in contrast to the findings by Voulgari, *et al*, where surprisingly, none of the non-anemic patients had increased levels of TNF-α or IL-1ß[8]. In addition, TNF-α-blocking agents reduce clinical disease activity and anemia in RA despite increasing serum levels of TNF-α, which may imply that their action is mediated through other mechanisms such as reducing IL-6 expression[31]. The introduction of specific therapy with monoclonal antibodies directed against IL-6 in the near future may elucidate the role of IL-6 in ACD and RA.

Anemia in RA is usually considered an inevitable consequence of the disease and given little attention, despite the fact that patients with RA are at increased risk for cardiovascular events, and anemia in itself has been associated with increased risks for cardiovascular disease and death[6,32,33]. Our study is one of the first to report on the longterm consequences of ACD in patients with RA, and the main finding was that patient survival during the first 5 to 10 years of disease was not influenced by the presence of ACD. Cardiovascular events (coronary events, cerebral ischemia) occurred less frequently (although this was not statistically significant) in patients with ACD, which may be attributed to the improvements in microcirculatory rheology that can be seen with reductions in erythrocyte mass[34]. On the other hand, and in view of the limited followup here for a disease that lasts a lifetime, it cannot be ruled out that the accelerated atherosclerosis in RA first becomes manifest later, and that ACD still may contribute to increased cardiovascular morbidity in the longer term. This issue will require longterm studies to be resolved. While ACD often is related to more severe disease in RA, we were unable to document an increase in other extraarticular manifestations, erosive disease, or need for surgical intervention. This may be due to our cohort of patients with early RA, whereas other studies investigated longterm RA. Only the number of patients taking corticosteroid therapy was increased in patients with ACD, but to our knowledge, there are no comparative data available for these outcome measures.

Our findings have limitations because we specifically aimed to study patients with RA in the earlier phase of the disease, when confounding of anemia by drug treatment is minimized. We did not study the longitudinal course of anemia to determine how therapeutic efforts may influence the frequency and type of anemia in RA at a later stage. An effect of prior NSAID treatment before contact with a rheumatologist was established cannot be fully excluded. Our RA cohort was relatively small, which may have limited the power to detect significant associations. Similarly, the retrospective design may have introduced unwarranted bias, despite our use of clear clinical endpoints. However, large discrepancies in RA management are unlikely, given the availability of local guidelines and the single-center setting.

The prevalence of ACD in RA patients with short disease duration was 25%, and had few clinical characteristics other than strongly increased CRP levels. ACD was associated with increased levels of IL-6 and EPO, indicating IL-6-mediated bone marrow suppression. ACD had no influence on RA-specific outcomes and mortality in the first 6 years of disease.

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