# Baseline Laboratory Test Abnormalities are Common in Early Arthritis but Rarely Contraindicate Methotrexate: Study of Three Cohorts (ESPOIR, VErA, and Brittany)

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***Objective:*** To evaluate the prevalence of baseline abnormalities in standard laboratory tests in patients with early arthritis and their impact on selection of disease-modifying antirheumatic drugs according to American College of Rheumatology (ACR) recommendations and/or of nonsteroidal anti-inflammatory drugs.

***Methods:*** In three cohorts of patients with early arthritis (the ESPOIR, VErA, and Brittany cohorts), we evaluated the prevalence of anemia (hemoglobin $<1$ 3 g/dL in men and 12 g/dL in women), leukopenia ($<3500$ per mm$^3$), thrombocytopenia ($<150\,000$ per mm$^3$), renal dysfunction (mild, creatinine clearance [CrCl] = 60–89.9 mL/min; moderate, CrCl = 30–59.9 mL/min; or severe, CrCl$<30$ mL/min), liver cytolysis (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] $>$ N or $>$ 2N), and systemic inflammation (erythrocyte sedimentation rate [ESR] $>$ 20 and C-reactive protein [CRP] $>$ 6).

***Results:*** We evaluated 1393 patients (1018 women and 375 men). Anemia was present in 363/1366 (26.5%) patients, leukopenia in 18/1372 (1.3%), and thrombocytopenia in 13/1371 (0.9%). ESR elevation was seen in 50.4% of patients and CRP elevation in 62.7%. The level of AST was above normal in 4% and of ALT in 10% of patients. No patient had severe renal dysfunction, 5.6% had moderate renal dysfunction, and 42.6% had mild renal dysfunction. Among the 1094 patients who had undergone all the tests, only 18 (1.64%, 95% confidence interval, 1–2.64) had a formal contraindication to methotrexate therapy according to ACR recommendations (4 had leukopenia, 12 had high ALT levels, and 2 had high ALT and AST levels).

***Conclusion:*** Patients with recent-onset arthritis often have anemia, mild or moderate renal dysfunction, and abnormal liver function. However, fewer than 2% have laboratory test abnormalities contraindicating methotrexate therapy.

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The early initiation of disease-modifying antirheumatic drugs (DMARDs) can prevent progression to full-blown rheumatoid arthritis (RA) [1]. Among DMARDs, methotrexate (MTX) is the most extensively evaluated. MTX therapy was significantly better than a placebo in both early arthritis (regarding the risk of RA development, inflammation, and number of joints with synovitis) and early RA (regarding anemia, inflammation, and number of joints with synovitis) [2–5].

A small number of patients treated with MTX experience life-threatening events including lung toxicity (lower respiratory tract infections and immunoallergic pneumonitis), bone marrow failure, particularly when renal function is impaired, and liver cytolysis. Nonsteroidal anti-inflammatory drugs (NSAIDs) are used routinely to treat early arthritis and can worsen preexisting renal dysfunction, thereby increasing the risks associated with MTX therapy [6–12]. Consequently, learned societies in France, Europe, and the US recommend that bone marrow, liver, and kidney function can be evaluated before the initiation of MTX therapy using laboratory tests at baseline and during the follow-up. A 2006 survey conducted in France showed that most rheumatologists obtained blood cell counts and liver and renal function tests in patients with early arthritis [13].

The objective of this study was to evaluate the results of routine laboratory tests obtained in patients with early arthritis and to determine their impact on treatment decisions. For this purpose, we collected baseline data from three French cohorts of patients with early arthritis (the ESPOIR, VErA, and Brittany cohorts) [14–16].

## PATIENTS AND METHODS

### Cohorts

We evaluated three cohorts, whose main characteristics are reported in Table 1.

- The *ESPOIR cohort* was a nationwide longitudinal prospective cohort study of adults (18–70 years of age) sponsored by the French Society for Rheumatology [14]. Inclusion criteria were inflammatory arthritis for at least 6 weeks but no longer than 6 months, involvement of more than two joints, clinical diagnosis of definitive or probable RA or clinical diagnosis of undifferentiated arthritis with a potential for progressing to RA, and no DMARD or steroid treatment since symptom onset; however, the use of glucocorticoids for no longer than 2 weeks, in a mean dosage not greater than 20 mg/day and with discontinuation at least 2 weeks earlier, did not prevent study inclusion. Patients with definite diagnoses of other inflammatory joint diseases or with considerable uncertainty regarding the risk of developing RA were excluded. The patients were recruited at 14 university hospital rheumatology departments using several methods to contact patients and physicians in each region. The patients were treated and followed up by local office-based rheumatologists. In all, 813 patients were recruited from November 2002 to April 2005 and have been followed longitudinally since then, with visits every 6 months at one of the 14 participating hospital centers. Approval was obtained from the institutional review board of the Montpellier University Hospital, which was the coordinating center for this nationwide study. Prior to inclusion, all patients gave their written informed consent to participation in this prospective follow-up study.
- The *VErA cohort* (very early rheumatoid arthritis) prospectively included patients in two French regions, i.e., the entire province of Haute-Normandie and the metropolitan area of Amiens [15], from 1998 to 2002. The cohort is chiefly comprised of European Caucasians. General practitioners and office- and hospital-based rheumatologists from the two regions recruited patients with new-onset inflammatory arthritis. To maximize recruitment with the goal of obtaining a representative sample, a vast information campaign was conducted once a year via print media, radio, and television. Patients were required to have swelling of at least two joints persisting for $\geq 4$ weeks and $< 6$ months and no history of local or systemic glucocorticoid therapy or DMARD therapy. Exclusion criteria were inflammatory back pain, pregnancy, and breast-feeding. At baseline, several clinical and laboratory parameters were collected. The study was approved by the local ethics committee.
- The *Brittany cohort* comprises 270 patients from Brittany, France, with arthritis of less than 1 year's duration, who were included prospectively between 1995 and 1997 in seven hospitals in Brittany (France). The patients were referred by general practitioners and rheumatologists who had been informed of the study. After 2 years of follow-up [16], the patients were evaluated for RA, defined as having a diagnosis of RA made by an office-based rheumatologist and taking a DMARD or glucocorticoid. Median follow-up was 30 months. All patients in the cohort had synovitis in at least one joint at baseline. Inclusion criteria were age of 18 years or older, synovitis in at least one joint, absence of a previous diagnosis of joint disease, and disease duration no greater than 1 year. Patients were excluded if the medical history and the physical examination suggested septic arthritis or crystal-induced arthritis.

Thus, the ESPOIR cohort was comprised of patients with RA of less than 6 months' duration and the VErA and Brittany cohorts of patients with arthritis of less than 6 months' and 1 year's duration, respectively. Females predominated in the three cohorts. None of these three cohorts had entrance criteria, which specifically exclude subjects at greater risk for laboratory abnormalities.

Table 1 Inclusion Criteria and Patient Characteristics (Values are the Proportion or the Median (Range) at Baseline in the Three Cohorts (Espoir, VErA, and Brittany)

| | ESPOIR ($n$ = 813) | VErA ($n$ = 310) | Brittany ($n$ = 270) |
|---|---|---|---|
| Inclusion criteria | | | |
| Main characteristics | | | |
| Sex F/M (%) | 624/189 (77%) | 211/99 (68%) | 183/87 (68%) |
| Age (years) | | | |
| Inclusion criteria | 18–70 | ≥18 | ≥18 |
| Median (range) | 50 (17–72) | 52 (19–84) | 51 (375–1018) |
| Inclusion period | 2002–2005 | 1998–2002 | 1995–1997 |
| Disease duration | | | |
| Inclusion criteria | >6 weeks, <6 months | >4 weeks, <6 months | <1 year |
| DMARDs | | | |
| Inclusion criteria | No | No | Possible |
| Methotrexate | 0 | 0 | 5/270 |
| Biologics | 0 | 0 | 0 |
| Steroids | | | |
| Inclusion criteria | ±0 | 0 | Possible |
| Dosage (prednisone) | 0 | 0 | 2 (0–60) |
| Number of joints with arthritis | | | |
| Inclusion criteria | ≥2 | ≥2 | ≥1 |
| Swollen joints* | 6/28 (0–28) | 6/66 (0–58) | 2/44 (0–34) |

DMARD, disease-modifying antirheumatic drug.
*Joint synovitis were evaluated on 28 (DAS28), 66 (ACR), and 44 (DAS 44) sites for Espoir, VErA, and Brittany cohorts, respectively.

## Definition of Laboratory Abnormalities

Tests were not conducted at a central lab and so they represented the routine practice. The "normal range" of the tests was similar in all centers, and we used international criteria to define abnormal tests.

Anemia was defined according to the World Health Organization (WHO) as a hemoglobin (Hb) level < 12 g/dL in women and 13 g/dL in men [17,18]. Leukopenia was defined as fewer than 3500 leukocytes/mm$^3$, neutropenia as fewer than 1500 neutrophils/mm$^3$, and lymphopenia as fewer than 1000 lymphocytes/mm$^3$. Thrombocytopenia was a platelet count lesser than 150 000 per mm$^3$, and thrombocytosis was a platelet count greater than 400 000 per mm$^3$. Liver transaminase levels were considered abnormal if they were above the upper limit of the normal range (40 IU). Renal function was assessed using the Cockroft–Gault formula (glomerular filtration rate [GFR] in mL/min = $k \times (140-\text{age}) \cdot \text{body weight/serum creatinine}$ (in µmol/L), where $k$ = 1.04 in females and 1.23 in males) [19]. Renal function was categorized according to the National Kidney Foundation classification scheme as follows: severe dysfunction, GFR < 30 mL/min (Stage 4, GFR = 15−29 mL/min and Stage 5, GFR < 15 mL/min); moderate dysfunction (Stage 3), GFR = 30−59 mL/min; mild dysfunction (Stage 2), GFR = 60−89 mL/min; and normal function (Stage 1), GFR ≥ 90 mL/min [20,21].

## Criteria for Drug Contraindications

Among pretreatment laboratory tests for patients with early arthritis, the most often listed in recommendations issued in France, Europe, and the US (Table 2) are blood cell counts, AST and ALT levels, and serum creatinine. We defined laboratory test abnormalities based on these recommendations.

- French authorities recommend [6–8] decreasing the MTX dosage by half in patients with a creatinine clearance between 20 and 50 mL/min and state that MTX is contraindicated in patients with a creatinine clearance lower than 20 mL/min, a bilirubin level higher than 85.5 µmol/L, or transaminase levels greater than 2–3 times the upper limit of normal.
- European authorities recommend [9–11] the following laboratory tests before initiating MTX therapy: AST, ALT, serum albumin, complete blood cell counts, serum creatinine, serological tests for the HIV and hepatitis B and C viruses, fasting blood glucose, lipid profile, and pregnancy test. Available data suggest that an estimated creatinine clearance of less than 79 mL/min may increase severe (pulmonary) MTX toxicity and that hypoalbuminemia may be associated with MTX-induced thrombocytopenia, hepatotoxicity, and pulmonary toxicity [22–25]. Contraindications are significant renal disease, hepatic disorders, leukocyte counts below $3.0 \times 10^9$ per L, platelet counts below $100 \times 10^9$ per L, age greater

Table 2 Recommendation About Pretreatment Laboratory Tests for Patients with Early Arthritis Issued in the US, Europe, and France

| | USA | Europe | France | | | Publication |
|---|---|---|---|---|---|---|
| | ACR | EULAR | HAS | VIDAL | SFR | 3E |
| CBC | + | + | + | + | + | + |
| Creatinine | + | + | + | + | + | + |
| AST | + | + | + | | + | +/− |
| ALT | + | + | + | + | + | + |
| GGT | | | | | | |
| AlkP | | | | + | | +/− |
| Bilirubin | | | | + | | |
| Albumin | | + | | + | + | + |
| ESR/CRP | | | + | | | |

CBC, complete blood cell counts; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase: AlkP, alkaline phosphatase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

than 70 years, malignancy, pregnancy or inadequate contraception, history of alcohol or other substance abuse, acute or chronic infection, and pulmonary disease.

– The 2008 American College of Rheumatology guidelines [12] for patients being considered for MTX therapy initiation derive primarily from observational studies and, to a lesser degree, from randomized controlled trials. Contraindications to resuming or starting MTX therapy are a leukocyte count $<3000$ per $mm^3$ (with Felty's syndrome and large granular lymphocyte syndrome accompanying RA being possible exceptions to this contraindication), platelet count $<50\ 000$ per $mm^3$, history of myelodysplasia or lymphoproliferative disease diagnosed and/or treated within the last 5 years, creatinine clearance below 30 mL/min, AST or ALT level more than twice the upper limit of normal, and active acute or chronic viral hepatitis.

Of these three sets of recommendations, the most detailed are the ACR recommendations. We therefore used the ACR recommendations to define laboratory test abnormalities in the study patients.

## Statistical Analysis

Statistical tests were performed using the Statistical Package for the Social Sciences (SPSS 13.0, 2005, SPSS Inc, Chicago, USA). Quantitative variables are described as means ± standard deviation (excepted for the population description) and qualitative variables as number (%). To compare the distributions of laboratory test results between patients with and without RA after 2 years, we used the chi-square test (or the Fisher exact test, if appropriate) for qualitative variables and the Mann–Whitney test for quantitative variables.

# RESULTS

We evaluated data from 1393 patients (1018 women and 375 men). Table 3 summarizes the main results. Some patients did not have all tests, explaining the difference of denominator.

## Prevalence of Hematological Abnormalities

Of the 1366 patients, 363 (26.5%) had anemia. Significant differences ($P \leq 0.0001$) in the prevalence of anemia occurred across the three cohorts (240/809 [29.6%] in the ESPOIR cohort; 50/301 [16.6%] in the VErA cohort; and 73/256 [28.5%] in the Brittany cohort). Leukopenia was found in 18 (1.3%) of 1372 patients and neutropenia in 16 (1.4%) of 1102 patients, without significant differences across cohorts. Thrombocytopenia was noted in 13 (0.9%) of 1371 patients, with small but significant differences across cohorts (7/809 [0.8%] in ESPOIR, 2/301 [0.6%] in VErA, and 4/261 [1.5%] in Brittany; $P = 0.045$).

## Prevalence of Liver Abnormalities

AST and ALT levels were elevated in 48/1100 (4.3%) and 113/1103 (10%) patients, respectively. A value more than twice the upper limit of normal was noted for AST in 12 (1.48%) of 811 patients and for both AST and ALT levels in 2 (0.25%) of 811 patients.

## Prevalence of Renal Dysfunction

No patient had severe renal dysfunction. Prevalences were 5.5% (57/1019) for moderate renal dysfunction and 42.5% (434/1019) for mild renal dysfunction.

## Prevalence of Inflammation

The erythrocyte sedimentation rate (ESR) was increased in 50.4% (686/1361) of patients overall (ESPOIR, 52%; VErA, 43.8%; and Brittany, 53%), and the C-reactive

Table 3 Percentage Patients with Laboratory Test Abnormalities in Three Cohorts of Patients with Early Arthritis (Espoir, VErA, and Brittany)

| | ESPOIR | VErA | Brittany | Total | *P* value |
|---|---|---|---|---|---|
| Anemia | 240/809 (29.6%) | 50/301 (16.6%) | 73/256 (28.5%) | 363/1366 (26.6%) | $P \leq 0.0001$ |
| Leukopenia | 10/809 (1.23%) | 6/301 (1.99%) | 2/262 (0.76%) | 18/1372 (1.31%) | 0.42 |
| Leukocyte <3000 | 3/809 (0.37%) | 1/301 (0.33%) | 1/262 (0.38%) | 5/1372 (0.36%) | |
| Neutropenia | 15/803 (1.87%) | 1/299 (0.33%) | — | 16/1102 (1.45%) | 0.58 |
| Lymphopenia | 51/804 (6.34%) | 22/299 (7.36%) | — | 73/1103 (6.62%) | 0.55 |
| Thrombocytopenia | 7/809 (0.86%) | 2/301 (0.66%) | 4/261 (1.53%) | 13/1371 (0.95%) | 0.0045 |
| Thrombocytosis | 128/809 (15.8%) | 29/301 (9.63%) | 45/261 (17.2%) | 202/1371 (14.7%) | |
| Normal platelet count | 674/809 (83.3%) | 270/301 (89.7%) | 212/261 (81.2%) | 1156/1371 (84.3%) | |
| Platelet < 50 000 per $mm^3$ | 2/809 (0.25%) | 0 (0%) | 0 (0%) | 2/1371 (0.14%) | |
| Severe RD (Cl < 30) | 0 | — | 0 | 0 | 0.63 |
| Moderate RD (30–59.9) | 43/799 (5.38%) | | 14/220 (6.36%) | 57/1019 (5.59%) | |
| Mild RD (60–89.9) | 346/799 (43.3%) | | 88/220 (40%) | 434/1019 (42.6%) | |
| Normal renal function | 410/799 (51.3%) | | 118/220 (53.6%) | 528/1019 (51.8%) | |
| AST > N | 38/799 (4.75%) | 10/301 (3.32%) | — | 48/1100 (4.36%) | 0.40 |
| AST > 2N | 2/799 (0.25%) | 0/301 (0%) | | 2/1100 (0.18%) | |
| ALT > N | 81/802 (10.1%) | 32/301 (10.6%) | — | 113/1103 (10.2%) | 0.43 |
| AST > 2N | 11/802 (1.37%) | 4/301 (1.32%) | | 15/1103 (1.36%) | |
| ESR > 20 | 417/801 (52%) | 136/310 (43.8%) | 133/250 (53.2%) | 686/1361 (50.4%) | 0.031 |
| CRP > 6 | 523/779 (67.1%) | 167/310 (53.9%) | 157/261 (60.1%) | 847/1350 (62.7%) | $P < 0.0001$ |

RD, renal dysfunction; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

protein (CRP) level was increased in 62.7% (847/1350) of patients overall (ESPOIR, 67%; VErA, 53.8%; and Brittany, 60.1%). No significant differences in these prevalences were found across cohorts ($P = 0.031$ for ESR and $P < 0.001$ for CRP).

## Prevalence of Abnormalities Associated with NSAIDs

NSAID therapy was not significantly associated with anemia, liver function abnormalities, or renal dysfunction. The prevalence of anemia was 32.6% (122/374) in NSAID users and 26.6% (95/356) in nonusers ($P = 0.079$). Mean corpuscular volume was not statistically different between the two groups. Transaminase elevation was not significantly associated with NSAID use. Mild or moderate renal dysfunction was less common among NSAID users than among nonusers ($P = 0.048$).

## Prevalence of MTX Contraindication

Substantial proportions of patients of our cohorts have anemia (26.6%), mild or moderate renal dysfunction (48.2%), and liver dysfunction (Table 3). However, fewer than 2% of patients (22/1393 patients, 1.58%) have a contraindication to MTX therapy according to ACR recommendations (leukocyte count <3000 per $mm^3$: 5 patients [0.36%]; platelet count <50 000 per $mm^3$: 2 patients [0.14%]; creatinine clearance below 30 mL/min: 0%; and AST or ALT level more than twice the upper limit of normal: 15 patients [1.36%]).

## DISCUSSION

In our study of three cohorts of patients with early RA (ESPOIR) or early arthritis (VErA and Brittany), anemia was found in about one-quarter of the patients, with significant differences in prevalence across the three cohorts. The other two most common laboratory test abnormalities were transaminase elevation and GFR reduction to the range indicating mild or moderate renal dysfunction. NSAID therapy was associated with a nonsignificant increase in the prevalence of anemia and with significant decreases in the prevalences of mild and moderate renal dysfunction (Table 4).

Baseline data must be collected before MTX therapy initiation in patients with early arthritis to serve as a reference for monitoring the course of the disease and the

Table 4 Comparison of Patients Taking Nonsteroidal Anti-inflammatory Drugs and Other Patients in the ESPOIR Cohort

| | NSAID users *N* (%) | NSAID nonusers *N* (%) | *P* value |
|---|---|---|---|
| Anemia | 122/374 (32.6%) | 95/356 (26.6%) | 0.079 |
| Mean corpuscular volume ($\mu^3$) | 88.61 (5.09) | 88.71 (4.75) | 0.89 |
| Aspartate aminotransferase > *N* | 15/371 (4%) | 18/353 (5%) | 0.49 |
| Alanine aminotransferase > *N* | 40/372 (10.7%) | 34/353 (9.6%) | 0.61 |
| Severe renal dysfunction | 0 | 0 | 0.048 |
| Moderate renal dysfunction | 19/373 (5%) | 20/348 (5.7%) | |
| Mild renal dysfunction | 141/373 (37.8%) | 161/348 (46%) | |
| Normal renal function | 213/373 (57%) | 167/348 (48%) | |

effectiveness and safety of the treatments. More specifically, renal dysfunction may require dosage adjustments or contraindicate some medications [26,27]. Patients given drugs with a potential for bone marrow, kidney, or liver toxicity must be monitored and, when possible, must receive specific preventive measures, particularly if baseline function is abnormal. Although the nephrotoxicity of NSAIDs and high-dose methotrexate has been convincingly documented, the risk associated with low-dose MTX therapy for RA is unclear. Methotrexate can induce bone marrow suppression, adverse gastrointestinal effects, hepatotoxicity, and pneumonitis. Renal dysfunction and advanced age are considered major risk factors for MTX toxicity, although the available studies produced conflicting results. A case report describes severe side effects of low-dose MTX in a patient with end-stage kidney disease. There are 7 other reports of severe irreversible toxicity of low-dose MTX therapy [28–30].

Data on the prevalence of abnormalities in the organs targeted by drug toxicities are of interest in patients with early arthritis. More specifically, the proportion of patients with renal dysfunction contraindicating methotrexate or NSAID therapy constitutes an important information. The baseline characteristics of patients who subsequently experience treatment toxicities need to be determined. We evaluated three cohorts to determine whether the results of baseline laboratory tests varied with the cohort inclusion criteria.

MTX is myelotoxic, and complete blood cell counts must therefore be obtained before starting methotrexate therapy. Leukopenia and thrombocytopenia were uncommon in our study, whereas anemia was found in a substantial proportion of patients, particularly in the cohort with the longest disease duration. Anemia is chiefly due to inflammation in patients with arthritis, and inflammation-related anemia does not contradict any of the drugs used to treat arthritis. Therefore, we suggest performing a ferritin assay routinely to separate inflammation-related anemia from iron-deficiency anemia. In those RA patients with anemia of chronic disease, the best treatment is effective control of the joint disease, which is usually achieved with DMARDs and/or glucocorticoid therapy [31,32]. NSAIDs increase the hematological toxicity of MTX by displacing MTX from its binding protein. Consequently, some authors suggested in the past that NSAIDs should not be used in patients taking more than 15 mg of MTX per week [33]. Nevertheless, clinicians currently considered that there is an overestimation of adverse events of MTX [34], and most clinicians prescribe NSAID with MTX in RA irrespective of the dosage. Anemia due to gastrointestinal bleeding contraindicates NSAID therapy.

The recommended tests for detecting liver dysfunction are AST and ALT assays. AST and/or ALT values greater than twice the upper limit of normal are considered to contraindicate MTX therapy. In contrast, gamma-glutamyltransferase elevation does not contraindicate the use of methotrexate [35,36]. In a previous study, the ALT assay alone detected all cases of cytolysis [35]. Very few patients in our study had liver dysfunction contraindicating MTX therapy. NSAIDs can also cause cholestatic hepatitis, cytolysis, or both. Cholestatic hepatitis is usually due to an immunoallergic mechanism and generally resolves upon treatment withdrawal. However, cases of life-threatening systemic hypersensitivity reactions with a rash, blood disorders, and interstitial nephritis have been reported. Hepatic cytolysis, in contrast, is due chiefly to drug toxicity. Although serological tests for the hepatitis viruses B (HBV) and C (HCV) are recommended in patients with liver abnormalities, we previously reported low seroprevalences of HCV ($n = 7$; 0.86%) and HBV ($n = 1$; 0.12%) in the ESPOIR cohort. HCV-seropositive patients had significantly higher transaminase levels (ALT, 41.5 IU vs. 23.2 IU, $P = 0.02$; and AST, 39.2 IU vs. 21.8 IU, $P = 0.001$), but only 2 patients had AST or ALT level above 40 IU and the prevalence of hepatitis B and C viruses was not greater than expected based on the data from the general population in the same geographic area [37,38].

Renal dysfunction, one of risk factors for drug toxicity, is difficult to assess because the serum creatinine concentration and estimated GFR are sometimes inaccurately determined in elderly RA patients. Renal function is assessed using the Cockcroft–Gault (CG) formula or the abbreviated Modification of Diet in Renal Disease (aMDRD) formula. There is no evidence to date that one of these methods is better than the other in RA patients or

the general population. A single study compared the CG formula and the complete MDRD formula in patients with RA ($n = 33$) [26]. The results showed that the CG formula was better than the MDRD formula [26]. A study suggests that the need for dosage adjustment or for avoiding specific drugs because of renal dysfunction may be underestimated in clinical practice: half of the patients with renal dysfunction did not have appropriate methotrexate dosage adjustments [27]. In patients with renal dysfunction who are at high risk for drug toxicity, drug dosages should be adjusted based on the degree of renal dysfunction, and nephrotoxic drugs should be avoided whenever possible. Our finding that mild or moderate renal dysfunction was less common among NSAID users than among nonusers indicates appropriate patient selection for NSAID therapy: rheumatologists probably do not prescribe NSAIDs to patients with anemia or renal dysfunction. Use of the CG or MDRD formula is necessary to detect mild renal dysfunction, and methotrexate and NSAID dosages should be adjusted based on the degree of renal dysfunction. Severe renal dysfunction is rare in patients with early arthritis.

Thus, our study of three cohorts of patients with early arthritis indicates that, even when recommendations for MTX therapy are followed scrupulously, very few patients have contraindications to first-line MTX therapy.

We did not evaluate the outcome of our patients according to the treatment, but a previous study showed that MTX was associated with a high rate of continuation and few clinically significant laboratory abnormalities [39].

In conclusion, substantial proportions of patients with early arthritis have anemia (26.6 0%, with a nonsignificantly higher prevalence in patients with a history of NSAID therapy), mild or moderate renal dysfunction (48.2%), and liver dysfunction. However, fewer than 2% of patients have a contraindication to MTX therapy according to ACR recommendations.

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