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 ≥ 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.