Editorial

Étude et Suivi: Rheumatoid Arthritis in the 21st Century

For over 20 years much research in rheumatoid arthritis (RA) has focused on early identification and treatment of patients to prevent longterm joint damage, disability, and morbidity. A multitude of studies have demonstrated that early intervention improves outcomes, and in particular, treatment during the so-called "window of opportunity," when patients first develop inflammatory arthritis, may halt development of chronic symptoms altogether[1,2]. We have new classification criteria[3], developed specifically to aid early identification of patients who are likely to need disease-modifying therapy, and a host of new biologic drugs, in particular anti-tumor necrosis factor therapies, that have revolutionized our ability to suppress disease activity[4]. So how close are we to achieving the aims of longterm remission and minimal disability in clinical practice?

In this issue of *The Journal*, Combe, *et al* report on the 5 year outcomes of the well established French ESPOIR cohort[5]. The developers of the ESPOIR "*Étude et Suivi des POlyarthritis Indifferences Recentes*" cohort, established to study and monitor early undifferentiated polyarthritis, should be congratulated on establishing a large nationwide cohort of patients with early undifferentiated inflammatory arthritis, providing real-world data on the progression of RA over time. By monitoring patients seen in clinic at regular intervals for a prolonged period of time, important data on longterm outcomes and treatment relevant to the general RA population become available. The aim of the present study was to investigate clinical outcomes 5 years after inclusion, identify their predictors, and describe treatment strategies in the 21st century. As they acknowledge, the lack of a comparator cohort means interpretation of predictive properties of baseline characteristics is limited; however, they are able to describe the disease course of their cohort over the 5-year period.

The findings of Combe, *et al* are particularly interesting if set against the background of previous reports, in some of the older longitudinal cohort studies from the 1980s and 1990s. Wiles, *et al* reported on predictors of 5-year Health Assessment Questionnaire (HAQ) scores in patients recruited to the Norfolk Arthritis Register (NOAR) from 1990 to 1992[6]. After 5 years, median HAQ was 0.875, and 47% of the cohort had at least moderate disability, defined by HAQ score ≥ 1; in a study from Sweden by Lindqvist, *et al* started in 1985, HAQ scores increased throughout followup and at 5 years, median HAQ was 1.0[7]; similarly, after 12 years followup in a cohort from the 1980s at Leiden University Medical Center, median HAQ was 0.87[8]. By comparison, in the modern treatment setting of ESPOIR, HAQ scores decreased over time and after 5 years the median HAQ score was just 0.3. Notably, at inclusion to these various cohorts, including ESPOIR, levels of functional disability were remarkably similar, and if anything, patients in ESPOIR had higher levels of functional disability at baseline.

Similarly, radiographic progression in the first 3 years was mild in ESPOIR, with mean change in modified Sharp score (ShS) of 8.8, which barely exceeds the minimal clinically important difference score of 5 points[9]. By comparison, in a correspondingly large cohort of patients with early arthritis recruited to a clinical trial in The Netherlands in 1990, Hulsmans, *et al* found roughly 3 times that rate of progression in ShS, with mean rates of progression of 8.6 points per year[10].

One of the key changes in this century has been the availability of testing for anti-citrullinated protein antibodies (ACPA)[11]. Testing for these antibodies has allowed us to identify those patients with the worst prognosis, particularly with regard to the development of erosions[12]. Further, their ability to predict outcomes allows us to target appropriate treatment strategies in those patients who will benefit most[13], engendering the principles of stratified medicine. As a result they are included, and significantly weighted, in the 2010 American College of Rheumatology/European League Against Rheumatism (EULAR) classification criteria, which are set to become the 21st century definition of RA. These new criteria, designed specifically for application early in the disease, have been shown to perform better as a predictor of poor

See Outcome in early RA, *page 1650*

outcome than the previous criteria set[14], in terms of erosive disease[15], absence of drug-free remission[16], and mortality[17]. Because 82% of patients in ESPOIR with 5 years' followup met 2010 criteria at baseline, the outcomes in this cohort should be generalizable to the new RA definition, and relevant to future research and clinical practice.

Inception cohorts such as ESPOIR are uniquely placed to monitor whether therapeutic targets and strategies, and the subsequent consequences of these strategies, recommended in national and international guidelines are indeed incorporated into routine practice. In 2010, EULAR published 15 recommendations for the management of RA with synthetic and biological disease-modifying antirheumatic drugs (DMARD)[18]. The first 3 recommendations include: (1) treatment with synthetic DMARD should be started as soon as the diagnosis of RA is made; (2) treatment should be aimed at reaching a target of remission or low disease activity as soon as possible in every patient; and (3) methotrexate (MTX) should be part of first treatment strategy in patients with active RA. In ESPOIR, probably the most significant difference seen, which may be responsible for many of the improved outcomes demonstrated compared to older observational cohorts, is the frequency with which disease-modifying therapy is prescribed. After 5 years in the ESPOIR study, over 90% of patients had received DMARD, with most being treated with MTX. In contrast, by the same timepoint, only about 50% of patients in the NOAR group, recruited in the early 1990s, had ever received DMARD or steroid; and the drug of choice at that time was sulfasalazine. For many years, it has been argued that RA is becoming less severe, with evidence to support this dating back long before the introduction of early aggressive treatment strategies[19,20]. Nevertheless, the striking differences in disease progression and outcomes described in the ESPOIR cohort versus those from the 1980s and 1990s highlight the influence of changes in treatment guidelines.

Clearly, outcomes in RA are changing; whether this relates to the natural history of the disease or improved treatment strategies, it is important that we have contemporaneous descriptions of longterm outcomes with which to inform our clinical practice, and our patients.

JENNIFER H. HUMPHREYS, MBChB, MRCP;
SUZANNE M.M. VERSTAPPEN, PhD,
Arthritis Research UK Epidemiology Unit,
Manchester Academic Health Science Centre,
University of Manchester,
Oxford Road,
Manchester, UK

Address correspondence to Dr. Verstappen;
E-mail: suzanne.verstappen@manchester.ac.uk

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