Best Practice & Research Clinical Rheumatology 23 (2009) 13–24

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

2

# What have we learnt about the development and progression of early RA from RCTs?

David L. Scott, BSc, MD, FRCP Professor of Clinical Rheumatology *

*King's College School of Medicine, Weston Education Centre, King's College, London SE5 9RS, UK*

*Keywords:*
early rheumatoid arthritis
DMARD
randomized controlled trial
placebo-controlled trial

Most randomized controlled trials (RCTs) investigating the treatment of early rheumatoid arthritis (RA) use the core set of measures proposed by consensus meetings in the 1990s; these include tender and swollen joint counts, pain, global assessments, disability, and acute-phase responders such as the erythrocyte sedimentation rate (ESR). Trials in early RA generally assess three key outcomes based on this core data set: symptoms and signs of inflammatory arthritis, progression of disability, and erosive damage. Adverse events are also recorded. This chapter considers the lessons learned from the various trials in terms of benefits and adverse effects of different treatment regimens.



## Introduction

### *Initial trials*

It was little more than 30 years ago that randomized controlled trials (RCTs) started to examine the treatment of early RA. Although it is problematic crediting any one RCT as being the first to study early RA, the evidence points towards the trial by Dwosh et al acting as the forerunner of future research in the field [1]. In this RCT the effects of azathioprine were compared with those of gold and chloroquine in RA of <5 years' duration. Thirty-three patients were enrolled and randomized to receive azathioprine, gold or chloroquine. All groups showed similar changes over time. The following year Mäkisara et al[2] reported a series of 100 patients with RA of up to 3 years' duration that were treated for the first time with either penicillamine or gold for 12 months. Both groups improved by similar amounts.

These two studies, only one of which was a definite trial, set the scene for future research in this field. Their key characteristics were examining patients with up to 5 years' disease duration treated

* Tel.: +44 207 848 5215; Fax: +44 207 848 5202.
*E-mail address:* david.l.scott@kcl.ac.uk

1521-6942/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.berh.2008.12.009

with disease-modifying drugs for up to 12 months, during which time a variety of clinical outcomes was assessed. Over the years, the maximum disease duration has fallen, sometimes to no more than 12 months, and the numbers of patients have increased. However, the general ethos of the trials remains unchanged.

*Key outcomes*

The dominant focus of treatment is improving the symptoms of early RA. Initially trials used joint counts, the erythrocyte sedimentation rate (ESR), and measures such as grip strength. These have changed over time, but only marginally. Almost all RCTs now use the core set of measures proposed by consensus meetings in the 1990s. These include tender and swollen joint counts, pain, global assessments, disability, and the ESR or another acute-phase responder. American College of Rheumatology (ACR) responder rates or disease activity scores (DAS) are usually calculated from these.

In the main, trials in early RA assess three key outcomes based on the core data set. The first is the symptoms and signs of inflammatory arthritis, which are usually assessed by ACR responder rates or changes in DAS. The second is the progression of disability, which is usually assessed by changes in a self-assessed measure such as the health assessment questionnaire (HAQ). The third is erosive damage, which is usually assessed on x-rays and measured using a standardized scoring system such as the Sharp or Larsen scores.

In addition to these conventional outcomes, trials invariably record adverse events. These are described in detail but rarely quantified, making comparisons of trials more difficult. One approach used in a systematic review is to compare withdrawals due to lack of effect.

*Identifying trials*

There have been a number of systematic reviews that have dealt entirely or partially with early-RA patients treated with disease-modifying anti-rheumatic drugs (DMARDs), steroids or biologics, especially tumour necrosis factor (TNF) inhibitors [3–11]. These used broadly comparable search strategies to identify trials in Medline and other databases using terms such as early rheumatoid arthritis, randomized controlled trial, DMARD, and the names of individual drugs. We have followed this search strategy to identify trials for this review. We have also excluded trials that use drugs not available in Europe, studies that have no obvious control group, very small studies, and papers that were not written in English. We divided the studies into four broad groups: placebo-controlled trials of DMARDs, delayed treatment studies, comparator trials, and combination studies. We have used descriptive methods rather than formal meta-analyses to compare the results.

## Placebo-controlled trials of disease-modifying drugs

There have been seven placebo-controlled trials of disease-modifying drugs in early RA. These have involved oral gold [12], sulphasalazine [13–15] and hydroxychloroquine [16–18]. These trials, which enrolled 790 patients, are summarized in Table 1.

All seven trials show evidence of clinical benefits, assessed by higher falls in joint counts, ESR, or combined measures such as DAS with active treatment. Three trials evaluated falls in HAQ; two showed a significant difference, and one showed no effect. Four trials evaluated erosive damage; two showed a significant reduction, and two showed no effect. Figures 1 and 2 show the extent of changes attributable to active treatment for DAS, ESR, and erosive damage from one trial by Choy et al comparing sulphasalazine with diclofenac. In this study there were greater falls in DAS and ESR with sulphasalazine and less erosive damage. However, a substantial proportion of patients who received diclofenac alone showed good clinical responses and did not have any evidence of radiological progression.

One trial not included in Table 1 evaluated the effects of early treatment with glucocorticoids in patients not given immediate DMARDs [19]; it reported reduced erosive damage which persisted at follow-up [20]. In this study glucocorticoids acted as a DMARD.

There are two complexities in evaluating these trials. First, in the main the patients enrolled had mild disease. As a consequence the results potentially underestimate the efficacy of disease-modifying