Early rheumatoid arthritis in Finland

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ABSTRACT

The first Finnish early rheumatoid arthritis (RA) cohort was established in 1973-75 at the Rheumatism Foundation Hospital in Heinola, a hospital for rheumatic diseases only. Since then early RA cohorts for the purposes of longitudinal observation have been established at the Jyväskylä Central Hospital and Helsinki University Hospital. Furthermore, 199 patients with early RA were enrolled in a multicenter randomized controlled study in 1993-95. The primary observations from these cohorts are summarized in this essay.

The Rheumatism Foundation Hospital early RA cohort (the Heinola Cohort)

In 1973-75, a total of 442 patients with: (i) age ≥ 16 years; (ii) one or more swollen joints; and (iii) disease duration ≤ 6 months were referred to the Rheumatism Foundation Hospital in Heinola. Of these patients 121 (27%) subsequently met the 1987 ACR classification criteria for RA (1) and were included in a prospective cohort of patients with early RA (2). At the 8-year follow-up in 1982, a final group of 103 rheumatoid factor (RF) positive patients was formed (33 men and 70 women) (3). The patients were reviewed 1, 3, 8, 15, 20, and 25 years after enrollment.

The treatment strategy in the Heinola Cohort was "early and active". At the time of diagnosis which occurred within six months of the first joint symptoms, intra-muscular (im) gold was started in 56% of patients, chloroquine (CQ) in 36%, and D-penicillamine (DPA) in 2 patients. During the first year, all but one patient were taking disease-modifying antirheumatic drugs (DMARDs). However, most of the patients discontinued the DMARDs which were available at that time due to side effects or inefficacy. After 8 years only 30% of patients were taking im gold or DPA, and 70% were taking CQ or no DMARDs (4, 5). The Heinola Cohort was established during the time when a limited number of DMARDs was available. Therefore, although the treatment strategy was active in the beginning, long-term benefits were not great due to discontinuation of the drugs. In retrospect, the Heinola cohort appears to represent, by and large, the natural history of RF-positive RA.

The Heinola cohort did provide considerable information concerning RA over 25 years of observation. In early studies of the prognostic factors and diagnostic criteria of early RA (2, 3, 6, 7), it was recognized that early radiographic destruction, positive rheumatoid factor, decreased grip strength, anemia, a high erythrocyte sedimentation rate (ESR), and higher age at enrollment were significant predictors of joint destruction at 3 years. While it was also shown that radiographic destruction in the early stages of RA was strongly associated with persistent synovitis of the joint, it was concluded that "... the most essential point in preventing the progress of joint destruction in RA is to suppress the long-term activity of synovitis." (8)

At that time, amyloidosis was an important consequence of RA in Finland, as other Finnish studies indicated that renal amyloidosis contributed to 15% of deaths (9, 10). After 15 years reactive secondary amyloidosis (RSA) was found by subcutaneous fat biopsy in 6 of 74 surviving patients (8.1%) in the Heinola Cohort, and 5 of the 24 deceased patients had had RSA. The 15-year incidence of RSA was 10.9% (11), and the 20-year incidence was 13.6% (5). Greater disease activity was associated with development of amyloidosis. Three of 48 patients who were initially treated with intramuscular gold and 7 of 30 treated with CQ developed RSA ($p = 0.04$). This observation re-opened the discussion as to the value of early and active treatment for RA (11), as it

was also observed that long-term im gold treatment was associated with fewer deaths from amyloidosis, and overall greater survival compared to those who could not take im gold over long periods (12).

Long-term radiographic outcomes have been a special interest in the Heinola Cohort. Progression of radiographic damage was shown to be most rapid during the first years in RA (13-16). Kaarela and Kautiainen (17) showed that progression of radiographic damage does not level, but continues over 20 years; 36% of patients had a Larsen score of ≥ 50% of maximum at 20 years (5). Radiographic destruction and the need for surgery over 15 to 20 years has been described in the Heinola Cohort in the subtalar and ankle joints (18, 19), first carpometacarpal joint (20-22), hands (23-27), feet (28, 29), hip (30, 31), shoulder (32) including the acromioclavicular (33, 34) and subacromial joints (35), elbow (36-38) and glenohumeral joint (39-41), and the cervical spine (42, 43).

The disease was considered severe in 29% of the patients over 20 years. The definition of severe disease included a Larsen score of ≥ 67% of maximum or a Health Assessment Questionnaire (HAQ) score of 2-3 (range 0-3) or 3 large joint replacements (5). The cumulative work disability rate was 80% at 20 years. However, as many as 31% of the patients who were of working age had already stopped working due to RA one year after the onset of their disease (44).

The Jyäskylä Cohort

In 1983-85 and 1988-1989, 135 patients were entered into two early RA cohorts at Jyväskylä Central Hospital (45, 46). The patients were treated early and actively with available DMARDs, later termed the "sawtooth" strategy (47), and followed prospectively with regular clinical visits. The assessments included self-report questionnaires for functional capacity and pain, joint counts, laboratory tests for inflammation, and hand and foot radiographs every one or two years. Treatment with DMARDs, employment status of the patients, and deaths were recorded.

An initial study of the Jyväskylä Cohort, as in other early RA cohorts in Finland, involved the prediction of erosions. In studies using scintigraphic methods, all but one of 47 (of 387) joints that developed erosions at two years had bone scan activity (^{99m}Tecnetium methylene-diphosphonate) all three times over the first year of the disease, while repeatedly inactive joints by the bone scan did not develop erosions (48). Therefore, it was concluded that bone scan can be of value to predict erosions.

During 1401 person years of observation, 135 cohort patients had a total of 606 therapeutic segments with DMARDs or combinations with a goal of remission, including sulfasalazine (SSZ), methotrexate (MTX), im and per oral gold, azathioprine, DPA, hydroxychloroquine (HCQ), cyclosporin-A, cyclophosphamide, podofyllotoxin derivatives, and prednisolone. The serial and continual treatment with DMARDs and combinations was safe. Inefficacy or loss of efficacy was the primary reason for discontinuation of DMARDs or combinations. No single DMARD/combination stood out as substantially more favorable than the others with respect to inefficacy, toxicity or drug survival during the first ten years of the disease (49).

Radiographic scores of the hands and feet of the 85 RF positive Jyväskylä Cohort patients were compared to the radiographic scores of the earlier Heinola Cohort. The major difference between these cohorts was in the treatments: the Jyväskylä Cohort was treated with various DMARDs according to the "sawtooth" strategy, while a decade earlier the Heinola Cohort patients were treated with im gold and CQ, which were discontinued in most patients due to side effects or inefficacy, as noted above. Radiographic scores of the Jyväskylä Cohort progressed over 8 years, but remained at lower levels than those of the Heinola Cohort. The median Larsen score was 12% of the maximum in the Jyväskylä Cohort at 8 years compared to 26% of the maximum in the Heinola cohort (4). Persistent clinical synovitis predicted subsequent radiographic destruction (50), which confirmed the findings in the Heinola Cohort (8) that joint erosions do not appear randomly but are preceded by clinically detectable symptoms and signs of inflammation in individual joints.

Atlantoaxial subluxations were found in 14 (14%) patients, associated with older age at the baseline, greater disease activity over the first 5 years, and early erosiveness in the peripheral joints, similar to findings in the Helsinki Cohort (see below) (51). Patients who had 10% or more of maximum radiographic damage in the hands and feet according to the Larsen score at 5 years were 15.9 times more likely to develop atlantoaxial subluxations at 8-13 years compared to patients whose peripheral joint damage remained < 10% of maximum radiographic damage (52).

The patients' functional capacity was well preserved over 13 years. The mean Health Assessment Questionnaire (HAQ) score was 0.55 at 8.5 years, and 0.75 at 13 years, while in several historical control cohorts with a follow-up period of 5 years or more the mean HAQ scores exceeded 1.0 (53).

Despite preservation of functional capacity, 44% of the 82 patients who were gainfully employed at the time of diagnosis became work disabled during the first 10 years of RA. Almost 20% of these patients became work disabled during the first 2 years after diagnosis. These findings were slightly more favorable than previous observations concerning work disability in RA patients, with a work disability rate of 50-60% during the first 10 years of RA (54).

Twenty-five patients died during the observation period. The mortality rate of 1.28 (95%CI 0.83-1.89) was higher than that for the population in Central Finland at that time, but was not statistically significantly different from the general population (55).

Jyväskylä Central Hospital RA Database

Jyväskylä Central Hospital is the only rheumatology center in the Central Finland District and serves a population of

264,000. All new patients with RA have been referred to this center for diagnostic studies and initiation of therapy for more than two decades. All patients with RA who have been seen in Jyväskylä Central Hospital since 1993 have been entered into the Jyväskylä Central Hospital RA Database, which was established in 1995. Patient demographic data, disease characteristics, disease activity, functional capacity according to the HAQ, radiographs, joint surgery, co-morbidities, therapies with DMARDs, work status, and deaths are included in the database and updated regularly. More than 2000 patients with RA are included in the database, and new patients are included in an ongoing manner, including 90-120 new patients with early RA per year since 1997 with prospective monitoring.

Patients in the RA Database were compared to a random sample of 2000 people from the Central Finland District. The comparison showed that smoking is associated with increased RA risk in men (56), confirming observations of previous studies (57). RA was associated with a more than 7-fold risk of disability compared with that in a general population (58). Increased disease activity and pain, rather than structural joint damage were found to be associated with functional disability in patients with RA (59).

The Helsinki Cohort

The Helsinki Cohort includes 150 patients with early RA, 87 enrolled in 1986-89, and 63 enrolled in 1991-93 (60). All patients were treated actively according to the "sawtooth" strategy (47), and followed prospectively to evaluate outcomes of early RA. The clinical approach was to provide early, aggressive therapy in order to prevent joint damage, as first advocated by Luukkainen (61).

Early studies were concentrated on laboratory data. High levels of RF at baseline and persistent RF positivity during the follow-up, as well as high levels of serum hyaluronate were seen (62). Positivity for antikeratin antibodies (63) and aberrant blood polymorphonuclear cell functions (64) were also found to be associated with radiographic progression. In analyses of pooled data from the Helsinki Cohort and the Jyväskylä Cohort, it was shown that increased disease activity measured by the Mallya score (including morning stiffness, pain, grip strength, Ritchie index, hemoglobin, and ESR) at the baseline, and RF positivity at one year predicted more severe radiographic outcomes in 6 years (65).

The ACR classification criteria (1) for RA include one imaging criterion: radiographic changes of erosions or periarticular osteopenia in the hands and/or wrists. In addition to radiographs of the hands/wrists, radiographs of the feet are traditionally taken in RA patients in Finland, as erosions commonly are seen in the feet before the hands in patients with early RA. The sensitivity of the ACR radiographic criterion was examined (66) in the 78 Helsinki Cohort patients who had definite or classic RA according to the 1958 criteria (67). At baseline, 6% of patients had erosions in the hands only, 23% in the metatarsophalangeal joints (MTPs) only, and 5% in both the hands and feet. After 2 years, 3% had erosions in the hands only, and 29% in the MTP joints only. These observations suggest that radiographic evaluation of the feet should be included in the ACR criteria for RA (66), particularly as there have been similar observations in other studies (45, 68).

There exist conflicting reports concerning the associations of age and the course and outcomes of early RA (60). In the Helsinki Cohort, disease activity at the onset was higher in older versus younger patients (> 55 versus < 55 years). However, the clinical course and radiographic progression were similar in both age groups over 3 years. The sawtooth therapy was equally tolerated in both of the groups (60).

The effect of treatment was compared in patients with very early RA who had symptoms for 4 months or less versus patients with 4-24 months of symptoms before initiation of treatment. Patients with a short duration of symptoms had more active disease at the onset. Radiographic progression did not differ significantly in either group over 3 years (69).

A total of 102 patients were working at the time of the diagnosis of RA. The rate of permanent work disability due to RA was 6%, 11%, 22%, and 30% at 1, 3, 5, and 7 years, respectively (70). Twenty-four of 150 patients died over 7-14 years. Mortality did not differ statistically significantly from the mortality rates in the Finnish population (71).

The FIN-RACo study

Eighteen Finnish rheumatology clinics participated in an investigator-initiated multicenter randomized controlled trial entitled the Finnish RA Combination Therapy Trial (FIN-RACo study) (72), which was initiated in 1993-95 with the enrollment of 199 patients with early RA. The patients were assigned randomly to two treatment arms for two years: 97 received a combination of MTX + SSZ + HCQ + prednisolone, and 98 received single drug therapy with SSZ, which was later substituted with MTX in 51 patients.

The primary outcome measure of the FIN-RACo study was remission, rather than the 20% improvement in the American College of Rheumatology Core Data Set (ACR20) or Disease Activity Score (DAS), which are often used as outcome measures in clinical trials in patients with RA. Remission frequencies at 2 years were 37% in the combination group, and 18% in the single-drug group (p=0.003) (72). The frequency of remission in the combination group was similar in patients with a short (0-4 months) and a long (> 4 months) delay in the institution of the therapy, but major differences were found in the single-drug group. 35% of patients with a short (0-4 months) delay in the institution of therapy were in remission at 2 years, while only 11% of those with a long (>4 months) delay were in remission at 2 years in the single-drug group (p = 0.021) (73). In addition, it was found that none of the patients in the combination group had atlantoaxial subluxations, while 6 single-drug patients had atlantoaxial subluxations at 2 years (74). Preliminary reports concerning 5-year outcomes confirm the advantages of combination therapy seen after 2 years in those patients with early RA (75, 76).

Conclusion

The philosophy of early aggressive therapy for RA was first articulated in 1978 by Luukkainen *et al*. (61), who wrote "... In our opinion gold treatment ought to be started in the early stages of RA, before the development of erosions. We are treating not only the actual inflammation of the joints but also the quality of the patient's life for many decades in the future." This treatment approach resulted from clinical rheumatology research and clinical care of patients with rheumatic diseases since the foundation of the Finnish Heinola Rheumatism Foundation Hospital in 1951, and is continuing over decades in the Finnish rheumatology community.

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