Prognostic factors in rheumatoid arthritis

Thesis

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Translated by László Palkonyay M.D. and John Williams
**1. Introduction**

Rheumatoid arthritis (RA) is a lifelong disabling disease, leading to progressive joint damage and subsequent disability. RA shows a broad variety of courses and outcomes. A proportion of patients have an aggressive form of the disease and will experience severe restrictions in functional capacity during the natural course of the disease.

Drug therapy, including glucocorticoids and disease-modifying drugs (DMARDs), aims to delay joint damage, subsequent functional loss, and reduce mortality. However, several long-term studies have not been able to show any major benefits of the classical DMARD treatment. After a disease duration of 10 years, disability and mortality were not influenced. A 5 year study of these therapeutic interventions led to the same conclusion: the beneficial effects of treatment were only significant in the first years of the disease.

A characteristic title of a typical paper from this period is as follows: "Rheumatoid arthritis: disappointing long-term outcomes despite successful short-term clinical trials." (Pincus T., J. Clin. Epidemiol. 1988.)

In recent years, more aggressive treatment with DMARDs have been proposed for RA patients, as well as an early switch to biologic agents, if conventional DMARDs are not effective. This approach could be of value with respect to the long-term outcome. The choice and dosage of drug therapy is usually tailored to disease activity and to a set of prognostic factors that have been identified to predict outcome. As aggressive treatment might be necessary and beneficial only to a smaller proportion of patients with RA, it is desirable to find out predictive factors for the selection of patients for such therapies.

1.1. Clinical, serological, radiological predictive factors in RA:

The prognosis of a disease is defined as the prediction of an expected outcome. Outcome is affected usually by a set of patient, disease, environment and/or treatment related factors.

Several studies have documented the value of prognostic factors either for radiological damage and joint destruction, functional disability or death. The results of these studies show that functional limitation measured by the HAQ-score is directly associated with radiographic damage, work disability, joint replacement surgery and mortality. Longitudinal studies are available combining outcome domains. Van Zeben elucidated prognostic factors in relationship to several different outcome measures and found that the outcome of RA can be predicted by a combination of variables that are readily available in the clinical setting.

1.2. Late-onset RA

Several authors compared late-onset RA (LORA) and adult-onset RA (AORA) and the differences in the clinical presentation, course, laboratory values, and outcome of LORA versus AORA have...
been established. Other trials could not confirm these findings.

1.3. Radiology in RA

Persistent inflammation in RA inevitably leads to generally irreversible joint damage which can be monitored on X-rays. Today, abnormalities seen on radiographs are an important measure to assess the amount of damage at a certain point in time, cross-sectionally, or to assess progression over time, longitudinally.

Radiology was chosen as part of the core set of outcome measures for longitudinal observational studies. Radiology is also part of the WHO/ILAR (World Health Organization / International League of Associations for Rheumatology) required core set of measures for long-term clinical trials in outcome studies of RA. They are considered the gold standard for this purpose. New imaging techniques such as MR and US offer new possibilities for the early detection of morphological damage.

Today several scoring methods are available for the quantification of structural damage for RA and the choice among these methods seems to be rather arbitrary.

1.4. Depression in RA:

Cross-sectional studies have demonstrated the presence of depression and other psychiatric disturbances in RA. However, according to an important prospective study, depression scores are not higher and nor are depressive symptoms more common in patients with RA compared to other clinical patients.

In summary: as far as prognostic factors, the role of age, quantifying radiological methods and the psycho-social features of the disease are concerned the medical literature on early RA is full of controversy.

Based on this scientific background, our working hypotheses are as follows:

1. Within the group of patients suffering from early RA, individuals with an unfavourable outcome represent only a minor subgroup, but we do not have any quantitative data of this subgroup from the Central European region.

2. High-risk patients with a poor prognosis can be recognized early if we can find predictive clinical, laboratory or radiological factors.

3. Adult-onset RA (AORA) and late-onset RA (LORA) are different entities and therefore their therapy can differ.

4. Radiological methods and, first of all, quantification methods, are very important in predicting poor prognosis.

5. Psycho-social factors play an important role in early RA and have an impact on poor disease outcome.
2. The objectives of our trial are as follows:

1. For the first time in the Central European region within the group of early RA patients in order to determine the proportion of patients with poor prognosis a longitudinal cohort study was carried out. (The definition of poor prognosis will be summarized later.)
   To select the prognostic factors among clinical, serological, radiological, parameters.
2. To compare the clinical, functional, laboratory parameters including serum COMP and anti CCP-levels of patients with AORA and LORA respectively. 
3. To assess radiographic changes quantitatively in rheumatoid arthritis using the Larsen score and to follow the damage longitudinally.
4. To investigate the psycho-social features of early RA.

3. Summary of our trial in 4 chapters

This prospective multi-centre follow-up study was carried out in 7 rheumatological centres in Central Europe (Austria, Hungary, and Slovenia), in an outpatient setting. Four arthritis clinics and three rehabilitation units participated in the study. We followed a cohort of 172 patients with early RA fulfilling the ACR-criteria (first symptoms of RA within the last three years before enrollment) over three years to find out the proportion of patients with unfavourable outcome and the variables predicting poor outcome. The majority of the patients were Hungarian (46%).

Poor outcome was defined by the following items: significant deterioration of Health Assessment Questionnaire (HAQ) score, need for treatment with biologicals, cytotoxic drugs or corticosteroid pulse therapy, surgery of joints or tendons, death of the patient. All the patients were classified as having good outcome unless fulfilling one or more of these criteria.

The results are summarized in the following 4 chapters.

3.1. Clinical, serological, radiological predictive factors in RA

This study examined parameters determined in the first three years of disease and their efficacy in predicting outcomes. Our data are derived from subjects with a mean disease duration of 17 months.

It is the first time that a Central European population was the object of a longitudinal study assessing prognosis.

All patients were seen at intervals of six months at their centre, a total of 7 visits being scheduled. Every study visit included an interview and a thorough physical examination by an experienced rheumatologist, administering the Health Assessment Questionnaire (HAQ) and several laboratory tests. X-rays of the hands and feet were performed on the first and final visit. The follow-up period of 3 years was chosen because the observation time was suitable for the
assessment of long-term changes in RA (except mortality, which would have required a much longer observation period), and would minimize the number of drop-outs because of failure to co-operate. Readily available routine parameters: clinical (swollen joint count, tender joint count, global pain (visual analogue scale, VAS), global disease activity (physician’s assessment, VAS), global disease activity (overall patient’s assessment, VAS), surgery since last visit, concomitant diseases duration of morning stiffness, extra-articular manifestations, HAQ score, drug toxicities/adverse events, current drug therapy, number of involved joints within the first 6 months of the disease, laboratory parameters (ESR, CRP, IgM, IgG, and IgA RF), novel markers (COMP, a-CCP, HLA-status), in addition professional, socio-economic status, education level served as independent variables predicting outcome.

172 patients were eligible for statistical evaluation. According to our comprehensive definition of outcome 24.4% of the patients would have poor outcome. By using different statistical methods, such as stepwise discriminant analysis, (forward selection and backward elimination) analysis of variance with normalized rank-data, parameters (determined at visit 1) predictive of poor outcome were identified. The identified parameters allow the prediction of a more progressive course of the disease.

The chi² test could identify several single parameters significantly more frequently at visit 1 in patients with poor outcome.

Taking together the results of the statistical calculation methods, several of the prognostic factors could unequivocally be determined by all statistical methods, while some only by one method. We can conclude that IgG and IgM rheumatoid factor, COMP, HAQ-score, Larsen score of feet, DAS-score, ESR, swollen and tender joint counts predicted worse outcome. An association with the presence of IgA rheumatoid factor, a-CCP and Larsen score of hands could not be established. The cumulative presence of more than one parameter increases the probability of a worse prognosis. Extra-articular manifestations were not associated with worse outcome in our patients. The most obvious reason is the exclusion of rheumatoid nodules. Other extra-articular manifestations are features of longstanding RA and are therefore found rarely in an early arthritis cohort. Education, surprisingly, did not predict prognosis, in contrast to US data: and here the different social security systems may be a factor.

The value of COMP may be underestimated in our results because a significant percentage of our patients received glucocorticoids already at visit 1.

3.2. LORA versus AORA

In this study we compared late-onset with adult-onset rheumatoid arthritis (the cut-off point is 60
years of age). 58 patients with late-onset rheumatoid arthritis (LORA) were compared to 117 patients with adult-onset rheumatoid arthritis (AORA) with respect to clinical and functional parameters. Furthermore, in 104 patients serum cartilage oligomeric matrix protein (COMP) was measured. Results were compared by means of the ANOVA statistical test and possible influences of age, gender and clinical parameters were evaluated by Spearman rank correlation. Except for a different distribution in gender (40% males in the LORA group) and a higher ESR, no differences could be found with respect to clinical parameters. However, a significantly higher HAQ score and significantly higher serum-COMP levels were seen in the LORA group. HAQ scores correlated not only with the disease activity parameters (C-reactive protein, disease activity score) but also with age. Serum-COMP levels showed a correlation with age as well, but not with disease activity. It was concluded that the higher serum-COMP levels in late-onset rheumatoid arthritis could be due to concomitant osteoarthritic processes in larger joints, which are not symptomatic. The age dependence of the HAQ score is only weak, but may be the reason why patients with LORA show a worse functional capacity compared to patients with adult-onset rheumatoid arthritis. Our conclusion is that LORA and AORA are not different disease entities and that therefore their therapy can be the same.

3.3. Radiological investigations

There are several methods in the literature for the quantification of radiological damage in RA. In our international study on the prognostic factors we used the classic Larsen score which evaluates 40 areas in the hands and feet (LS40).

We present here a new, modified, short Larsen score method, which evaluates only 12 key areas in the hands and wrists (LS12). The 12 areas assessed in our study were the same as those suggested by Wolfe et al. (*J. Rheumatol, 2000*), with the exception of two. We omitted the first carpometacarpal area, which is often affected by osteoarthritis, and included the fourth MCP joint because for the reader of the radiographs it is convenient to evaluate the second to the fifth MCP joints.

In our cross-sectional analysis, 122 patients were randomly allocated to 2 groups: 64 in the first group and 58 in the second. We determined the mean value of LS 40 and LS 12 in both groups. Using the two-sample t test, we did not find a significant difference between the mean LS 40 of the first group and the mean LS 12 of the second group. In a longitudinal analysis the mean LS 40 and LS 12 at the baseline and after 3 years, progression and correlations were determined. There was a correlation between LS 40 and LS 12 longitudinally. The results show that LS 12 correlates strongly with LS 40 both in cross-sectional and longitudinal studies. Our conclusion is that the short Larsen score (LS 12) is effective when evaluating quantitatively radiological damage in RA.

3.4. Psycho-social aspects of RA
In our Austro-Hungarian comparative study we performed the first published transcultural cross-sectional and longitudinal study in the literature on depressive symptoms in RA. M. Kopp and her collaborators published the data of a representative survey of the Hungarian population, based on the examination of 12,000 people. In our trial we used their comprehensive method to detect psychosocial disturbances in early RA patients. In addition we used their data as controls. We compared the prevalence of depression between 55 Hungarian and 42 Austrian patients with RA, using the Beck Depression Inventory (BDI). The mean depression score was higher in the Hungarian patients when compared to the Austrian patients. Despite their geographical and cultural proximity, significant differences were detected between Austrian and Hungarian patients. Compared to representative national population data, mild symptoms of depression were detected in 73 Hungarian early RA patients, which was independent of corticosteroid use. In the Hungarian subgroup the BDI scores were found to be stable during the follow-up.

Longitudinally, there is a correlation between depression as measured by the BDI and the functional status of the patient as measured by HAQ, with exception of the baseline visit. (At the baseline visit the patients have still not been treated and the HAQ value is generally high.)

We could demonstrate that some of the conflicting results of the literature on the prevalence of depression in RA can be explained by problems of methodology. Studies assessing depression in RA patients must be compared to validated national data of the the population as a whole. The psychological and socio-economic characteristics of Hungarian patients were investigated by a large number of standardized tests developed for a national representative survey of the Hungarian population in 1995 to detect 17 conditions, including symptoms of depression, anxiety, vital exhaustion, ways of coping, neurotic disorder, personality characteristics, social and economic status. At the baseline visit the neurotic disorder as measured by one of these tests, the Juhász Neurosis Rating Scale, is strongly correlated to the HAQ values measured at the seventh visit and thus reflects the functional status after 3 years. This test is not validated outside Hungary, otherwise it could be used as a prognostic sign in early RA.

In order to measure the symptoms of depression as a relevant risk factor in RA, the validated BDI seems to be a reliable instrument.

Our study confirms that depression deserves more attention in the care of patients with RA.

4. Conclusions
1. According to our comprehensive definition of outcome, in the Central European region 24.4% of early RA patients can expect a poor outcome of the disease.
2. IgG and IgM rheumatoid factor, COMP, HAQ-score, Larsen score of feet, DAS-score, ESR,
swollen and tender joint counts predicted a worse outcome.

2. A comparison of patients with late-onset RA versus early onset RA did not reveal any significant differences. A significantly higher HAQ score and a significantly higher serum COMP-level in late-onset RA could be explained by concomitant osteoarthritis. LORA and AORA are not different disease entities and therefore the same therapies can be used.

3. For the first time in the literature we introduced a new modified short Larsen score (LS 12) based on the evaluation of 12 key areas in the hands and wrists. In the cross-sectional and longitudinal analysis we proved that the short Larsen score is effective when evaluating radiological damage in early RA.

4.1. In the first transcultural study in the literature we detected significant differences in the prevalence of depression between Austrian and Hungarian patients, despite the geographical and cultural proximity of the two populations.

4.2. Compared to representative national population data, mild symptoms of depression were detected in 73 Hungarian early RA patients, which was independent of corticosteroid use.

4.3. Longitudinally, there was a correlation between depression as measured by the BDI and the functional status of the patients as measured by HAQ.

4.4. We could demonstrate that some of the conflicting results of the literature concerning the prevalence of depression in RA can be explained by methodological problems.

4.5. At the baseline visit the neurotic disorder as measured by the Juhász Neurosis Rating Scale strongly correlated to the functional status after 3 years.

4.6. For measuring symptoms of depression as a relevant risk factor in RA, the validated BDI score seems to be a reliable instrument.

5. Publications of the author related to this topic


IF: 0,964


IF: 1,154


IF: 1,178


Abstracts of the author related to this topic


IF: 0,301


IF: 0,303


\textbf{IF: 0.541}


\textbf{IF: 1.968}


\textbf{IF: 2.444}


\textbf{IF: 3.436}