Early disease activity suppression and younger age predict excellent outcome of recent-onset rheumatoid arthritis patients treated with conventional disease-modifying anti-rheumatic drugs

I. Contreras-Yánez, M. Rull-Gabayet, V. Pascual-Ramos

Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México D.F., México.

Abstract

Objective

Sustained remission (SR) is the target of treatment offered to patients with rheumatoid arthritis (RA). The objective of the present paper is to describe predictors of favourable outcomes in a cohort of early RA patients.

Methods

Data from 89 patients with 3 years of consecutive assessments and traditional treatment were analysed. SR was defined as ≥6 consecutive months with 2011 ACR/EULAR remission criteria. Excellent outcome (EO) was defined according to patient's perception. Descriptive statistics, logistic regression models and Cox regression were used.

Results

At baseline, patients were predominantly females (n=78), had rheumatoid factor (n=70) and (mean±SD) age of 38.8±13.6 years. After (mean±SD) 37.1±2.5 months, 75 patients achieved ≥1 SR state and 35 an EO. The former had lower disease activity, disability and comorbidity and better functional status at baseline than their counterparts (p≤0.05); they also accumulated lesser disability (p≤0.03). Lower C-reactive protein and disease activity and lesser comorbidity predict SR (p≤0.04). Patients with EO were younger, better educated, had lower disease activity, better functional status and lesser comorbidity at baseline than their counterparts (p≤0.05). They achieved a first sustained remission state (p≤0.001) sooner and accumulated lesser disability and incident erosive disease (p≤0.002). Younger age and lower disease activity were prognosticators of EO (p≤0.02). When age, baseline disease activity and time to first SR were investigated as predictors of EO, younger age (HR:0.95, 95% CI: 0.91–0.98, p=0.003) and earlier SR (HR:0.49, 95% CI: 0.39–0.61, p≤0.001) were relevant.

Conclusion

Younger patients with lower disease activity achieved earlier SR which, in addition to age, was predictor of EO.

Key words

rheumatoid arthritis, outcome and process assessment, remission induction

Irazú Contreras-Yánez
Marina Rull-Gabayet, MD
Virginia Pascual-Ramos, MD

Please address correspondence and reprint requests to:
Virginia Pascual-Ramos, MD,
Department of Immunology and Rheumatology,
Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán,
Vasco de Quiroga 15, Sección XVI,
14000 Tlalpan, México.
E-mail: virtichu@gmail.com

Received on May 31, 2011; accepted in revised form on October 27, 2011.

Competing interests: none declared.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that often causes joint destruction and disability (1). The severity of cases has diminished during recent decades due to an earlier diagnosis and a more aggressive treatment with disease-modifying anti-rheumatic drugs (DMARDs) (2-5). Follow-up procedures recommended for patients include disease activity, disability and therapeutic response assessments. Furthermore, in light of recent therapeutic advances, a remission-like state has now become the ultimate goal of treatment (6-8). Various definitions for remission have been proposed (9-14). Moreover, remission can be defined in terms of a specific date or in terms of a period. Thus, the proportion of patients classified as being in remission varies depending on the definition applied (15). There is no validated definition for sustained remission, which is the most clinically desirable state.

In the literature, there are few reports on variables associated with excellent outcomes. Known variables are the absence of rheumatoid factor (RF) (16), male sex (17), lower clinical and serologic markers of disease activity (18, 19), low baseline health assessment questionnaire (HAQ) score (18, 19), treatment strategy (8, 20-24), good response to treatment with DMARDs (22) and completion of first treatment (25). A better understanding of variables that favour remission may help to identify patients who are candidates for particular therapeutic strategies and follow-ups. Even more, predictors should be investigated in real clinical settings where "unselected" patients are also represented.

Our primary purpose was to describe the frequency and baseline predictors of favourable outcomes at three years of follow-up in a cohort of early rheumatoid arthritis patients treated with conventional DMARDs. Sustained remission (SR) and excellent outcome (EO) were the two end-points evaluated (see definitions below).

Material and methods

Study population

The Early Arthritis Clinic of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, a referral centere for rheumatic diseases in México City, was established in February 2004. Patients with disease duration of less than a year and with RA attend the clinic. They are evaluated every 2 months during the first two years of follow-up and thereafter every 2, 4 or 6 months according to patients' and disease characteristics.

Up to September 2010, 139 consecutive patients had been referred to the clinic by their primary care physician. Ten patients were not enrolled because a different diagnosis was established. Additionally, 31 patients with early RA had insufficient scheduled follow-up (less than 3 years) and 9 were lost to follow-up within the first 3 years. Finally, data from 89 patients who had early disease and at least 3 years of follow-up were analysed and their baseline characteristics did not differ from the 9 patients lost to follow-up. Eighty-five (96%) met at least 4 of the American College of Rheumatology 1987 revised criteria for the classification of RA (26).

Clinical evaluations

Standard baseline and consecutive evaluations were performed by the same rheumatologist and included at least 66 swollen and 68 tender joint counts, a physician-filled visual analogue scale (VAS) for overall disease activity, erythrocyte sedimentation rate (ESR) determination by Westergren and C-reactive protein (CRP) determination by nephelometry. Treatment (corticosteroids, DMARDs and other drugs) and comorbidity were recorded. At baseline, a complete medical history and sociodemographic characteristics were obtained and RF and antibodies to cyclic-citrullinated peptides (a-CCP) determined by nephelometry and second generation ELISA, respectively.

At baseline and consecutive evaluations, patient-reported outcomes were assessed and included at least the HAQ (27), two 100 mm patient-VAS, one for pain and one for overall disease activity and the Medical Outcomes Study Short Form 36 (SF-36) (28). In addition, Disease activity score, 28 joints evaluated (DAS28) was scored (29).

Radiographic evaluation

Digitised images of radiographs of the hands and feet were scheduled at baseline and yearly thereafter. Radiographs were read in chronological order by a radiologist and a rheumatologist. RA was classified as erosive (at least one unequivocal cortical bone defect or break) or as non-erosive by both physicians. Disagreement in classification was resolved by consensus.

Definitions

Sustained remission (SR)

At least 6 months (3 consecutive visits at two months apart) with scores on the 28 tender joint counts, 28 swollen joint counts, CRP (in mg/dL) and patient overall disease activity assessment, all ≤1 (14). When patients never achieved at least one sustained remission period they were defined has having "persistent disease activity" (PDA).

Excellent outcome (EO)

It was defined on the basis of patient's perception. We first identified patients whose mean of 3 years-follow-up consecutive overall disease activity-VAS was ≤1 mm (0–10 scale) and found 57 patients. We then calculated their (mean±SD) months of follow-up in remission (continuous or interrupted), 22.4±8.8 months, which correspond to a "proportion of their entire follow-up in remission" of 60±23%. EO was defined when patients achieved ≥ 60% of their follow-up in remission.

Statistics

Student *t*-test, one-way ANOVA and χ^2 were used for normally distributed variables and Mann-Whitney U-test for non-normally distributed variables.

In order to summarise disability over follow-up, mean of consecutive HAQ scores from corresponding evaluations was calculated.

The extent that patients achieved SR as the number of SR states (if any) achieved, the duration of each SR state and the length of time in remission (interrupted or not) for the entire follow-up were determined. SR duration was calculated for each SR state as months from first to last consecutive remission state defined by the American College of Rheumatology (ACR) / European League against Rheumatism (EULAR) remission criteria (14). The duration of remission during the 3-year follow-up was calculated as the sum of the duration of individual remission states. Finally, the proportion of time in remission was calculated for each patient, as the ratio of sum of months in remission and months of follow-up.

To identify baseline predictors of outcomes, logistic regression models were used. We selected either achieving at least one SR state or achieving an EO as dependent variables. Those variables bivariately showing a significance level of $p \leq 0.05$ were included in a regression model. The full multivariate model was reduced by stepwise removal of baseline variables with a significance level of $p \leq 0.05$. Correlation between variables was also analysed.

Finally, a multivariate Cox proportional hazard model was constructed. The dependant variable was patient achieving EO. Variables entered in the multivariate model were age when entering the clinic, baseline DAS28 and months to first SR state.

All statistical tests were 2-sided and evaluated at the 0.05 significance level. Statistical analysis was performed using the SPSS/PC programme (v.12.0; Chicago, IL, USA).

Ethics

The study was conducted according to the guidelines of the Declaration of Helsinski. The appropriate ethical approval was granted from the Institutional Review board of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán and written informed consent was obtained from each patient.

Results

Characteristics of the early RA population

Information from 89 early RA patients is summarised in Table I. At baseline, most of the patients were middle-aged female, with early and active disease and serum autoantibodies. Their (mean±SD) follow-up up to the end of the study was of 37.1±2.5 months. Twenty-six patients (29.2%) had been prescribed corticosteroids and 34 (38.2%) DMARDs by their primary care physician.

During the study period, 75 patients (84.3%) achieved at least one period of SR, meanwhile 14 (15.7%) had persistent disease activity. Time to achieve the first sustained remission state was of (mean±SD) 13.6±8.8 months and it was maintained for (mean±SD) 19.6±10.7 months. Forty-seven patients (62.7%) achieved one SR state, 26 patients (34.7%) 2 SR periods and 2 patients (2.7%) 3 periods of SR.

Thirty-five patients from the entire cohort (39.3%) achieved an EO.

Predictors associated to sustained remission

Table I shows baseline differences within patients who achieved at least one SR period and their counterparts. The former had lower clinical and serological disease activity, they had lower disability and a poorer health-related quality of life (according to SF-36) than persistently active patients. Persistently active patients accumulated more comorbidity/patient than their counterparts.

To identify baseline predictors of SR, a logistic regression model was applied. Variables entered into the model were DAS28 (highly correlated to physician-VAS, Spearman's Rho of 0.8, $p \leq 0.001$), SF-36 mental sub-score, HAQ (highly correlated to SF-36 physical subcore, Spearman's Rho of -0.8, $p \leq 0.001$), CRP (highly correlated to ESR, Spearman's Rho of 0.8, $p=0.001$) and number of comorbidity/patient. Lower DAS28 (OR:0.43, 95% CI: 0.2–0.9, $p=0.02$), lower CRP (OR:0.74, 95% CI: 0.6–0.9, $p=0.04$) and lower number of comorbidity/patient (OR:0.37, 95% CI: 0.2–0.8, $p=0.01$) were prognosticators of achieving at least one SR state.

We investigate sustained remission as an extended concept. Patients with SR had lesser deterioration in physical function than their counterparts ([mean±SD] HAQ over follow-up was of 0.20±0.19 *vs*. 0.47±0.38, $p=0.001$). Also, 20 out of 71 patients ([21.1%], 4 patients had erosive disease at baseline) who achieved at least one SR state developed incident erosions at 3 years *vs*. 7 out of 13 patients with PDA ([54%], 1 patient had erosive disease at baseline, $p=0.1$).

Table I. Baseline characteristics of the study population and comparison of patients and disease characteristics among patients who achieved at least one sustained remission state (SRS) and patients with persistent disease activity (PDA).

Baseline characteristics*	Study population n=89*	Patients with ≥1 SRS n=75*	Patients with PDA n=14*	*p*-value
Age, years	38.8 ± 13.6	38.8 ± 13.2	38.6 ± 16	1
♀ Gender, n (%)	78 (87.6)	67 (89.3)	11 (78.6)	0.4
Years of scholarship	10.8 ± 3.8	10.9 ± 3.9	10.6 ± 3	0.78
Disease duration, months	5.2 ± 2.7	5.2 ± 2.7	4.9 ± 2.7	0.69
n of ACR 1987 RA criteria	5.2 ± 1	5.2 ± 1	5.6 ± 0.8	0.15
n of patients with RF, (%)	70 (78.7)	57 (76)	13 (93)	0.29
n of patients with a-CCP, (%)	65 (73.9)**	53 (71.6)**	12 (85.7)	0.34
n of patients with RF and a-CCP, (%)	59 (67)**	48 (64.9)**	11 (78.6)	0.37
n of patients with erosions, (%)	5 (5.6)	4 (5.3)	1 (7.1)	0.58
DAS28	6.1 ± 1.4	5.9 ± 1.3	7.2 ± 1.1	**0.001**
Physician-VAS, mm	45.1 ± 21.8	42 ± 20.1	61.5 ± 23.9	**0.002**
RADAI	5.5 ± 2.2	5.3 ± 2.2§	6.6 ± 2‡	0.08
Patient pain-VAS, mm	60.2 ± 26	58.3 ± 26.2	70 ± 22.7	0.12
Patient overall disease-VAS, mm	62 ± 27.7	60.3 ± 27.7	70.9 ± 26.6	0.19
SF-36 mental sub-score	42.2 ± 21	44.2 ± 21.8	31.6 ± 12.4	**0.005**
SF-36 physical sub-core	33 ± 18.2	34.8 ± 18.8	23.3 ± 10.7	**0.003**
HAQ	1.5 ± 0.9	1.4 ± 0.9	2 ± 0.8	**0.03**
ESR, mm/H	31.1 ± 22.6	28.9 ± 22	42.8± 22.5	**0.03**
CRP, mg/Dl	2 ± 2.5	1.6 ± 2	4.1 ± 3.8	**0.03**
n of comorbidity/patient	0.7 ± 0.9	0.6 ± 0.9	1.1 ± 1.2	**0.05**
n (%) of patients with corticosteroids	26 (29.2)	23 (30.7)	6 (42.9)	0.37
n (%) of patients with DMARDs	34 (38.2)	29 (38.7)	5 (35.7)	1

*Data correspond to variable at baseline and are presented as mean±SD unless otherwise indicated.
**One missing baseline value; §five missing baseline values; ‡one missing baseline value.
ACR: American College of Rheumatology; RA: reumatoid arthritis; RF: rheumatoid factor; a-CCP: antibodies to cyclic citrullinated peptides; DAS28: disease activity score, 28 joints evaluated; VAS: visual analogue scale; RADAI: rheumatoid arthritis disease activity index; SF-36: medical outcomes study short form 36; HAQ: health assessment questionnaire; ESR: erythrocyte sedimentation rate; CRP: C reactive protein; DMARDs: disease-modifying anti-rheumatic drugs.

Predictors associated to excellent outcome

Thirty-five patients achieved an excellent outcome. Their characteristics were compared to their counterparts and are summarised in Table II: patients with EO were significantly younger and better educated, had a lower baseline disease activity and a better health-related quality of life and lesser comorbity/patient.

To identify baseline prognosticators of EO, the following variables were entered into a logistic regression model: age when entering the clinic, years of scholarship, DAS28 at baseline (highly correlated to SF-36 score, Spearman's Rho of -0.74, $p \leq 0.001$), ESR and number of comorbidity/patient. Younger age (OR:0.93, 95%CI: 0.8–0.9, $p=0.002$) and lower DAS28 (OR:0.64, 95%CI: 0.44–0.90, $p=0.02$) were both predictors of EO.

Patients with EO achieved a first remission state sooner (6.9±3.3 months *vs*. 23.7±10, $p \leq 0.001$) and their first remission state was maintained longer (23.7±9.7 months *vs*. 9.5±5 months, $p=\leq 0.001$) than their counterparts. The relationship between age when entering the clinic, baseline DAS28 and early sustained remission achievement (as defined within the first year of follow-up = dependent variable) was investigated using a logistic regression analysis. Both, younger age (OR:0.95, 95% CI: 0.91–0.99, $p=006$) and lower DAS28 (OR:0.6, 95% CI: 0.42–0.87, $p \leq 0.007$) were predictors of early SR achievement.

Finally, the potential role of age, baseline DAS28 and time of first SR state as predictors of an excellent outcome were investigated using a Cox regression analysis. Younger age (HR:0.95, 95% CI: 0.91–0.98, $p=0.003$) and earlier SR achievement (HR:0.49, 95% CI: 0.39–0.61, $p \leq 0.001$) were associated to EO (dependant variable).

Patients with EO had lower disability during and at last follow-up than their counterparts [(mean±SD) HAQ: 0.13±0.08 *vs*. 0.31±0.29, $p \leq 0.001$ and 0.06±0.15 *vs*. 0.21±0.44, $p=0.03$, respectively). Also they developed lesser frequently incident erosive disease at 3 years: 12% *vs*. 45%, $p=0.002$.

Description of treatment during follow-up

On entering the clinic, DMARDs were prescribed to all the patients and the median±SD of DMARDs/patients was of 2±0.7. In addition, 29 patients (32.6%) were receiving corticosteroids. At the last evaluation, 31 patients (34.8%) were taking corticosteroids, 86 (97%) were taking DMARDs and the median±SD of DMARDs/patients was of 2.1±0.9, (Table III). The most frequent DMARD combination was methotrexate, sulphasalazine and chloroquine/hydroxychloroquine. Only three patients received biologics at some point during their follow-up.

Patients who achieved at least one SR state received similar treatment with DMARDs than their counterparts (Table III). Patients with SR received corticosteroids less frequently during their follow-up (Table III). Treatment among patients with and without excellent outcome was also compared showing that, patients with EO had fewer DMARDs at last follow-up and lower (mean±SD) accumulated number of DMARDs/patient (data not shown).

Discussion

Our study showed that a substantial proportion of early RA patients who received treatment with DMARDs achieved at least one sustained remission state. We defined disease remission according to the ACR/EULAR remission criteria (14). The criteria are considered stringent but achievable and were selected as they represent a consensus remission definition which can provide a uniform approach to assess remission. The criteria were designed for use in clinical trials, although their utility in real-life clinical settings had been encouraged to be examined. In the literature, percentage of early RA patients who achieve remission due to traditional DMARDs institution is

Table II. Comparison between patients who achieved or not an excellent outcome during their 3 years of follow-up.

Baseline variables*	Patients with an excellent outcome n=35*	Patients without an excellent outcome n=54*	*p*-value
Age, years	33.1 ± 9.7	42.5 ± 14.5	**0.001**
♀ Gender, n (%)	32 (91.4)	46 (85.2)	0.52
Years of scholarship	12.1 ± 3.8	10 ± 3.6	**0.01**
Disease duration, months	5.3 ± 2.7	5.1 ± 2.7	0.8
n of ACR 1987 RA criteria	5.1 ± 1	5.3 ± 1	0.5
n of patients with RF, (%)	26 (74.3)	44 (81.5)	0.4
n of patients with a-CCP, (%)	24 (68.6)	41 (77.4)**	0.5
n of patients with RF and a-CCP, (%)	22 (62.9)	37 (69.8)**	0.6
n of patients with erosions, (%)	2 (5.7)	3 (5.6)	1
DAS28	5.7 ± 1.5	6.4 ± 1.2	**0.03**
Physician-VAS	40.7.1 ± 19.4	47.9 ± 22.9	0.1
RADAI	5.5 ± 2.3§	5.5 ± 2.1‡	0.9
Patient pain-VAS, mm	58.3 ± 29.9	60.8 ± 24.7	0.7
Patient overall disease-VAS, mm	59.6 ± 28.9	60.5 ± 24.1	0.9
SF-36 score	42 ± 21.4	32.9 ± 14.4	**0.003**
HAQ	1.4 ± 0.9	1.6 ± 0.9	0.4
ESR, mm/H	25.3 ± 20.1	34.8 ± 23.5	**0.05**
CRP, mg/Dl	1.4 ± 1.9	2.4 ± 2.8	0.09
n of comorbidity/patient	0.4 ± 0.5	0.9 ± 1.1	**0.02**

*Data correspond to variable at baseline and are presented as mean±SD unless otherwise indicated; **one missing baseline value; §two missing values; ‡four missing values.
ACR: American College of Rheumatology; RA: rheumatoid arthritis; RF: rheumatoid factor; a-CCP: antibodies to cyclic citrullinated peptides; DAS28: disease activity score, 28 joints evaluated; VAS: visual analogue scale; RADAI: rheumatoid arthritis disease activity index; SF-36: medical outcomes study short form 36; HAQ: health assessment questionnaire; ESR: erythrocyte sedimentation rate; CRP: C reactive protein.

Table III. Disease treatment during follow-up among groups of patients defined according to outcome.

	Study population n=89*	Patients with ≥1 remission state n=75*	Persistently active patients n=14*	*p*-value
n (%) patients with baseline CTs	29 (32.6)	23 (30.7)	6 (42.9)	0.37
(Mean±SD) baseline DMARDs/patient	2 ± 0.7	1.9 ± 0.7	2.2 ± 0.6	0.12
n (%) patients with CTs at last follow-up	31 (34.8)	21 (28)	10 (71.4)	**0.004**
(Mean±SD) DMARDs/patient at last follow-up	2.1 ± 0.9	2 ± 0.9	2.4 ± 0.9	0.24
n (%) patients with CTs during follow-up	37 (41.6%)	28 (37.3)	9 (64.3)	0.08
(Mean±SD) DMARDs/patient during follow-up	2.5 ± 0.7	2.5 ± 0.7	2.6 ± 0.6	0.6

*Data presented as (mean±SD) unless otherwise indicated.
n: number; CTs: corticosteroids; DMARDs: disease modifying anti-rheumatic drugs.

highly variable, ranging from 15 to 69% and the studies cannot be compared because the definition and criteria of remission used are not uniform (19, 30-36).

We included "sustainability" in the remission definition as it is considered the most desirable state. SR has also been a matter of interest and the literature reports that its frequency ranges from 16% to 51% (37-39). Differences are explained because of the lack of a validated definition. In our study, both, sustained remission and excellent outcome, translated into lesser disability and structural damage, which evidence that definitions used represent that current and extended concept of remission.

Lower baseline CRP and DAS28 and lesser comorbidity were associated to a higher probability of achieving a SR state. Also, younger age and lower baseline DAS28 were associated to an earlier first remission state which ultimately was a predictor of excellent outcome. Schipper *et al*. (40) analysed data from an inception cohort of RA patients. They defined SR according to the DAS and if lasting at least 6 months. Fifty-two percent of their patients achieved remission and 36% achieved SR. Male gender, younger age and low DAS at baseline were predictive to reach remission rapidly, and a shorter time to remission was the only determinant to SR. Verstappen *et al*. (22) studied the frequency and duration of remission from 562 patients conventionally treated with recent-onset RA. Thirty-six percent of them achieved at least one period of remission. Predictors of remission were good response to treatment, less pain, absence of rheumatoid factor and lower joint score. Other authors have identified various factors at the onset of the disease that are associated to remission, including absence of RF (16), low clinical and serological disease activity (18, 19), age (41), gender (17, 18, 41) and low HAQ (16, 18, 19). In addition, specific therapeutic regimens have been identified as optimal to achieve better individual responses and remission rates (8, 15, 20, 21, 23- 25, 32-36). It will be inappropriate and was not the intent of the present study to analyse the impact of treatment on remission.

Limitations of our study include the following. We arbitrarily chose a 6-month lag time to meet the definition of "sustained" remission, because the FDA requires that an ACR 70 response be maintained for at least six months before a patient is considered to have achieved a major clinical response (13). Nonetheless, our rate of SR was consistent with rates reported in the literature in related studies (30-33, 40). We defined excellent outcome based on patient's perception. Patients-reported outcomes have been shown to be as effective as the traditional physician- and laboratory-reported outcomes in reflecting long-term morbidity (42). Additionally, in a study which included patients with similar demography, disease characteristics and treatment, patients-reported health-related quality of life improved early in the disease

course, remain favourable for longer follow-up and were longitudinally associated to improvements in disease activity and function (43). We showed that early response to treatment was a main determinant to maintain an EO, but we were unable to define the optimum treatment. Most of our patients were receiving aggressive and tight treatment with combined DMARDs and the effect of particular therapeutic regimens could not be analysed. In addition, this is a cohort study which by definition is vulnerable to treatment selection bias. There were baseline differences in disease activity within patients with favourable and unfavourable outcomes, and these could explain why patients with persistent disease activity received a more intensive treatment as reflected by corticosteroids use. We applied regression analysis and included treatment as confounder, which is a statistical strategy to deal with confounding. Structure is an important dimension of the concept of remission and is not included in the definition used. It could be argued that those patients with excellent outcome who developed incident erosive disease should be reclassified. Nonetheless, patients with better outcomes had lesser disability and radiographic progression, as it has recently been confirmed (44). In addition, radiologic progression occurs in relation to disease activity, but persistent remission may not fully be protective (45, 46). We did not use any scoring validated method to quantify structural damage, but frequency and times of radiographic assessments were standardised. Finally, remission might not only be dependent on baseline characteristics and initial treatment, but also on other variables relevant over longstanding follow-up (46-48).

In conclusion, RA treatment should be directed to achieve a rapid and sustained response as it predicts, along with younger age, a longstanding excellent outcome. Accordingly, we need to focus on identifying treatment strategies that may target early remission. Lasting remission translates into better outcomes and can be achieved with traditional DMARDs in a substantial proportion of patients whose conditions reflect those of daily medical practice. Higher clinical and serological disease activity and comorbidity at baseline may identify patients at risk of deleterious outcomes.

References

1. WELSING PM, VAN GESTEL AM, SWINKELS HL, KIEMENEY LA, VAN RIEL PL: The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. *Arthritis Rheum* 2001; 44: 2009-17.
2. WELSING PM, FRANSEN J, VAN RIEL PL: Is the disease course of rheumatoid arthritis becoming milder? Time trends since 1985 in an inception cohort of early rheumatoid arthritis. *Arthritis Rheum* 2005; 52: 2616-24.
3. KRISHNAN E, FRIES JK: Reduction in long-term disability in rheumatoid arthritis from 1977 to 1998: a longitudinal study of 3035 patients. *Am J Med* 2003; 115: 371-6.
4. KREMERS HM, NICOLA P, CROWSON CS, O´FALLON WM, GABRIEL SE: Therapeutic strategies in rheumatoid arthritis over a 40-year period. *J Rheumatol* 2004; 31: 2366-73.
5. IRVINE S, MUNRO R, PORTER D: Early referral, diagnosis and treatment of rheumatoid arthritis: evidence for changing medical practice. *Ann Rheum Dis* 1999; 58: 510-3.
6. PAULUS HE: Defining remission in rheumatoid arthritis: what is it? Does it matter? *J Rheumatol* 2004; 31: 1-4.
7. EMERY P, SALMON M: Early rheumatoid arthritis: time to aim for remission? *Ann Rheum Dis* 1995; 54: 944-7.
8. GRIGOR C, CAPELL H, STIRLING A *et al*.: Effect of treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomized controlled trial. *Lancet* 2004; 364: 263-9.
9. PINALS RS, MASI AT, LARSEN RA, and THE SUBCOMMITTEE FOR CRITERIA OF REMISSION IN RHEUMATOID ARTHRITIS OF THE AMERICAN RHEUMATISM ASSOCIATION DIAGNOSTIC AND THERAPEUTIC CRITERIA COMMITTEE: Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum* 1981; 24: 1308-15.
10. PREVOO ML, VAN'T HOF MA, KUPER HH, VAN LEEUWEN MA, VAN DE PUTTE LB, VAN RIEL PL: Modified disease activity scores that includes twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 44-8.
11. ALETAHA D, WARD MM, MACHOLD KP, NELL VP, STAMM T, SMOLEN JS: Remission and active disease in rheumatoid arthritis. Defining criteria for disease activity states. *Arthritis Rheum* 2005; 52: 2625-36.
12. VAN DER HEIJDE DM: Radiographic imaging: the "gold standard" for assessment of disease progression in rheumatoid arthritis. *Rheumatology* (Oxford) 2000; 39 (Suppl.1): 9-16.
13. FDA. Rheumatology Working Group of the Medical Policy Coordinating Committee (MPCC) of the Center for Drug Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH). Guidance for industry: clinical development programs for drugs, devices, and biologics products for the treatment of rheumatoid arthritis (RA), 1999. http://www.fda-gov/cder/guidance/1208fnl.pdf. (accessed 3 August 2005).
14. FELSON DT, SMOLEN JS, WELLS G *et al*.: American College of Rheumatology/European League against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis* 2011; 70: 404-13.
15. MÄKINEN H, HANNONEN P, SOKKA T: Definitions of remission for rheumatoid arthritis and review of selected clinical cohorts and randomised clinical trials for the rate of remission. *Clin Exp Rheumatol* 2006; 24 (Suppl. 43): S22-28.
16. EBERHARDT K, FEX E: Clinical course and remission rate in patients with early rheumatoid arthritis: relationship to outcome after 5 years. *Br J Rheumatol* 1998; 37: 1324-9.
17. FORSLIND K, HAFSTROM I, AHLMEN M, SVENSSON B: Sex- a major predictor of remission in early rheumatoid arthritis? *Ann Rheum Dis* 2007; 64: 46-52.
18. GOSSEC L, DOUGADOS M, GOUPILLE P *et al*.: Prognostic factors for remission in early rheumatoid arthritis: a multiparameter prospective study. *Ann Rheum Dis* 2004; 63: 675-80.
19. SVENSSON B, SCHAUFELBERGER C, TELEMAN A, THEANDER J: Remission and response to early treatment of RA assessed by the Disease Activity Score. *Rheumatol* 2000; 39: 1031-6.
20. SVENSSON B, BOONEN A, ALBERTSSON K, VAN DER HEIJDE D, KELLER C, HAFSTRÖM, FOR THE BARFOT STUDY GROUP: Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate. A two year randomized trial. *Arthritis Rheum* 2005; 52: 3360-70.
21. GOEKOOP-RUITERMAN YPM, DE VRIES-BOUWSTRA JK, ALLAART CF *et al*.: Cinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt Study). A Randomized Controlled Trial. *Arthritis Rheum* 2005; 52: 3381-90.
22. VERSTAPPEN SM, VAN ALBADA-KUIPERS GA, BIJLSMA JW, BLAAUW AA, SCHENK Y, HAANEN HC *et al*.; and on behalf of THE UTRECHT RHEUMATOID ARTHRITIS COHORT STUDY GROUP (SRU): A good response to early DMARDs treatment of patients with rheumatoid arthritis in the first year predicts remission during follow-up. *Ann Rheum Dis* 2005; 64: 38-43.
23. JACOBS J, VAN EVERDINGEN AA, VERSTAPPEN SM, BIJLSMA JW: Follow-up radiophraphic data on patients with rheumatoid arthritis who participated in a two-year trial of prednisone therapy or placebo. *Arthritis Rheum* 2006; 54: 1422-8.
24. SOKKA T, MAKINEN H, PUOLAKKA K, MOTTONEN T, HANNONEN P: Remission as the treatment goal – the FIN-RACo trial. *Clin Exp Rheumatol* 2006; 24 (Suppl. 43): S74-6.
25. SVENSSON B, AHLMÉN M, FORSLIND K,

for the BARFOT STUDY GROUP: Treatment of early RA in clinical practice: a comparative study of two different DMARD/corticosteroid options. *Clin Exp Rheumatol* 2003; 21: 327-32.
26. ARNETT FC, EDWORTHY SM, BLOCK DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
27. RAMEY DR, RAYNAULD JP, FRIES JF: The health assessment questionnaire 1992; status and review. *Arthritis Care Res* 1992; 5: 119-29.
28. KOSINSKI M, KELLER SD, WARE JE JR, HATOUM HT, KONG SX: The SF-36 Health Survey as a generic outcome measure in clinical trials of patients with osteoarthritis and rheumatoid arthritis: Relative validity of scales in relation to clinical measures of arthritis severity. *Med Care* 1999; 37: MS23-29.
29. PREVOO ML, VAN'T HOF MA, KUPER HH, VAN LEEUWEN MA, VAN DE PUTTE LB, VAN RIEL PL: Modified disease activity scores that includes twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 44-8.
30. MAKINEN H, KAUTIAINEN H, HANNONEN P, SOKKA T: Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? *Ann Rheum Dis* 2005; 64: 1410-3.
31. SOKKA T, HETLAND ML, MÄKINEN H *et al*.: Remission and Rheumatoid arthritis. Data on patients receiving usual care in twenty-four countries. *Arthritis Rheum* 2008; 58: 2642-51.
32. ST CLAIR EW, VAN DER HEIJDE DM, SMOLEN JS *et al*.: Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a ramdomized, controlled trial. *Arthritis Rheum* 2004; 50: 3432-43.
33. BREEDVELD FC, WEISMAN MH, KAVANAUGH AF *et al*.: The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early aggressive rheumatoid arthritis who had not have previous methotrexate treatment. *Arthritis Rheum* 2006; 54: 26-37.
34. MÖTTÖNEN T, HANNONEN P, LEIRISALO-REPO M *et al*.; AND THE FIN-RACO TRIAL GROUP: Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. *Lancet* 1999; 353: 1568-73.
35. HAFSTRÖM I, ALBERTSSON K, BOONEN A, VAN DER HEIJDE D, LANDEWÉ R, SVENSSON B; BARFOT STUDY GROUP: Remission achieved after 2 years treatment with low-dose prednisolone in addition to disease-modifying anti-rheumatic drugs in early rheumatoid arthritis is associated with reduced joint destruction still present after 4 years: an open two years continuation study. *Ann Rheum Dis* 2009; 68: 508-13.
36. HENRIQUE DA MOTA LM, MAGALHÃES LAURINDO IM, FREIRE DE CARVALHO JF, LUIZ DOS SANTOS NETO L: Prognostic evaluation of early rheumatoid arthritis. *Swiss Med Wkly* 2010; 140: w13100.
37. MÄKINEN H, KAUTIAINEN H, HANNONEN P *et al*.: Combination of traditional disease modifying drugs in early rheumatoid arthritis is associated with sustained remission and reduced radiographic progression. *J Rheumatol* 2007; 34: 316-21.
38. COHEN G, GOSSEC L, DOUGADOS M *et al*.: Radiological damage in patients with rheumatoid arthritis on sustained remission. *Ann Rheum Dis* 2007; 66: 358-63.
39. MACHOLD KP, STAMM TA, NELL VPK *et al*.: Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease. *Rheumatology* 2007; 46: 342-9.
40. SCHIPPER LG, FRANSEN J, A DEN BROEDER A, VAN RIEL PLCM: Time to achieve remission determines time to be in remission. *Arthritis Res The* 2010; 12: R97.
41. WOLFE F, HAWLEY DJ: Remission in rheumatoid arthritis. *J Rheumatol* 1985; 12: 245-52.
42. SANDERSON T, KIRWAN J: Patient-reported outcomes of arthritis: time to focus on personal life impact measures? *Editorial Arthritis Rheum* 2009; 61: 1-3.
43. UUTELA T, HANNONEN P, KAUTIAINEN H, HAKALA M, HÄKKINEN A: Sustained improvement of health-related quality of life in patients with early rheumatoid arthritis: A ten-year follow-up study. *Clin Exp Rheumatol* 2011; 29: 65-71.
44. VAN TUYL LHD, FELSON DT, WELLS G, SMOLEN J, ZHANG B and BOERS M FOR THE AMERICAN COLLEGE OF RHEUMATOLOGY AND THE EUROPEAN LEAGUE AGAINST RHEUMATISM COMMITTEE TO DEFINE REMISSION FOR CLINICAL TRIALS: Evidence for predictive validity of remission on long-term outcome in rheumatoid arthritis: a systematic review. *Arthritis Rheum* 2010; 62: 108-17.
45. MOLENAAR ET, VOSKUYL AE, DINANT HJ, BEZEMER PD, BOERS M, DIJKMANS BA: Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. *Arthritis Rheum* 2004; 50: 36-42.
46. MARKATSELI TE, PAPAGORAS C, DROSOS A: Prognostic factors for erosive rheumatoid arthritis. *Clin Exp Rheumatol* 2010; 28: 114-23.
47. PASCUAL RAMOS V, CONTRERAS-YÁÑEZ I, VILLA AR, CABIEDES J, RULL-GABAYET: Medication persistence over two years of follow-up in a cohort of early rheumatoid arthritis patients: associated factors and relationship with disease activity and disability. *Arthritis Res Ther* 2009; 11: R26.
48. CONTRERAS-YÁÑEZ I, CABIEDES J, VILLA AR, RULL-GABAYET M, PASCUAL-RAMOS V: Persistence on therapy is a major determinant of patient-, physician-, and laboratory-reported outcomes in recent-onset rheumatoid arthritis patients. *Clin Exp Rheumatol* 2010; 28: 748-51.