Outcome of Patients with Rheumatoid Arthritis: Cross-Sectional Study of a Single-Center Real-World Inception Cohort

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ABSTRACT: **Background:** Tight control of disease activity is the recommended target of therapy for rheumatoid arthritis (RA).

Objectives: To determine the outcome of RA with respect to disease activity and the rate of remission, as measured by the DAS-28, in a real-world inception cohort.

Methods: We conducted an observational cross-sectional study of a single-center real-world inception cohort of 101 consecutive patients being treated for RA in 2009–2010 in a rheumatology outpatient clinic. Patients were managed at the discretion of the attending rheumatologist with the goal of achieving remission. DAS-28 scores were calculated and analyzed by clinical and treatment variables derived from the medical files.

Results: Mean patient age was 58.6 ± 13.4 years and mean duration of disease 10.7 ± 7.9 years. Disease remission (DAS-28 ‹ 2.6) was achieved in 26.7% of patients and low disease activity (› 2 .6 DAS-28 ‹ 3.2) in 17%. Monotherapy with a conventional disease-modifying anti-rheumatic drug (C-DMARD, 21% of patients at last follow-up) was associated with a significantly lower mean DAS-28 score and C-reactive protein level than combined C-DMARD treatment (79% of patients), and with shorter disease duration than combined treatment with C-DMARDs or C-DMARD(s)+biological DMARD (40% of patients). Rheumatoid factor and anti-cyclic citrullinated peptide positivity had no effect on DAS-28 scores. Time from diagnosis was inversely correlated with DAS-28 scores.

Conclusions: The achievement of low disease activity and remission in a significant portion of our inception cohort of patients with RA suggests that the treat-to-target strategy is feasible and effective in routine clinical practice.

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KEY WORDS: treat-to-target, rheumatoid arthritis (RA), DAS-28, remission, disease-modifying anti-rheumatic drugs (DMARDs)

Rheumatoid arthritis is an autoimmune inflammatory erosive joint disease. Early and aggressive therapy using medication with proven efficacy and safety is the mainstay of the evidence-based approach to treatment. The conventional disease-modifying anti-rheumatic drugs in use for the last two decades – which include methotrexate, hydroxychloroquine, sulfasalazine and leflunomide – have been associated with substantial amelioration of symptoms and lower work disability and mortality rates [1-5]. However, not all patients achieve a good response and the result is disease progression. In 1998, biologic therapy with tumor necrosis factor-alpha blockers was introduced to achieve better control of RA activity. This was followed by other biological DMARDs targeting different pathways in the inflammatory process. For example, abatacept targets cytotoxic T lymphocyte-associated antigen 4, rituximab acts by depleting CD20+ B lymphocytes, and tocilizumab blocks interleukin-6 receptor. The promising efficacy and safety results for DMARDs in several randomized controlled studies [5-10] paved the way for the development of treatment guidelines by the American College of Rheumatology and the European League Against Rheumatism [10,11]. Both groups emphasized the importance of early and intensive treatment with C-DMARDs and B-DMARDs to halt signs and symptoms and minimize damage. Based on the body of clinical and observational drug and strategy trials [8-11], an international task force formulated treat-to-target recommendations for achieving sustained disease remission or at least a low disease activity state [13].

The DAS-28 (Disease Activity Score, using 28 joint counts) is a validated instrument for the assessment of RA activity. It combines the number of swollen and tender joints, levels of inflammatory markers, namely C-reactive protein and erythrocyte sedimentation rate, and the patient's subjective assessment of his/her global health rated on a Visual Analog Scale of 0 to 100 [12]. A DAS-28 score of < 2.6 implies RA remission, < 3.2 implies low disease activity, while > 5.1 implies very active disease.

The aim of the present study was to determine the outcome of rheumatoid arthritis with respect to disease activity and the

RA = rheumatoid arthritis
DMARDs = disease-modifying anti-rheumatic drugs
C-DMARDS = conventional DMARDs
B-DMARDs = biological DMARDs

rate of disease remission, as measured by the DAS-28, in a "real-world" inception cohort of established RA routinely followed in our clinic.

PATIENTS AND METHODS

An observational cross-sectional study design was used. The study sample consisted of patients receiving treatment for RA during the period 1 January 2009 to 31 December 2010 at the Rheumatology Unit of Rabin Medical Center, a university-affiliated tertiary hospital in central Israel. The diagnosis in all cases was based on the American College of Rheumatology criteria (1987). We included only patients who were diagnosed with RA at the beginning of or within one year prior to their first consultation at our clinic and who remained under continuous follow-up thereafter. The patients were managed at the discretion of the attending physician. The study was approved by the Institutional Review Board, with waiver of informed consent.

The patients' medical records (written and electronic) were analyzed for the following parameters: age at diagnosis, gender, ethnicity (Jewish or Arab), serum CRP level and ESR at diagnosis and last visit, rheumatoid factor and anti-cyclic citrullinated peptide seropositivity, type and duration of DMARD use, and the interval from diagnosis to initiation of treatment with a B-DMARD.

Disease activity at the last visit was determined by global physician assessment, and the CRP and ESR values were compared with those at diagnosis. The DAS-28 was scored for each patient (using ESR or CRP) and the results were defined as follows: remission (score < 2.6), low disease activity (score 2.6 to < 5.1) and very active disease (score > 5.1). The DAS-28 findings were analyzed by background and treatment variables.

At the time of the DAS-28 assessment (2009 through 2010) all prescriptions in Israel of all C-DMARDs and of three TNFα inhibitors (infliximab, etanercept, adalimumab) as well as rituximab were covered by the National Health Insurance. This included TNF inhibitors for patients whose disease remained active despite treatment with three C-DMARDs, and rituximab for patients whose disease remained active despite treatment with a TNFα inhibitor or who had a contraindication or intolerance for TNF inhibitors. Abatacept and tocilizumab were not approved in Israel for the treatment of RA at the time of the study.

Statistical analysis was performed using SPSS software (version 18). Student's two-tailed *t*-test was used for comparison of the data. A *P* value of 0.05 or less was considered statistically significant.

CRP = C-reactive protein
ESR = erythrocyte sedimentation rate
TNFα = tumor necrosis factor-alpha

RESULTS

PATIENT CHARACTERISTICS

The study group comprised 101 patients. Mean age at diagnosis (initial visit to the Rheumatology Unit) was 58.6 ± 13.4 years (range 26–79 years) and mean disease duration was 10.7 ± 7.9 years (range 0.5–30 years). Seventy-three percent of the patients were female; almost all (97%) were Jewish.

DISEASE CHARACTERISTICS

The baseline characteristics of our cohort are depicted in Table 1. A total of 75.1% of patients (75/99) were RF positive and 73% (46/63) were anti-CCP antibody positive; 3.2% of the 63 patients tested for both factors were anti-CCP antibody positive and RF negative.

Mean serum CRP level was 2.5 ± 2.9 mg/dl (range 0.1–27) at diagnosis (n=65) and 1.4 ± 2.3 mg/dl (range 0.08–16) at the last visit (n=88). Corresponding values for mean ESR were 49.56 ± 32.11 mm/hr (n=85) and 44.38 ± 29.04 mm/hr (n=91), range 0–143 and 4–120 mm/hr, respectively.

TREATMENT MODALITIES

All patients were treated with at least one C-DMARD during follow-up: at the last visit 21% of patients (n=21) were receiving one C-DMARD (methotrexate, hydroxychloroquine, or sulfasalazine), and 79% (n=80) were receiving a combination of two or more. As depicted in Table 2, the patients who were on a combination C-DMARD therapy had significantly longer disease duration, a higher CRP level and more active disease at the last study visit. Forty-one patients (40%) were treated with B-DMARDs frequently together with methotrexate and/or other C-DMARDs: most of our patients were treated with a TNF inhibitor (63.4%) and the rest with rituximab (36.6%). The time from diagnosis to initiation of a B-DMARD was 2.6 ± 0.9 years in patients diagnosed within 5 years preceding the study period and 13.1 ± 5.8 years for patients diagnosed 15–20 years prior to the study period. This difference was statistically significant ($P = 0.002$).

CCP = anti-cyclic citrullinated peptide
RF = rheumatoid factor

Table 1. Baseline characteristics of an inception cohort of 101 patients with rheumatoid arthritis

Age (yr) (mean ± SD)	58.6 ± 13.4
Duration of disease (yr) (mean ± SD)	10.7 ± 7.9
ESR at diagnosis (mm/hr) (mean ± SD)	49.56 ± 32.11
CRP at diagnosis (mg/dl) (mean ± SD)	2.5 ± 2.9
RF positive (% of tested, n)	75.1% (n=75)
Anti-CCP positive (% of tested, n)	73% (n=46)

ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, RF = rheumatoid factor, anti-CCP = anti-cyclic citrullinated peptide antibody

Table 2. Disease characteristics of patients treated with one C-DMARD compared to patients treated with a combination of C-DMARDs

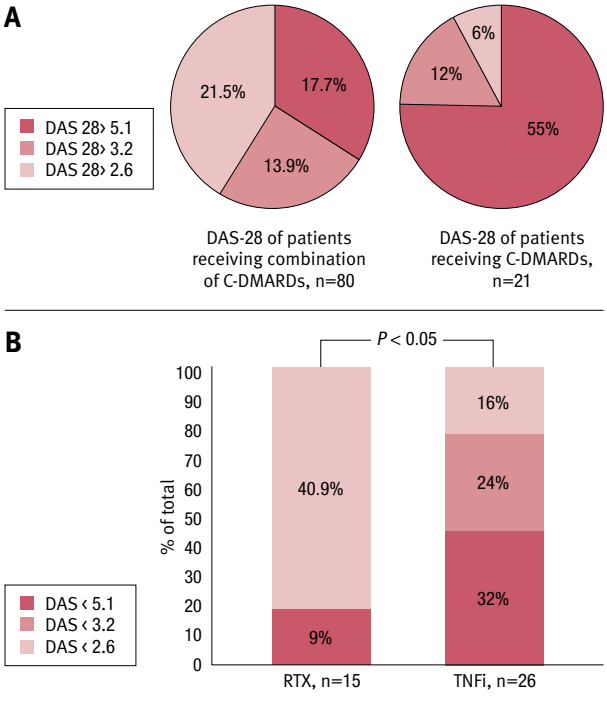
	C-DMARD monotherapy	Combination of C-DMARDs	*P* value
Age (yr) (mean ± SD)	60.7 ± 12.9	58.05 ± 13.6	NS
Duration of disease (yr) (mean ± SD)	5.5 ± 6.14	12 ± 9 .01	‹ 0.05
CRP at diagnosis (mg/dl) (mean ± SD)	3.9 ± 14.1	5.62 ± 16.5	‹0.05
CRP at last visit (mg/dl) (mean ± SD)	1.2 ± 1.7	1.98 ± 5.95	‹0.05
% RF positive (n tested)	65 (n=20)	63 (n=80)	NS
% CCP positive (n tested)	73.3 (n=15)	72.9 (n=48)	NS
DAS-28 at last visit (mean ± SD)	2.5 ± 1.2	3.9 ± 1.52	‹ 0.001

Table 3. Patients' characteristics according to disease activity score at the last visit

	Responders (DAS-28 ‹ 3.2) (n=44)	Non-responders (DAS-28 › 3.2) (n=57)	*P* value
Age (yr) (mean ± SD)	58.7 ± 14.4	58.5 ± 12.7	NS
Duration of disease (yr) (mean ± SD)	8.77 ± 7.5	12.3 ± 7.9	0.02
CRP at first visit (mg/dl) (mean ± SD)	2.14 ± 3.33	1.52 ± 1.89	NS
ESR at first visit (mm/hr) (mean ± SD)	45.1 ± 29.2	54.3 ± 34.3	NS
RF positivity % (n of tested)	68.1% (30 of 44)	77.1% (44 of 57)	NS
CCP positivity % (n of tested)	66.6% (22 of 33)	64% (22 of 34)	NS
B-DMARD treatment at last visit	36% (n=16)	43.8% (n=25)	NS

NS = not statistically significant, B-DMARD = biological disease-modifying anti-rheumatic drugs

Figure 1. [A] Patients treated with only one C-DMARD during the entire follow-up period had lower DAS-28 at the last visit than those treated with a combination of C-DMARDs, 2.5 ± 1.2 vs. 3.9 ±1.52, respectively, *P* ‹ 0.001. **[B]** Patients treated with TNF-inhibitors had less active disease than patients treated with rituximab (DAS-28 3.6 ± 1.76 vs. 4.7 ± 1.79, *P* ‹ 0.05, respectively).



DISEASE OUTCOME

Disease remission or low disease activity was achieved in 43% of the inception cohort at the time of the last study visit. Disease remission (DAS-28 < 2 .6) was documented in 26.7% of patients (n=27), and another 17% (n=17) had low disease activity (2.6 < DAS-28 < 3.2). Among the remaining patients, 40% (n=40) had active disease at the last follow-up (3.2 < DAS-28 < 5.1) and 17% (n=17) had very active disease (DAS-28 > 5.1).

Table 3 depicts patients' characteristics according to disease outcome. Disease duration was significantly longer among those patients who had active disease (DAS-28 > 3.2) at the last study visit ($P = 0.02$). Inflammatory markers at diagnosis, seropositivity, or the use of B-DMARDs were not found to significantly affect the DAS-28 score at the last study visit.

Analysis of outcome by type of treatment yielded a significantly lower mean DAS-28 score in patients receiving C-DMARD monotherapy (n=21) than in those receiving a combination of C-DMARDs (n=80) (2.5 ± 1.2 vs. 3.9 ± 1.52, $P < 0.001$). Patients prescribed only one C-DMARD during follow-up had milder disease as reflected by a significantly lower serum CRP level, both at study inception (3.9 ± 14.1 vs. 5.62 ± 16.5 mg/dl, $P < 0.05$) and at the last visit (1.2 ±1 .7 vs. 1.98 ± 5.95 mg/dl, $P < 0.05$) than patients treated with a combination of C-DMARDs. The mean duration of disease was significantly shorter in the patients who received C-DMARD monotherapy (5.5 ± 6.14) than in those treated with a combination of C-DMARDs (12 ± 9.01, $P < 0.05$) or a B-DMARD (13.3 ± 6.54, $P < 0.05$), again reflecting milder disease [Figure 1].

Mean DAS-28 score was significantly higher in the rituximab-treated patients (n=15) than in the TNF inhibitor-treated patients (n=26) (4.7 ± 1.79 vs. 3.6 ± 1.6, $P < 0.05$), which reflects Israel's National Health Insurance guidelines that allow the prescription of rituximab only to those patients whose disease remains active despite therapy with a TNFα inhibitor [Figure 1].

There was no difference in the DAS-28 score between the RF-positive (n=75) and RF-negative (n=24) patients (3.73 ± 1.47 vs. 3.46 ± 1.9), or the anti-CCP antibody-positive (n=46) and negative (n=17) patients (3.55 ± 1.5 vs. 3.75 ± 2.0). There was also no significant difference in DAS-28 score between B-DMARD-treated patients who were RF positive (n=28) or RF negative (n=12) (4.13 ± 1.59 vs. 3.77 ± 1.99).

Analysis of disease activity at the last visit yielded a significantly higher DAS-28 rate in patients whose disease duration

was 11 years or more (4.09 ± 1.43, n=55) than in patients with RA of shorter duration (3.26 ± 1.45, $P < 0.005$, n=46).

Multivariate analysis of disease outcome as measured by DAS-28 according to patient's age, disease duration, use of C-DMARDs and B-DMARDs ever or at the time of the study did not reveal significant differences between the groups of patients.

DISCUSSION

The present study analyzed disease activity in a cross-sectional inception cohort of patients with RA under regular follow-up at a tertiary medical center. Treatment consisted of C-DMARDs with or without B-DMARDs prescribed at the discretion of the attending rheumatologist. Disease activity was analyzed with the DAS-28. These practices are based on findings that routine treatment with conventional and biological DMARDs can dramatically improve the course and outcome of RA [8-11]. In addition, surveys in the literature reported that 14% of 600 rheumatologists regularly performed joint counts [14] and that 46% of 900 rheumatologists applied the DAS-28 every 3 months [15]. The EULAR Task Force advocated a treat-to-target strategy in RA aimed at achieving remission or minimally active disease with early and aggressive treatment [13]. In our inception cohort, we achieved the goal of tight control of RA as advocated by the EULAR Task Force [13] in 43% of the patients, with 26.7% of patients scoring < 2.6 on the DAS-28 at the last follow-up visit which implies disease remission. As expected, patients who were treated with one C-DMARD had milder and shorter disease, as reflected by their higher rate of DAS-28 score < 2.6. Seropositivity for RF and/or anti-CCP antibody did not affect the likelihood of achieving tight control.

Clinical remission of RA is associated with reduced radiographic progression of joint erosions and improved functional ability [16]. The possibility of achieving remission by intensive management and tight control was proven by several randomized controlled studies: FIN-RACo (the Finnish Rheumatoid Arthritis Combination Therapy study) [17], TICORA (the Tight Control of Rheumatoid Arthritis study) [7], CAMERA (the Computer Assisted Management in Early Rheumatoid Arthritis study) [18], and BeSt (the Behandel Strategieën study) [6]. However, all of them were limited by the methodological design, which warranted strict inclusion and exclusion criteria and per-protocol treatment and follow-up. Very few studies have investigated implementation of the treat-to-target approach in daily clinical practice, and all of them focused on patients with early RA. In the Dutch Rheumatoid Arthritis Monitoring Remission Induction Cohort study, 47% of patients achieved remission (DAS-28 < 2.6) after 6 months of follow-up and 58.1% did so after 12 months [19]. These findings were supported by the GUEPARD and ESPOIR data comparing tight control and routine care in patients with recent-onset active RA [20]. Our results are comparable to the results of those studies, with the successful achievement of tight control of RA in daily clinical practice in patients with long-standing disease (mean follow-up period 10.7 ± 7.9 years) managed with one or more C-DMARD or combined C-DMARD and B-DMARD therapy, prescribed at the discretion of the attending rheumatologist, with no pre-set goal or per-protocol management guidelines. The rates of disease remission (DAS-28 < 2.6) and low disease activity (DAS-28 < 3.2) in the present study were compatible with those reported in both the randomized control trials [6,7,17,18] and the studies of recent-onset RA [19,20], suggesting that the goal of tight control proposed by the EULAR Task Force [13] is feasible and achievable in routine clinical practice, even in patients who have been diagnosed with RA many years prior to the introduction of biologic therapies.

Given the good results of the DAS-28-driven randomized controlled studies, we may assume that an improved outcome could be achieved in an even higher percentage of patients were the treat-to-target strategy applied to RA management in daily practice. Further long-term follow-up studies are needed to determine the benefit of this approach.

The results of this study support the use of a disease activity score such as the DAS-28 to guide the practicing rheumatologist in the management of patients with RA. Our achievement of low disease activity or remission in a significant portion of our patients with RA suggests that the treat-to-target strategy is feasible and effective in routine clinical practice.

EULAR = European League Against Rheumatism

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Capsule

Paneth cells as a site of origin for intestinal inflammation

The recognition of autophagy related 16-like 1 (*ATG16L1*) as a genetic risk factor has exposed the critical role of autophagy in Crohn's disease. Homozygosity for the highly prevalent *ATG16L1* risk allele, or murine hypomorphic (HM) activity, causes Paneth cell dysfunction. As *Atg16l1*^{HM} mice do not develop spontaneous intestinal inflammation, the mechanism(s) by which ATG16L1 contributes to disease remains obscure. Deletion of the unfolded protein response (UPR) transcription factor X-box binding protein-1 (*Xbp1*) in intestinal epithelial cells, the human orthologue of which harbors rare inflammatory bowel disease risk variants, results in endoplasmic reticulum (ER) stress, Paneth cell impairment and spontaneous enteritis. Unresolved ER stress is a common feature of inflammatory bowel disease epithelium, and several genetic risk factors of Crohn's disease affect Paneth cells. Adolph et al. show that impairment in either UPR (*Xbp1*$^{\Delta IEC}$) or autophagy function (*Atg16l1*$^{\Delta IEC}$ or *Atg7*$^{\Delta IEC}$) in intestinal epithelial cells results in each other's compensatory engagement, and severe spontaneous Crohn's-disease-like transmural ileitis if both mechanisms are compromised. *Xbp1*$^{\Delta IEC}$ mice show autophagosome formation in hypomorphic Paneth cells, which is linked to ER stress via protein kinase RNA-like endoplasmic reticulum kinase (PERK), elongation initiation factor 2α (eIF2α) and activating transcription factor 4 (ATF4). Ileitis is dependent on commensal microbiota and derives from increased intestinal epithelial cell death, inositol requiring enzyme 1α (IRE1α)-regulated NF-κB activation and tumor necrosis factor signaling, which are synergistically increased when autophagy is deficient. ATG16L1 restrains IRE1α activity, and augmentation of autophagy in intestinal epithelial cells ameliorates ER stress-induced intestinal inflammation and eases NF-κB overactivation and intestinal epithelial cell death. ER stress, autophagy induction and spontaneous ileitis emerge from Paneth cell-specific deletion of *Xbp1*. Genetically and environmentally controlled UPR function within Paneth cells may therefore set the threshold for the development of intestinal inflammation upon hypomorphic ATG16L1 function and implicate ileal Crohn's disease as a specific disorder of Paneth cells.

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Eitan Israeli

"The ability to simplify means to eliminate the unnecessary so that the necessary may speak"

Hans Hofmann (1880-1966), German-born American abstract expressionist painter. He believed that abstract art was a way to get at the important reality. In his youth Hofmann gravitated towards science and mathematics and developed and patented such devices as the electromagnetic comptometer, a radar device for ships at sea, a sensitized light bulb, and a portable freezer unit for military use