

# Prevalence of remission in patients with rheumatoid arthritis in daily clinical practice: long-term data from a tertiary care centre

N. Gildemeister<sup>1,2</sup>, I. Redeker<sup>1,2</sup>, B. Buehring<sup>2,3</sup>, I. Andreica<sup>1,2</sup>,  
D. Kiefer<sup>1,2</sup>, X. Baraliakos<sup>1,2</sup>, J. Braun<sup>1,2</sup>, U. Kiltz<sup>1,2</sup>

<sup>1</sup>Ruhr Universität Bochum, Germany; <sup>2</sup>Rheumazentrum Ruhrgebiet, Germany;  
<sup>3</sup>St. Josef, Wuppertal, Germany.

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## Abstract

### Objective

We aimed to study remission rates in patients with RA in a tertiary care centre over a long-term observation period.

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### Methods

In a monocentric cohort study with a prospective and a retrospective part, adult RA patients were included. Patient's characteristics and outcome parameters were documented prospectively (clinical visit). Data of the initial visit (index visit) and date of first occurrence of remission were taken retrospectively from the hospital information system. Remission was defined as DAS28 <2.6 and sustained remission (SR) was defined as remission lasting >6 months. Logistic regression analysis was used to analyse factors associated with remission and SR.

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### Results

A total of 136 RA patients were included with retrospective data available over a period of 47.9 (18.9) months. One third already had erosions and severe limitations in physical function at baseline. The vast majority (n=109) of patients achieved a state of remission at least once over time (80.1%). At the clinical visit, 40 patients (29.4%) were in remission. Remission was achieved 14.9 months (13.8) after the index visit and by 54.1%, 23.9%, 13.8%, and 8.3% of patients within the first, second, third, and fourth year, respectively. SR was achieved by 65 patients (47.8%) within the observation period.

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### Conclusion

Most patients achieved remission at least once within the observation period and almost 50% of patients also achieved SR. This study shows that the target of achieving remission should be constantly pursued, as we were able to show that even in the fourth year of treatment, patients still achieved remission.

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### Key words

rheumatoid arthritis, remission, outcome

Nils Gildemeister  
 Imke Redeker, PhD  
 Bjoern Buehring, MD PhD  
 Ioana Andreica, MD  
 David Kiefer, MD  
 Xenofon Baraliakos, MD PhD  
 Juergen Braun, MD PhD  
 Uta Kiltz, MD PhD

Please address correspondence to:  
 Uta Kiltz

Rheumazentrum Ruhrgebiet  
 am Marien Hospital,  
 Universitätsklinik der  
 Ruhr-Universität Bochum,  
 Claudiusstr. 45,  
 44649 Herne, Germany.

E-mail: uta.kiltz@elisabethgruppe.de

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## Introduction

Rheumatoid arthritis (RA) is the most frequent inflammatory rheumatic musculoskeletal disease that usually runs a chronic course. Even though the disease-associated signs and symptoms can definitely be improved, it can usually not be cured and complete absence of signs and symptoms in the course of the disease is rare. Nevertheless, the main goal of treatment in RA is remission or, at least, low disease activity (LDA) of patients. The treat-to-target (T2T) approach has been identified and accepted as the best way to achieve this (1). Thus, the standardised assessment of disease activity by validated tools is of central importance to monitor patients' disease status. Several instruments such as Disease Activity Score with 28 joints (DAS28), Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) are available for assessment of disease activity (2). The T2T strategy implies that disease activity is regularly assessed. If the target of remission or LDA is not achieved, treatment must be adapted accordingly (3). High disease activity in RA is associated with an increase of mortality, comorbidity, deterioration of physical function, work impairment and reduced quality of life (4–6). In comparison, achievement of remission is superior to LDA to influence these relevant outcomes (4). In addition to the established conventional synthetic (cs)disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX), biologic (b) DMARDs such as the TNF inhibitors (TNFi) and the targeted synthetic (ts) DMARDs such as the JAK inhibitors have been approved for the treatment of active RA in the last decades. This has resulted in a greater proportion of RA patients achieving remission (7). Moreover, the reduction of inflammation of patients in remission is also associated with an inhibition of radiographic progression (8).

The number of RA patients in remission differs depending on the setting and several other parameters including age, disease duration and activity, function, comorbidity, education, life-style and environmental factors. In clinical trials, the proportion of patients achiev-

ing remission varies between 5–80% and in clinical cohorts between 10–50% (9–12). Risk factors for a severe course of disease include symptom duration, morning stiffness  $\geq 1$  hour, erosions in hands and/or feet, number of affected joints ( $\geq 3$  joints), positivity for rheumatoid factor (RF) and anti-citrullinated antibodies (ACPA) (13). Among these, early and consistent use of DMARDs within the first 3–6 months after disease onset seems to be crucial. Controlled studies in patients with early RA demonstrated that based on a T2T strategy, 74% of patients achieved remission/LDA as compared to 49% in the non T2T (standard therapy) control group (14). The T2T strategy has also been successful in inhibiting radiographic progression (15). In the German multicentre, non-interventional prospective observational study CAPEA, using DAS-28, 40% of patients with early RA achieved clinical remission at 6 months and 21% LDA (16). In a Norwegian cohort study, ACR/EULAR Boolean remission was achieved by 42% of patients with early RA at 6 months (11). However, remission rates over longer periods of time in a real-life setting have not been extensively studied.

In many countries, RA patient care is provided in outpatient settings by rheumatologists in collaboration with primary care physicians. In Germany, RA patients can also be treated in a specialist outpatient clinic which usually concentrates on particular patients with a severe or complicated disease course in an interdisciplinary team (17) (tertiary care). Data on remission in patients with RA treated in tertiary care centres are lacking to date.

The main objective of this study was to evaluate the remission rate over time in a cohort of RA patients presenting to the outpatient clinic of a tertiary care centre.

## Materials and methods

### Patients

Adult patients with a clinical diagnosis of RA were eligible for inclusion if their first visit at our outpatient clinic was between January 2012 and December 2018 and if  $\geq 3$  visits were available in the hospital information system. Vis-

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its occurred regularly every 3 months. The rationale for using the timeframe of January 2012 to December 2018 was the European Medicines Agency's (EMA) approval of the last bDMARD tocilizumab, the EMA approval of the first tsDMARD in 2017 and the implementation of the T2T recommendations in clinical routine. The choice of a time span of one year between 2017 and 2018 is based on the period in which remission is likely to be achieved in individual patients. Patients with difficulties to read and understand written German language were excluded from the study. The study was approved by the Ethical Committee of the Ruhr-Universität Bochum, Germany (19-6801) and all patients gave written informed consent before participation. The study complies with the Declaration of Helsinki.

#### Study visits

Patients were enrolled during a regular outpatient visit prospectively (*clinical visit*). Data of the initial visit at our outpatient clinic were taken retrospectively (*index visit*). Date of first occurrence of remission defined as DAS-28 <2.6 was retrospectively taken from the hospital information system (*remission visit*).

#### Data collection

All patients underwent a standardised assessment including collection of patients and disease characteristics as well as patient-reported outcomes. Prospective data were taken at the clinical visit for demographic (age, gender, education, work status) and clinical data (symptom duration, diagnosis since, body mass index (BMI), smoking status, disease status including joint count, presence of comorbidities according to the Charlson comorbidity index (CCI) (18, 19) and further comorbidities common in patients with RA (fibromyalgia, coronary heart disease, osteoporosis/osteopenia, degenerative spinal diseases), laboratory (RF and ACPA titre) and imaging results (presence of radiographic damage) as well as prescribed pharmacological treatment. Imaging data was taken from patient charts. Medication data were grouped according to substance classes (DMARDs), glucocorticoids (GC), and pain medica-

tion. Duration/dosage of treatment were recorded. Disease status were assessed by validated outcome parameters such as for pain and patient global (numerical rating scale (NRS) 0–10), disease activity (DAS-28, SDAI), (20–24), disease impact [Rheumatoid Arthritis Impact of Disease (RAID)] (25), patient global assessment (PtGA) (NRS) 0–10 and physical function. DAS-28 score were based on number of swollen and tender joints, C-reactive protein concentration, and patients' global assessment of disease activity. Physical function was assessed by using the "Funktionsfragebogen Hannover" (FFbH) score (26), which strongly correlates with the Health Assessment Questionnaire (HAQ) (27). Values of FFbH were converted into HAQ values by the published formula: HAQ score =  $3.16 - (0.028 \times \text{FFbH score})$  (28). Severe physical impairment is defined by FFbH  $\leq 67\%$  corresponding to a HAQ  $\geq 1.23$  (29). Patients were asked at the clinical visit whether medication had been changed or stopped in the last 6 months due to the pandemic situation during recruitment period. Retrospective data for disease activity, physical function, physician global assessment (PhGA) (NRS) 0–10, CRP and therapy at index and remission visit were taken from the hospital information system.

#### Outcome

Remission was defined based on DAS-28, SDAI and ACR/EULAR Boolean criteria and were categorised according to their validated thresholds (2, 30). Sustained Remission (SR) was defined as DAS28 <2.6 during at least two consecutive visits over at least six months. Proportion of RA patients in remission determined with a DAS28 <2.6 at any time point between 2012 and 2018 and time being in remission during observation period was evaluated as the primary endpoint.

#### Statistics

The results are presented as means  $\pm$  standard deviation for quantitative variables and as absolute and percentage frequencies for qualitative variables. The Mann-Whitney U-test was used to distinguish between groups. For cat-

egorical data, the chi-square test was used, for paired nominal data McNemar. Uni- and multivariable logistic regression analyses were used to examine the association between remission (dependent variable) and various patients' characteristics (independent variables) additionally adjusted for potential confounders (age, sex). Separate models were calculated: one with DAS-28 remission (model 1) and one with SR (model 2) as outcome. All variables from the univariable analysis were included in the multivariable analysis. A  $p$ -value <0.05 is considered to indicate statistical significance.

#### Results

A total of 136 patients with RA were consecutively recruited between July 2020 and January 2021.

#### Index visit

The index visit occurred on average 47.9 (18.9) months before the clinical visit. At that point in time, the mean symptom duration was 5.7 (8.0) years. This was substantially longer for patients referred for a second opinion (10.7 (8.7) years). Some patients ( $n=18$ ) had no DMARD treatment (13.2%) and 13 used GC monotherapy (9.6%). Monotherapy with csDMARDs and bDMARDs was used by 81 (59.6%) and 6 (4.4%) patients, respectively. 82 (60.3%) patients used MTX at the index visit. Combination of DMARDs were applied in 18 (13.2%) patients, most often csDMARD/bDMARD in 12 (8.8%), csDMARD/csDMARD in 4 (2.9%) and csDMARD/tsDMARD in 2 (1.5%). 71 (65.1%) patients used GC. The DMARDs used at the different visits can be found in supplement 1.

#### Clinical visit

Patients' demographics and disease characteristics are depicted in Table I. At the clinical visit, patients were mostly female (73.3%), 57.2 (14.5) years old, and nearly half of them (44.1%) came for a second opinion. The majority of patients had a non-university level of education (74.3%), and 62 patients of working age (62%) were employed, while 52 patients were retired (38.2%) of whom 23 received disability

**Table I.** Patients and disease characteristics at the clinical visit grouped by remission status.

Characteristics*	Patients (n=136)	Patients who achieved remission (n=109)	Patients who did not achieve remission (n=27)	p-value**	Patients who achieved sustained remission (n=65)	Patients who did not achieve sustained remission (n=71)	p-value**
Age, in years	57.2 (14.5)	56.2 (14.8)	61.5 (12.3)	0.18	55.0 (15.2)	59.2 (13.6)	0.119
Gender female, n (%)	100 (73.5)	80 (73.4)	20 (74.1)	0.9	43 (66.2)	57 (80.3)	0.06
Education, university level, n (%)	19 (14.0)	17 (15.6)	2 (7.4)	0.27	13 (20.0)	6 (8.5)	0.052
Employment, n (%)	64 (46.7)	56 (51.4)	8 (29.6)	0.4	39 (60.0)	25 (35.2)	<b>0.007</b>
Smoking status never, n (%)	59 (43.4)	47 (43.1)	12 (44.4)	0.9	29 (44.6)	30 (42.3)	0.781
Time (years) since RA symptoms	9.7 (8.6)	9.1 (8.6)	12.1 (8.5)	0.13	9.6 (9.6)	9.8 (7.7)	0.333
Time (years) since RA diagnosis	7.8 (7.6)	7.2 (7.3)	9.9 (8.4)	0.131	7.7 (7.9)	7.8 (7.3)	0.8
Time (years) attending outpatient clinic	3.6 (1.6)	3.72 (1.6)	3.2 (1.7)	0.62	3.9 (1.8)	3.4 (1.4)	0.103
BMI, kg/m <sup>2</sup>	27.3 (4.9)	27.0 (4.9)	28.5 (4.7)	0.09	26.7 (4.6)	27.9 (5.0)	0.22
TJC, 0-28	6.1 (6.0)	4.7 (4.9)	11.7 (7.1)	<b>&lt;0.001</b>	3.2 (3.9)	8.7 (6.5)	<b>&lt;0.001</b>
SJC, 0-28	1.6 (2.8)	1.0 (1.6)	3.8 (4.8)	<b>&lt;0.001</b>	0.6 (1.1)	2.5 (3.5)	<b>&lt;0.001</b>
ACPA positive (%)	77 (56.6)	62 (56.9)	15 (55.6)	0.9	38 (58.5)	39 (54.9)	0.678
RF positive (%)	85 (62.5)	69 (63.3)	16 (59.3)	0.698	44 (67.7)	41 (57.7)	0.231
CRP, mg/dl	0.6 (1.1)	0.5 (0.9)	1.1 (1.6)	<b>0.017</b>	0.3 (0.3)	0.9 (1.4)	<b>&lt;0.001</b>
Erosions, n (%)	43 (31.6)	33 (30.3)	10 (37.0)	0.7	20 (30.8)	30 (32.4)	0.846
Comorbidities yes#, n (%)	103 (75.7)	77 (70.6)	26 (96.3)	<b>0.005</b>	47 (66.2)	60 (84.5)	<b>0.013</b>
Charlson Comorbidity Index), 0-29	0.8 (1.1)	0.7 (1.1)	0.9 (1.1)	0.15	0.7 (0.9)	0.9 (1.2)	0.6
Comorbidities CCI yes, n (%)	64 (47.1)	47 (43.1)	17 (63.0)	0.06	29 (44.6)	35 (49.3)	0.585
No. of patients using GC n (%)	53 (39.0)	34 (31.2)	19 (70.4)	<b>&lt;0.001</b>	18 (27.7)	35 (49.3)	<b>0.010</b>
Prednisolone dosage, mg/d	4.9 (3.6)	4.7 (3.6)	5.21 (3.6)	0.42	3.9 (1.8)	5.4 (4.1)	0.4
No. of patients on csDMARD n (%)	93 (68.4)	75 (68.8)	18 (66.7)	0.83	46 (70.8)	47 (66.2)	0.567
No. of patients on bDMARD n (%)	63 (46.3)	50 (45.1)	13 (48.1)	0.83	31 (47.7)	32 (45.1)	0.759
No. of patients on tsDMARD n (%)	17 (12.4)	11 (10.1)	6 (22.2)	0.09	6 (9.2)	11 (15.5)	0.309
No. of previous b- or tsDMARD	1.6 (1.9)	1.4 (1.7)	2.3 (2.39)	<b>0.026</b>	1.3 (1.6)	1.8 (2.1)	0.117
Patient global assessment (PtGA), 0-10	4.4 (2.5)	4.1 (2.5)	6 (1.9)	<b>&lt;0.001</b>	3.4 (2.4)	5.4 (2.2)	<b>&lt;0.001</b>
Physician global assessment (PhGA), 0-10	3.4 (2.5)	2.9 (2.3)	5.7 (2.1)	<b>&lt;0.001</b>	2.1 (2.0)	4.6 (2.3)	<b>&lt;0.001</b>
DAS-28-CRP	3.5 (1.4)	3.2 (1.2)	4.7 (1.2)	<b>&lt;0.001</b>	2.7 (1.0)	4.2 (1.3)	<b>&lt;0.001</b>
DAS-28-CRP <2.6, n (%)	40 (29.4)	40	0 (0)		32 (49.2)	7 (0.10)	<b>&lt;0.001</b>
Sustained remission, n (%)	65 (47.8)	65	0 (0)		71 (100.0)	0 (0)	
SDAI	16.2 (12.3)	13.2 (9.9)	28.2 (14.1)	<b>&lt;0.001</b>	9.6 (7.9)	22.2 (12.6)	<b>&lt;0.001</b>
Boolean	16 (11.8)	16	0		14 (21.5)	2 (0.03)	<b>&lt;0.001</b>
HAQ	1.3 (0.7)	1.2 (0.7)	1.8 (0.7)	<b>&lt;0.001</b>	1.0 (0.6)	1.6 (0.7)	<b>&lt;0.001</b>
HAQ ≥1.28, n (%)	60 (44.1)	38 (34.9)	22 (81.5)	<b>&lt;0.001</b>	18 (27.7)	42 (59.2)	<b>&lt;0.001</b>
RAID, 0-10	4.1 (2.3)	3.7 (2.3)	5.66 (2.0)	<b>&lt;0.001</b>	3.0 (2.2)	5.0 (2.0)	<b>&lt;0.001</b>

\*values are mean; # based on Charlson comorbidity index plus further comorbidities common in patients with RA; \*\* Chi-Square or Mann-Whitney U-test. BMI: Body Mass Index; DAS28-CRP. Disease Activity Score with 28 joints and CRP; HAQ: Health Assessment Questionnaire; RAID: Rheumatoid Arthritis Impact of Disease; SDAI: Simplified Disease Activity Index.

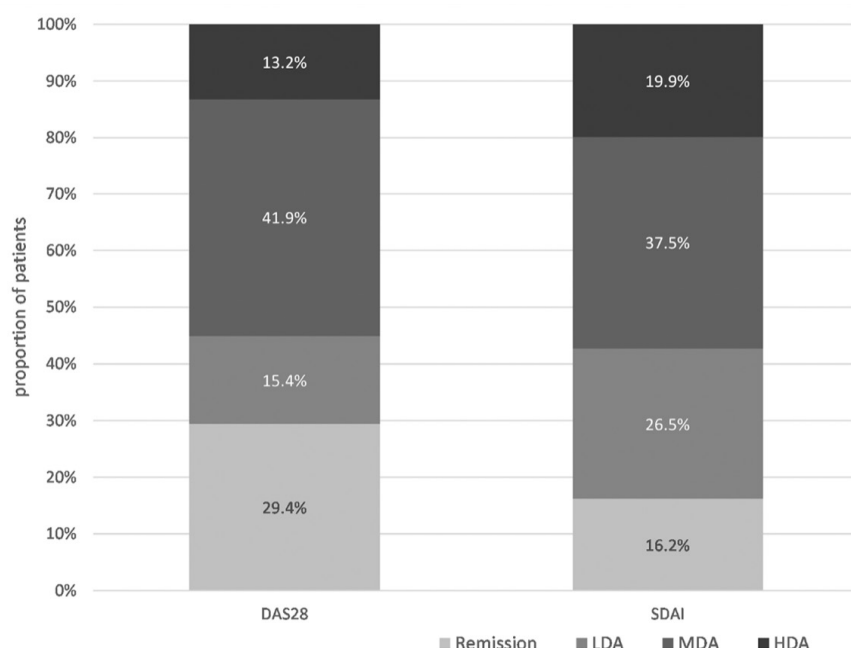
pensions (44.2%), about half (n=12) because of RA and 11 for other reasons. Current joint symptoms were common with 6.1 (6.0) tender joints and 1.6 (2.8) swollen joints. Structural damage of either hand or feet was documented in 43 patients (31.6%). The pain level reported by patients was 4.4 (2.4) and global disease activity was rated with 4.4 (2.5). Physical function was impaired with a HAQ score of 1.3 (0.7) with 60 patients (44.1%) having severe limitations (HAQ ≥1.23). The impact of the disease as assessed by RAID was 4.1 (2.3). Comorbidities according to CCI were present in 64 patients (47.1%). Patients with comorbidities tended to be older (62.5 vs. 52.3 years), had a longer

disease duration (9.2 vs. 6.5 years), higher disease activity (DAS-28: 3.6 vs. 3.3), more impaired physical function (HAQ: 1.5 vs. 1.1), and had previously used a higher number of b- and tsDMARD (3.9 vs. 3.1).

At the clinical visit, the vast majority of patients (n=133) were currently treated with DMARD (97.8%), and all patients had been treated with DMARD at some time in the past. Nearly all patients (n=135) had at least taken one csDMARD (99.3%) with on average 1.9 (1.0) substances used. The most frequently used csDMARD was MTX in 130 patients (95.6%). MTX had been discontinued in 47 patients (36.2%), the main reason of discontinuation be-

ing intolerance in 36 patients (76.6%). More than half (n=80) of the patients (58.8%) had previously used at least one bDMARD (mean number 1.3 (1.6)). TNFi was used most frequently: by 69 patients (50.7%), tsDMARDs by 26 (19.1%) and IL6-Antagonists by 24 patients (17.6%), respectively. Monotherapy of csDMARDs, bDMARDs and tsDMARDs was used by 46 (33.8%), 26 (19.1%) and 13 patients (9.6%), respectively. MTX was used by 83 patients (61.0%) for a mean duration of 4.0 (3.2) years. Combinations of DMARDs were applied in 48 patients (35.8%), most often csDMARDs with bDMARDs in 37 patients (27.2%), csDMARDs with csDMARDs in 7





**Fig. 1.** Disease activity at the clinical visit according to SDAI and DAS28.

Disease activity states at the clinical visit according to SDAI and DAS28 are graphically depicted. The disease activity categories were calculated according to ACR/EULAR thresholds and depicted as horizontally stacked-bar charts. For DAS28 calculation the CRP formula was used.

**Table II.** Disease characteristics at different visits.

Characteristic n=136 <sup>1</sup>	Clinical visit, n=136 <sup>1</sup>	Index visit, n=136 <sup>1</sup>	p-value <sup>2</sup>	Remission visit, n=109 <sup>1</sup>	p-value <sup>2</sup>
DAS-28 CRP	3.5 (1.4)	3.6 (1.4)	0.2	2.0 (0.4)	<b>&lt;0.001</b>
DAS-28 CRP <2.6	39 (29%)	12 (23%)	0.5	109 (100%)	
Boolean remission	16 (12%)	5 (9.4%)	>0.9	23 (21%)	0.063
CRP, mg/dl	0.6 (1.1)	1.0 (2.0)	<b>0.045</b>	0.4 (0.6)	0.3
CRP ≥ 0.5mg/dl	52 (38%)	65 (50%)	0.086	34 (31%)	0.9
ESR, mm/h	15.8 (25.1)	18.1 (17.5)	0.4	12.5 (10.0)	0.2
HAQ-DI	1.3 (0.7)	1.2 (0.6)	0.062	1.0 (0.6)	<b>0.007</b>
PtGA (NRS, 0-10)	4.4 (2.5)	4.9 (2.3)	0.2	3.1 (2.0)	<b>&lt;0.001</b>
Patients on csDMARD	93 (68%)	99 (73%)	0.5	88 (81%)	<b>0.004</b>
Patients on bDMARD	63 (46%)	18 (13%)	<b>&lt;0.001</b>	45 (41%)	0.3
Patients on tsDMARD	17 (12%)	2 (1.5%)	<b>0.001</b>	2 (1.8%)	<b>0.008</b>
Prednisolone	53 (39%)	100 (74%)	<b>&lt;0.001</b>	71 (65%)	<b>&lt;0.001</b>
Prednisolone dosage (mg/d)	4.9 (3.6)	10.5 (12.0)	<b>0.017</b>	5.7 (4.7)	0.2

<sup>1</sup>Mean (SD); n (%); <sup>2</sup>Compared to clinical visit. Paired t-test; McNemar's Chi-squared test with continuity correction.

DAS28: Disease Activity Score in 28 joints; CRP: C-reactive protein; PtGA: Patients Global Assessment; NRS: Numerical Rating Scale.

patients (5.1%) and csDMARDs with tsDMARDs in 4 (2.9%). At the clinical visit, GC intake was noted in 53 patients (39%) in a mean daily dosage of 4.9 (3.6 mg). Additional intake of pain medication was reported by 72.1% of patients, in 43 cases (31.6%) taken as an on-demand medication. Due to the COVID-19 pandemic, 22 patients (16.7%) had stopped or changed their DMARD medication in the 6 months prior to the clinical visit.

#### Outcomes at the clinical visit

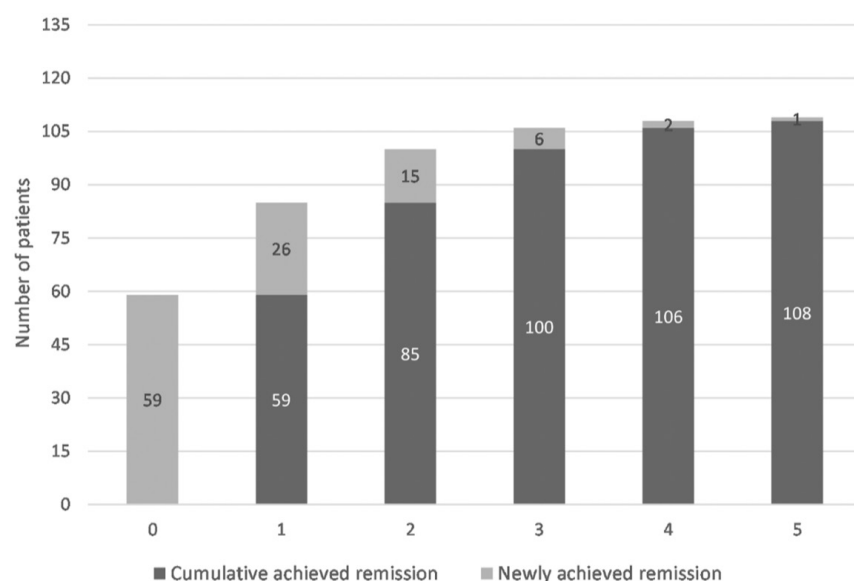
Mean disease activity (DAS-28) was 3.5 (1.4) and 16.2 (12.3) for SDAI. Proportion of patients fulfilling remission criteria varied according to their respective thresholds (Fig. 1). Boolean remission was least likely to be achieved: in only 16 patients (11.8%), followed by SDAI in 22 (16.2%), and DAS-28 in 40 cases (29.4%). Additionally, the number and proportion of patients fulfilling criteria for low disease activity

(LDA) was 36 using SDAI (26.5%) and 21 using DAS-28-CRP (15.4%). Moderate disease activity (MDA) was seen in 51 (37.5%) and 57 patients (41.9%), and high disease activity (HDA) in 27 (19.9%) and 18 patients (13.2%), respectively. Although mean disease activity did not differ between index and clinical visit, proportion of patients in remission and proportion of patients with negative CRP were higher at clinical visit compared to index visit (Table II). Proportion of patients on bDMARD increased between index and clinical visit from 13.2% to 46.3% ( $p \leq 0.001$ ). GC were more frequently prescribed at the index and remission visit compared to the clinical visit, but dosage of prednisolone could be decreased substantially between index and clinical visit ( $p \leq 0.001$ ). Stop of GC were possible in 47 patients (34.6%) during the observation period.

#### Remission visit

A state of clinical remission (DAS-28 <2.6) between index and clinical visit was at least once achieved by 109 patients (80.1%). Remission was achieved on average 14.9 (13.8) months after the index visit. Of those 109 patients, 59 achieved remission within the first year (54.1%), 26 in the second (23.9%), 15 in the third (13.8%) and 9 patients (8.3%) after 3 years (Fig. 2). The DAS-28 score was 2.0 (0.4) in patients reaching remission for the first time. Fewer patients ( $n=23$ ) also fulfilled Boolean remission criteria (21.1%). Patients remained in remission for 15.9 (10.4) months. SR based on a definition of DAS28 <2.6 over  $\geq 6$  months and  $\geq 2$  visits was achieved by 65 patients (47.8%) between the initial and the clinical visit.

HAQ score and PtGA was significantly lower at the remission visit compared to the clinical visit. Monotherapy of csDMARDs, bDMARDs and tsDMARDs were used by 53 (48.6%), 14 (12.8%) and 1 (0.9%), respectively. MTX was taken by 79 patients (72.5%). Any combination of DMARDs was administered to 35 patients (32.1%), most often ( $n=31$ ) for the combination csDMARDs/bDMARDs (28.4%), while a combination of csDMARDs was



**Fig. 2.** Time to first occurrence of remission in years.

The time until a remission was first recorded is depicted graphically in full years as horizontally stacked-bar charts. After the year in which the first visit with DAS28 <2.6 was recorded, patients were considered to be in cumulative achieved remission.

**Table III.** Regression analysis DAS28 remission and sustained remission.

DAS28-Remission							
Characteristic	n	Univariable analysis			Multivariable analysis		
		OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value
Age (years)	136	0.97	0.94, 1.00	0.088	0.99	0.95, 1.02	0.4
Sex, male vs. female	136	1.04	0.41, 2.87	>0.9	1.07	0.39, 3.16	0.9
Symptom duration at index visit (years)	136	0.96	0.91, 1.01	0.071	0.97	0.92, 1.02	0.2
Education, university level, yes vs. no	136	2.31	0.61, 15.2	0.3	1.23	0.27, 8.69	0.8
CRP level (mg/dl) at index visit	129	1.12	0.88, 1.76	0.5	1.15	0.82, 1.91	0.5
Comorbidities <sup>#</sup> , 136	0.09	0.01, 0.47	<b>0.022</b>	0.13	0.01, 0.750.061	yes vs. no	

DAS-28-Sustained Remission							
Characteristic	n	Univariable analysis			Multivariable analysis		
		OR <sup>1</sup>	95% CI <sup>1</sup>	p-value	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value
Age (years)	109	0.99	0.96, 1.01	0.3	1.00	0.96, 1.03	0.8
Sex, male vs. female	109	2.70	1.08, 7.49	<b>0.042</b>	4.39	1.55, 14.1	<b>0.008</b>
Symptom duration at index visit (years)	109	1.01	0.96, 1.06	0.8	1.03	0.97, 1.10	0.3
Education, university level, yes vs. no	109	2.50	0.81, 9.40	0.13	2.55	0.71, 10.7	0.2
CRP level (mg/dl) at index visit	102	0.88	0.66, 1.07	0.3	0.84	0.64, 1.02	0.12
Comorbidities <sup>#</sup> , yes vs. no	109	0.57	0.23, 1.35	0.2	0.48	0.16, 1.39	0.2

<sup>#</sup> based on Charlson comorbidity index plus further comorbidities common in patients with RA.

<sup>1</sup>OR: odds ratio; CI: confidence interval.

recorded in 3 patients (2.8%) and one patient took a csDMARD and a tsDMARD (0.9%). The majority (n=71) of patients used GC (65.1%). No DMARD

therapy was noted in 3 patients (2.8%) and another 3 were on GC monotherapy (2.8%). Comparative data of the different visits is depicted in Table II.

### Association of remission with patient and disease characteristics

Patients who did not reach a state of remission had higher joint counts, higher PtGA and PhGA scores, and impact of disease, more impairments in physical function, used more often GC, and had higher numbers of prior b/tsDMARDs at the clinical visit (Table I). Age, body weight, smoking status, disease duration and ACPA status were not different between groups. Male sex was the only factor associated with SR in uni- (OR 2.7 (95%CI 1.08–7.49)) and multivariable analysis (OR 4.39 (CI95 1.55–14.1)) (Table III). In just univariable logistic regression analysis, we found patients with comorbidities having a significantly decreased odds ratio for DAS-28 remission (OR 0.09, CI 0.01–0.47). This negative tendency, albeit in a non-significant manner, remained in multivariable analysis (OR 0.13, CI 0.01–0.75) (Table III).

Patients reaching SR had a significantly better outcome regarding physical function [HAQ 1.0 (0.6) vs. 1.4 (0.7)  $p \leq 0.001$ ] and disease impact [RAID 3.0 (2.2) vs. 4.7 (2.0)] at the clinical visit when compared with patients unable to sustain their remission. (data not shown)

### Discussion

In this combined retrospective and prospective study, only 29.4%, 16.2% and 11.8% of patients were in DAS-28-, SDAI- and Boolean remission at the clinical visit, respectively. However, 80.3% did achieve a DAS-28 remission at least once in the observation period. Furthermore, more than half of the patients in remission had sustained remission for at least 6 months. The majority of patients achieved remission within the first year after the initial visit. However, also in the third year of follow up 13.8% of patients went into remission for the first time. Importantly, in case remission was achieved these patients spent more than half (51.1%) of their follow up time in remission.

SR was identified in 47.8% of patients in our study. Similar findings were observed in other studies as well. In a Swedish registry study with 29,084 patients, SR lasting >6 months was achieved at least once by 41.9% us-

ing DAS-28 but only by 21.3% using the SDAI and by 17.5% according to ACR/EULAR Boolean criteria (31). Although the majority of patients never achieved SR, patients with early RA were more likely to achieve SR than patients with longer standing disease (31). Regarding tertiary care studies, a Chinese study found SR rates of 51.6% for DAS-28, 44.0% for SDAI and 42.4% for ACR/EULAR Boolean criteria (32). In a cross-sectional study from a Portuguese tertiary care centre similar levels of disease activity (DAS-28 median 3.2 vs. 3.4) and rates of remission (29.4% vs. 26%) were observed (33). In two further studies using DAS28-ESR similar results to our study were found: in a large Swedish registry study (SR 41.9%) (31) and in a Chinese tertiary care hospital (SR 51.6%) (34) – despite the fact that our patients had more functional disability compared to the Portuguese (HAQ 1.3 vs. 1.1) and the Swedish patients (HAQ 1.3 vs. 1.04) or were older than the Chinese patients (57 vs. 50 years). However, our remission rates might be slightly overestimated due to the fact that DAS28-CRP is known to come up with higher rates of remission compared to DAS28-ESR (35). Compared with the German early RA cohort CAPEA DAS28 point prevalence remission rate in our cohort was distinctly lower (40% vs. 29.4%) (16). However, we investigated patients with an established disease course in which lower rates of remission has been seen in other cohorts as well. In a Canadian cohort, patients with established RA achieved DAS28 remission less often compared to those with early RA (30 vs. 40%) and prevalence of remission rate was comparable with our study (36). Time to remission with a mean of 14.9 months in our cohort was considerably higher than the timeframe recommended in the T2T approach (3). This can in part be explained by the heterogeneity of the cohort. Almost half of our cohort presented for a second opinion and these patients presented with a longer disease duration and were not DMARD naive. Previous studies had reported high rates of remission within the first 6 months in DMARD naive patients (37). Xie *et al.* found treatment

naive status and short disease duration to be predictors of early remission (38). Male sex was the only predictor associated with reaching SR in our study. Male sex being a predictor of remission was also recently highlighted in a review by Garaffoni *et al.* (39). Favalli *et al.* showed that disease activity is higher and response to b/tsDMARDs is lower in women compared to men, which might explain the lower remission rates (40). In the CORRONA cohort female patients also had a higher baseline disease activity irrespective of disease duration (CDAI 18.7 vs. 17.4 early RA, 16.6 vs. 15.8 established RA) (41). In this cohort, male sex was also associated with higher likelihood of SR (OR 1.38 (CI95 1.07–1.78)) in early RA, though not in established RA (41). Beside male sex, a meta-analysis involving clinical cohorts and registry studies found younger age, lower baseline disease activity and higher education to be predictors of DAS28 remission (42). However, these predictors were not identified in our cohort.

Rates of remission has to be evaluated in the light of concomitant medication. Majority of patients in our cohort received treatment with csDMARDs but less than 50% b- or tsDMARDs. However, number of b- and tsDMARDs increased from index visit to the clinical visit significantly. Although 39% of patients at the clinical and 63% at the remission visit were treated with GCs dosage of GCs were tapered over time between index- and clinical visit by 53%. The rate of GC users at the clinical visit are still high but might reflect the need of the patients treated in tertiary care centres. The divergent effect of increase in proportion of patients using b/tsDMARD while proportion of patients on GC decreased was also noted in a retrospective study from a tertiary care centre in Saudi Arabia (43). The inverse correlation between bDMARD and GC usage was noted in the CAPEA cohort as well (16).

Our monocentric study has some limitations. Only patients treated in our specialised tertiary centre were included in the study which may represent a selection bias. Therefore, generalisability is difficult, and it is possible that patients

with a more severe course and higher disease activity have been included. Additionally, patients treated in our outpatient clinic had to have an established diagnosis and therefore were either seen for a second opinion or after the diagnosis had been recently established in our inpatient clinic. This might have led to the high number of patients already taking DMARD medication at the index visit (86.7%) and consecutively to the comparatively low disease activity at the index visit. Because the retrospective arm of our study relied on data from routine care and physician global is only being recorded since the start of 2020, newer composition scores for disease activity as SDAI and CDAI could only be obtained for the clinical visit. Moreover, missing data for disease activity at visits in the past could have led to underreported rates of remission and sustained remission. Due to missing data in the hospital information system, some results could not be investigated in more detail, for example, standardised assessment of physical function.

In conclusion, for the majority of patients, remission is an attainable goal in clinical practice. However, it should be possible to achieve sustained remission in a higher proportion of patients even though higher states of disease activity tended to recur as seen by decreasing rates for sustained remission and point prevalence. Identifying the reasons for this is an important aim for future studies. Specifically, the interplay of education level, physical function and clinical pathway should be deciphered in more detail by adjusted analyses.

### Acknowledgment

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### Significance and innovations

What is already known on this topic?

- Remission is the treatment target in RA and known to lead to superior outcomes in physical function and quality of life, as well as to reduced mortality, compared to higher states of disease activity.
- Remission rates differ heavily depending on setting and definitions of remission.



What this study adds

- DAS28 Remission is attainable for the majority of patients but can take more than one year to achieve.
- More than half of the patients in remission had sustained remission for at least 6 months.

How this study might affect research, practice or policy

- The goal of achieving remission must be pursued over the long term and more effective strategies need to be developed to maintain sustained remission.

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