Which Factors Influence Radiographic Progression During Treatment with Tumor Necrosis Factor Inhibitors in Clinical Practice? Results from 930 Patients with Rheumatoid Arthritis in the Nationwide Danish DANBIO Registry

Lykke Midtbøll Ørnbjerg, Mikkel Østergaard, Pernille Bøyesen, Niels Steen Krogh, Anja Thormann, Ulrik Tarp, Uta Engling Poulsen, Jakob Espesen, Annette Schlemmer, Niels Graudal, Gina Kollerup, Dorte Vendelbo Jensen, Ole Rintek Madsen, Bente Glintborg, Torben Christensen, Hanne Lindegaard, Wolfgang Bøhme, Annette Hansen, Anne Rødgaard Andersen, and Merete Lund Hetland

ABSTRACT. ***Objective.*** To investigate baseline characteristics associated with radiographic progression and the effect of disease activity, drug, switching, and withdrawal on radiographic progression in tumor necrosis factor (TNF) inhibitor-naive patients with rheumatoid arthritis (RA) followed for about 2 years after anti-TNF initiation in clinical practice.

Methods. DANBIO-registered patients with RA who had available radiographs (anti-TNF initiation and ~2 yrs followup) were included. Radiographs were scored, blinded to chronology with the Sharp/van der Heijde method and linked with DANBIO data. Baseline characteristics were investigated with univariate regression and significant variables included in a multivariable logistic regression analysis with ± radiographic progression [Δ total Sharp score (TSS) > 0] as dependent variable. Effect of time-averaged C-reactive protein (CRP), 28-joint Disease Activity Score with CRP (DAS28-CRP), and treatment status at followup were investigated with univariate regression analysis.

Results. The study included 930 patients. They were 75% women, 79% positive for IgM-rheumatoid factor (IgM-RF), median age was 57 yrs (range 19–88), disease duration 9 yrs (1–59), DAS28-CRP 5.0 (1.4–7.8), TSS median 15 [3–45 interquartile range (IQR)] and mean 31 (SD 40). Patients started treatment with infliximab (59%), etanercept (18%), or adalimumab (23%). At followup (median 526 days, IQR 392–735), 61% were treated with the initial anti-TNF, 29% had switched TNF inhibitor, and 10% had withdrawn. Twenty-seven percent of patients had progressed radiographically. ΔTSS was median 0.0 [0.0–0.5 IQR/mean 0.6 (SD 2.4)] units/year. Higher TSS, older age, positive IgM-RF, and concomitant prednisolone at baseline were associated with radiographic progression. Time-averaged DAS28-CRP and time-averaged CRP, but not type of TNF inhibitor, were associated with radiographic progression. Patients who stopped/switched during followup progressed more than patients who continued treatment.

Conclusion. High TSS, older age, IgM-RF positivity, and concomitant prednisolone were associated with radiographic progression during 2 years of followup of 930 anti-TNF–treated patients with RA in clinical practice. High disease activity and switching/stopping anti-TNF treatment were associated with radiographic progression. (First Release Oct 1 2014; J Rheumatol 2014;41:2352–60; doi:10.3899/jrheum.131299)

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From the DANBIO registry and Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Glostrup Hospital, Glostrup; Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway; Zitelab Aps, Copenhagen; Department of Rheumatology, Aarhus University Hospital, Aarhus; Rheumatism Hospital, University of Southern Denmark, Gråsten; Department of Internal Medicine, Lillebælt Hospital, Vejle; Department of Rheumatology, Aarhus University Hospital, Aalborg; Department of Rheumatology, Copenhagen University Hospital Rigshospitalet; Department of Rheumatology, Copenhagen University Hospital Frederiksberg, Copenhagen; Department of Rheumatology, Helsingør Hospital, Helsingør; Department of Rheumatology/C, Copenhagen University Hospital Gentofte, Hellerup; Department of Internal Medicine, Holbæk Hospital, Holbæk; Department of Rheumatology, Copenhagen University Hospital Slagelse, Slagelse; Department of Rheumatology, Odense University Hospital, Odense; Department of Medicine, Hospital of South West Jutland, Esbjerg; Center

for Rheumatology and Spine Diseases, Copenhagen University Hospital Glostrup, Glostrup, Denmark.

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L.M. Ørnbjerg, MD; M. Østergaard, MD, PhD, DMSc; A. Thormann, MD; M.L. Hetland, MD, PhD, DMSc, DANBIO registry and Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Glostrup Hospital, and Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen; P. Bøyesen, MD, PhD, Department of Rheumatology, Diakonhjemmet Hospital; N.S. Krogh, consultant, Zitelab Aps; U. Tarp, MD, DMSc, Department of Rheumatology, Aarhus University Hospital; U.E. Poulsen, MD, Rheumatism Hospital, University of Southern Denmark; J. Espesen, MD, Department of Internal Medicine, Lillebælt Hospital; A. Schlemmer, MD, Department of Rheumatology, Århus University Hospital, Aalborg; N. Graudal, MD, DMSc, Department of Rheumatology, Copenhagen University Hospital Rigshospitalet; G. Kollerup, MD, PhD, Department of Rheumatology, Copenhagen University Hospital Frederiksberg; D.V. Jensen, MD, Department of Rheumatology, Helsingør Hospital; O.R. Madsen, MD, PhD, DMSc; A. Hansen, MD, Department of Rheumatology/C, Copenhagen University Hospital Gentofte; B. Glintborg, MD, PhD, Department of Internal Medicine, Holbæk Hospital; T.G. Christensen, MD, Department of Rheumatology, Copenhagen University Hospital Slagelse; H. Lindegaard, MD, PhD, Department of Rheumatology, Odense University Hospital; W. Bøhme, MD, Department of Medicine, Hospital of South West Jutland; A.R. Andersen, MD, Center for Rheumatology and Spine Diseases, Copenhagen University Hospital Glostrup.

Address correspondence to Dr. L.M. Ørnbjerg, DANBIO and Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Glostrup Hospital, Nordre Ringvej 57, DK-2600 Glostrup, Denmark. E-mail: lykke@oernbjerg.dk

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Rheumatoid arthritis (RA) is characterized by progressive joint destruction resulting in severe disability, increased morbidity, and mortality[1,2]. Randomized controlled trials (RCT) and observational studies of tumor necrosis factor-α inhibitors (anti-TNF) have demonstrated good efficacy on both clinical symptoms and radiographic outcome in 60–70% of patients[3,4,5,6,7,8]. Because anti-TNF therapy is costly and associated with adverse effects, characterization of patients likely to benefit from treatment is important.

Several observational registries have identified baseline factors associated with clinical response to anti-TNF[7,9,10,11]. Another key element of treatment evaluation with major implications for longterm outcome is halting of radiographic progression[1]. Posthoc analyses of RCT have identified risk factors for radiographic progression despite anti-TNF therapy[12,13], but have limited external validity because of stringent selection criteria[14]. Observational studies from clinical practice investigating baseline characteristics associated with halting of joint destruction during anti-TNF therapy are lacking.

Studies of disease-modifying antirheumatic drugs (DMARD) have shown a strong association between disease activity and radiographic outcome[15,16]. In contrast, RCT of anti-TNF have shown that patients can benefit radiographically from anti-TNF treatment despite limited or no effect on disease activity, suggesting an uncoupling of inflammation and radiographic progression[17,18,19]. The association between disease activity and radiographic progression in patients with RA treated with anti-TNF in clinical practice is unknown.

We aimed to identify baseline characteristics associated with radiographic progression during anti-TNF treatment of patients with RA in a real-world setting. Further, we aimed to investigate the effect of disease activity, drug, treatment switching, and withdrawal on radiographic progression.

MATERIALS AND METHODS

Patients. We included all anti-TNF-naive patients with RA who were in the DANBIO registry and who started treatment with adalimumab (ADA), etanercept (ETN), or infliximab (IFX) before July 1, 2007, and had 2 relevant sets of conventional radiographs (baseline and followup). The baseline radiographs preceded initiation of anti-TNF treatment by < 3 months and were preferably obtained 0–3 months after initiation, while the followup radiographs were obtained > 6 months after the baseline ones (preferably 2 yrs after anti-TNF initiation).

The DANBIO registry is a prospective observational cohort study initiated in 2000 and covering > 90% of Danish patients with RA who are treated with anti-TNF. Details of DANBIO and the Danish treatment strategy have been published[20]. According to Danish law, informed consent and ethical approval were not required for the present study.

Radiographic assessment. Radiographs were collected, digitized, and anonymized. An experienced reader blinded to patient identity and image sequence read the radiographs according to the Sharp/van der Heijde method[21]. Because foot radiographs were missing from a large proportion of patients, only radiographs of hands and wrists were scored (range 0–280). Annual radiographic progression rates in the individual patients were calculated by subtracting total Sharp score (TSS) at followup from TSS at baseline and dividing the change in TSS with the number of days between the 2 radiographs and multiplying by 365 days. Radiographic progression was defined as a change in TSS > 0, and rapid radiographic progression was defined as a change in TSS > smallest detectable change (SDC)[22,23]. SDC was 3.9 TSS units/year.

The intraobserver intraclass correlation coefficient (ICC; 1-way random effects model)[24] for TSS change was 0.35.

Clinical data. Disease Activity Score in 28 joints based on 3 variables including C-reactive protein (CRP; DAS28-CRP), patient's global assessment (VAS global), and Health Assessment Questionnaire (HAQ) scores were obtained from the DANBIO registry or patient files at 3 visits/timepoints: closest to the date of anti-TNF initiation (baseline), 2 years before anti-TNF start (pre-baseline), and the clinical visit closest in time to the followup radiograph (followup). DAS28-CRP with 3 variables

was chosen owing to few VAS global registrations at the pre-baseline visit.

Patient files were reviewed and data were registered on DMARD and glucocorticoid (GC) treatment (oral, intramuscular, intraarticular, or intravenous) in the study period and the 2 years prior to anti-TNF initiation. Administered GC were converted into corresponding prednisolone dosages based on the assumption that 3 mg betamethasone, 20 mg methylprednisolone, and 20 mg triamcinolone are all equivalent to 25 mg prednisolone.

All CRP measurements were collected, and time-averaged CRP was calculated for the study period and the 2 years prior to anti-TNF start [available in 650 and 620 patients; median (interquartile range [IQR]) number of measurements 14 (9–21) and 19 (12–29), respectively[25]]. In addition, time-averaged DAS28-CRP, 28 swollen joint count (SJC), 28 tender joint count (TJC), and VAS global in the study period were calculated. These variables were available in 880, 892, 891, and 884 patients, respectively, and based on median (IQR) 7 (5–11) number of measurements.

Statistical analyses. Descriptive statistics for continuous variables are presented as medians with ranges or IQR in parentheses, and categorical variables are presented as frequencies with percentages in parentheses. Differences between groups were analyzed using nonparametric statistics.

Radiographic data were analyzed with both parametric and nonparametric analyses according to the recommendations of van der Heijde, *et al*[23]. Analyses were 2-sided with significance level $p < 0.05$. Logistic regression analyses were used to identify factors associated with radiographic progression. Baseline factors were analyzed with univariate analyses, and significant variables ($p < 0.10$) were included in a multivariable logistic regression analysis with backward selection. These were tested as categorical variables: sex, type of anti-TNF, concomitant methotrexate (MTX; yes/no), concomitant prednisolone (yes/no), anti-TNF monotherapy (yes/no), IgM-rheumatoid factor (IgM-RF) positivity (yes/no), anticyclic citrullinated peptide antibody (anti-CCP) positivity (yes/no), and current smoking (yes/no). These were tested as continuous variables: baseline DAS28-CRP, CRP, SJC, TJC, VAS global, HAQ, age, disease duration, number of previous DMARD, calendar year of treatment initiation, and TSS. In the multivariable analysis, IgM-RF but not anti-CCP was included because of missing anti-CCP data. A separate multivariable analysis including only patients with anti-CCP data was performed as well as an analysis using rapid radiographic progression as the definition of progression. Analyses were performed with R version 2.13.0 (R Foundation for Statistical Computing[26].

RESULTS

Study population. By July 1, 2007, 2599 anti-TNF-naive patients with RA had been registered in DANBIO at the initiation of their first anti-TNF treatment and 1044 had 2 relevant sets of radiographs of hands and wrists. Insufficient radiographs (overexposure or underexposure, wrong positioning of hands) hindered scoring in 38 patients, leaving 1006 patients. After a review of patient files, 76 additional patients were excluded because of errors in DANBIO registration (erroneous diagnosis or registration of treatment, etc.). Demographic characteristics and disease activity are presented in Table 1 for the 930 included patients and the 1555 patients from whom we were unable to obtain 2 relevant radiographs.

Disease activity and treatment during the 2 years prior to anti-TNF start. From pre-baseline visit to baseline visit (median interval 777 days, IQR 654–1137) the median DAS28-CRP in patients with available data at both timepoints (n = 194) increased from 4.3 (IQR 3.0–5.3) to 5.0 (IQR 4.3–5.8; $p < 0.0001$, Wilcoxon signed-rank test). Time-averaged CRP was 26 (SD 35) mg/l (n = 620), and 462 patients (75%) had a time-averaged CRP above 10 mg/l. Patients were treated with median 2 (range 1–6) different DMARD during the period. A total of 783 patients (84%) received MTX (median time-averaged dose 10.5 mg weekly, median dose during treatment 15 mg/weekly) and 643 patients (69%) received GC (median time-averaged dose 2.2 mg prednisolone per day, median dose during treatment 8.6 mg per day) at some time.

Table 1. Demographic characteristics and baseline disease activity in included and excluded patients. Values are the median (range) except where indicated.

	Study Population, n = 930	DANBIO Patients without Relevant Radiographs, n = 1555	p
Male sex	233 (25%)	437 (28%)	0.09[1]
IgM-RF–positive*	704 (79%)	597 (81%)	0.26[1]
Anti-CCP–positive*	275 (64%)	201 (72%)	0.03[1]
Age, yrs	57 (19–88)	58 (15–89)	0.17[2]
Disease duration, years	9 (1–59)	9 (0–17)	0.86[2]
Current smokers	294 (38%)	229 (40%)	0.66[2]
No. previous DMARD	3.2 (0–9)	3.4 (0–9)	< 0.0001[2]
DAS28-CRP	5.0 (1.4–7.8)	4.9 (1.2–8.0)	0.009[2]
CRP, mg/l, mean (SD)	31 (38)	28 (32)	0.04[3]
HAQ score	1.25 (0–3.0)	1.375 (0–3.0)	0.04[2]
Total Sharp score, units	15 (0–235)	NA	
Erosive disease	765 (82%)	NA	

*Positive titer at least once during disease course. [1] Chi-square; [2] Mann-Whitney U test; [3] t test. The Disease Activity Score in 28 joints (DAS28-CRP) was based on 3 variables, including C-reactive protein (CRP). In the study population, the number of patients with available data ranged from 836 to 930, except for anti-CCP (n = 432) and smoking (n = 573). In the DANBIO registry patients without relevant radiographs, the number of patients with available data ranged from 273 (anti-CCP) to 1555. Anti-CCP: anticyclic citrullinated peptide antibodies; DMARD: disease-modifying antirheumatic drug; IgM-RF: IgM-rheumatoid factor; HAQ: Health Assessment Questionnaire; NA: not applicable.

Treatment during the study period. At baseline, patients started treatment with IFX (59%), ETN (18%), or ADA (23%). At the followup radiograph, 564 patients (61%) were treated with the initial anti-TNF while 273 patients (29%) had switched to another biological drug, and 93 patients (10%) had withdrawn from biological treatment. Of the 273 patients who switched treatment, 250 patients switched to a different anti-TNF, while 6/3/14 patients switched to abatacept/anakinra/rituximab, respectively.

A majority of patients (745, 80%) received concomitant treatment with MTX (median time-averaged dose 15 mg weekly, median dose during treatment 15 mg weekly), while 555 patients (60%) received GC (median time-averaged dose 2.2 mg prednisolone per day, median dose during treatment 7.3 mg per day), which was a lower proportion of patients

($p < 0.001$, chi-square) compared to the 2 years prior to anti-TNF treatment. Details on DMARD and anti-TNF treatment are presented in Tables 2 and 3, respectively.

Disease activity during the study period. From baseline to followup visit, median DAS28-CRP decreased from 5.0 (IQR 4.3–5.8) to 3.0 (IQR 2.1–3.9; $p < 0.0001$, Wilcoxon signed-rank test), and 328 patients (35%) achieved DAS28-CRP remission (DAS28-CRP < 2.6). Time-averaged DAS28-CRP was 3.4. VAS global decreased from 65 mm (IQR 45–78) to 28 mm (12–51; $p < 0.0001$, Wilcoxon signed-rank test), HAQ score from 1.25 (IQR 0.75–1.85) to 0.75 (IQR 0.25–1.375; $p < 0.0001$, Wilcoxon signed-rank test), and mean CRP level from 31 (38) mg/l to 14 (23) mg/l ($p < 0.001$, paired t test). Time-averaged CRP was 15 (16)

Table 2. DMARD treatment during the study period. Values are the median (interquartile range). All glucocorticoids were converted into corresponding prednisolone dosages.

DMARD	No. Patients Taking Drug	Treatment Period, Days	Dose While Taking Treatment	Time-averaged Dose During Study Period*
Methotrexate	745	487 (359–691)	15 (10–20) mg/w	15 (10–20) mg/w
Sulfasalazine	193	283 (51–441)	2000 (2000–2000) mg/d	716 (146–2000) mg/d
Hydroxychloroquine	121	230 (46–534)	200 (200–250) mg/d	84 (8–200) mg/d
Gold, intramuscular	5	74 (30–321)	47 (29–50) mg/w	6 (1–14) mg/w
Azathioprine	40	409 (120–570)	100 (50–103) mg/d	50 (9–100) mg/d
D-penicillamine	6	417 (224–550)	250 (43–463) mg/d	206 (17–463) mg/d
Cyclosporine	16	71 (36–136)	200 (150–200) mg/d	11 (8–60) mg/d
Leflunomide	40	221 (26–366)	20 (11–20) mg/d	4 (1–9) mg/d
Prednisolone	555	209 (8–436)	7.33 (5–17) mg/d	2.2 (0.5–5) mg/d

* In patients who at some timepoint received therapy with the drug. DMARD: disease-modifying antirheumatic drug; mg/w: milligram/week; mg/d: milligram/day.

Table 3. TNF inhibitor treatment during the study period. Values are the median (interquartile range) when not otherwise indicated.

	IFX*	ETN	ADA
No. patients, total 930	546	171	213
First-dose anti-TNF, mg/treatment	200 (200–250)	50 (50–50)	40 (40–40)
Maintenance dose anti-TNF at Week 16, mg/treatment in patients still taking drug	200 (200–250)	50 (50–50)	40 (40–40)
Maintenance frequency, weekly intervals at Week 16 in patients still taking drug	8 (8–8)	1 (1–1)	2 (2–2)
Status at followup, no. patients (%)			
Taking first anti-TNF	305 (56)	126 (73)	133 (62)
Switched from first anti-TNF	183 (33)	33 (20)	57 (27)
Withdrawn	58 (11)	12 (7)	23 (11)
Reasons for withdrawal, no. patients (%)			
Loss/lack of effect	30 (52)	5 (42)	9 (39)
Adverse events	21 (36)	5 (42)	7 (30)
Remission	1 (2)	0 (0)	2 (9)
Other	6 (10)	2 (9)	5 (22)
Reasons for switch, no. patients (%)			
Loss/lack of effect	115 (64)	23 (68)	45 (79)
Adverse events	54 (30)	11 (32)	11 (19)
Other	11 (6)	0 (0)	1 (2)
No. patients taking monotherapy, n = 132 (%)	31 (24)	59 (45)	42 (32)
Status at followup, no. patients (%)			
Taking first anti-TNF	10 (31)	43 (73)	21 (50)
Switched from first anti-TNF because of LOE/AE/other	7 (23)/7 (23)/1 (3)	9 (15)/2 (3)/0 (0)	11 (26)/4 (10)/1 (2)
Withdrawn because of LOE/AE/other	3 (10)/3 (10)/0 (0)	1 (2)/4 (7)/0 (0)	2 (5)/1 (2)/2 (5)

* Body weight 72 kg (16.5), mean (SD). Mean (SD) infliximab dose at initiation 223 (51) mg, corresponding to 3 mg/kg in accordance with the Danish recommendations (1 patient was treated with 5 mg/kg). Mean (SD) interval for infliximab treatment at Week 16, 7.8 (0.6) weeks. IFX: infliximab; ETN: etanercept; ADA: adalimumab; anti-TNF: anti–tumor necrosis factor treatment. LOE: loss/lack of effect; AE: adverse event.

mg/l, lower than in the previous 2 years ($p < 0.001$, paired t test). A total of 316 patients (49%) had a time-averaged CRP > 10 mg/l.

Radiographic progression. The median interval between baseline and followup radiographs was 529 days (IQR 392–735, range 180–2164). Median (IQR)/mean (SD) TSS increased from 15 (3–45)/31 (40; baseline radiograph) to 16 (3–48)/32 (40; followup radiograph; $p < 0.001$, Wilcoxon signed-rank test, paired t test). Median (IQR)/mean (SD) erosion score and joint space narrowing score each increased, from 8 (1–26)/18 (25) to 9 (1–26)/19 (25) and from 6 (0–20)/13 (17) to 6 (0–21)/13 (17), respectively. Radiographic progression was observed in 251 patients (27%), while 39 patients (4%) experienced rapid radiographic progression. A decrease in TSS was observed in 101 patients (11%). Median (IQR) decrease was –0.9 (–0.6 to –1.6). Four of these exceeded the SDC.

Baseline factors associated with radiographic progression during anti-TNF treatment. In univariate analyses, concomitant treatment with prednisolone, IgM-RF positivity, anti-CCP positivity, age, CRP level, and TSS were associated with radiographic progression (Table 4). In a multivariable analysis including IgM-RF but not anti-CCP (while adjusting for sex), concomitant treatment with prednisolone, IgM-RF positivity, increasing age, and baseline TSS remained independently associated with radiographic progression (Table 4 and Figure 1A). Including anti-CCP (replacing IgM-RF), positive anti-CCP (OR 1.72, 95% CI 1.06–2.87) and age (OR 1.36, 95% CI 1.12–1.66, per 10-yr increase) were independently associated with radiographic progression (n = 432). The fractions of explained variation (Nagelkerkes R^2) in the 2 models were 0.07 and 0.06, respectively. When both IgM-RF and anti-CCP were included in the model, IgM-RF was independently associated with radiographic progression while anti-CCP was not (data not shown).

Sensitivity analyses comparing patients included in the final model with patients excluded from the final model owing to missing data (n = 41) showed similar baseline characteristics and radiographic progression (data not shown).

With rapid radiographic progression as a dependent variable, IgM-RF positivity (OR 11.2, 95% CI 2.4–198.5) and CRP level (OR 1.007, 95% CI 1.001–1.011 per mg/l increase) were associated with rapid radiographic progression in univariate and multivariable analyses. Nagelkerkes R^2 was 0.06.

Type of anti-TNF did not influence radiographic progression in the overall cohort (Table 4) nor in the subgroup of patients who continued the initial anti-TNF during the whole followup period (n = 564; ADA vs ETN, OR 1.3, 95% CI 0.7–2.3; ADA vs IFX, OR 1.2, 95% CI 0.7–2.0). Radiographic progression rates were similar between the drugs in the group of patients who continued

Table 4. Univariate and multivariable logistic regression analyses of baseline predictors of radiographic progression. Data were adjusted for sex. Variables in bold face were included in the multivariable model.

Predictors	Univariate Analyses, Coefficient, OR (95% CI)	p	Multivariable Analyses, Coefficient, OR (95% CI)	p
Male sex	–0.08, 0.91 (0.65–1.30)	0.623		
Type of TNF-I (adalimumab as reference)				
Infliximab	–0.01, 0.99 (0.63–1.55)	0.96		
Etanercept	–0.05, 0.94 (0.66–1.35)	0.75		
Concomitant MTX (if treated)	–0.18, 0.83 (0.60–1.17)	0.28		
Concomitant prednisolone (if treated)	**0.45, 1.56 (1.18–2.17)**	**0.002**	**0.34, 1.39 (1.03–1.89)**	**0.03**
TNF-I monotherapy	0.06, 1.06 (0.70–1.60)	0.771		
IgM-RF (if positive)	**0.70, 2.0 (1.4–3.1)**	**0.0007**	**0.56, 1.75 (1.16–2.60)**	**0.008**
Anti-CCP (if positive)	**0.66, 1.93 (1.19–3.19)**	**0.009**		
Current smoking (if yes)	0.11, 1.12 (0.80–1.55)	0.518		
DAS28-CRP, per unit increase	0.05, 1.05 (0.92–1.20)	0.41		
CRP level, per mg/l increase	**0.004, 1.004 (1.0001–1.008)**	**0.032**		
SJC, per joint increase	0.01, 1.01 (0.99–1.04)	0.29		
TJC, per joint increase	–0.01, 0.99 (0.96–1.004)	0.121		
VAS global (per mm increase)	0.0006, 1.0006 (0.99–1.007)	0.83		
HAQ, per unit increase	**0.17, 1.18 (0.97–1.44)**	**0.093**		
Age, per 10-yr increase	**0.29, 1.34 (1.19–1.52)**	**< 0.0001**	**0.26, 1.30 (1.14–1.48)**	**0.001**
Disease duration, per yr	0.01, 1.01 (1.0005–1.03)	0.135		
No. previous DMARD	0.07, 1.07 (0.97–1.2)	0.172		
Calendar year of treatment initiation	–0.05, 0.95 (0.89–1.03)	0.253		
Total Sharp score, per 10-unit increase	**0.07, 1.07 (1.03–1.10)**	**0.0002**	**0.05, 1.05 (1.01–1.09)**	**0.02**

The disease activity score in 28 joints (DAS28-CRP) was based on 3 variables including C-reactive protein (CRP). Anti-CCP: anticyclic citrullinated peptide antibodies; DMARD: disease-modifying antirheumatic drug; IgM-RF: IgM-rheumatoid factor; HAQ score: Health Assessment Questionnaire; TNF-I: tumor necrosis factor inhibitor; SJC: swollen joint count; TJC: tender joint count; VAS: visual analog scale; MTX: methotrexate.

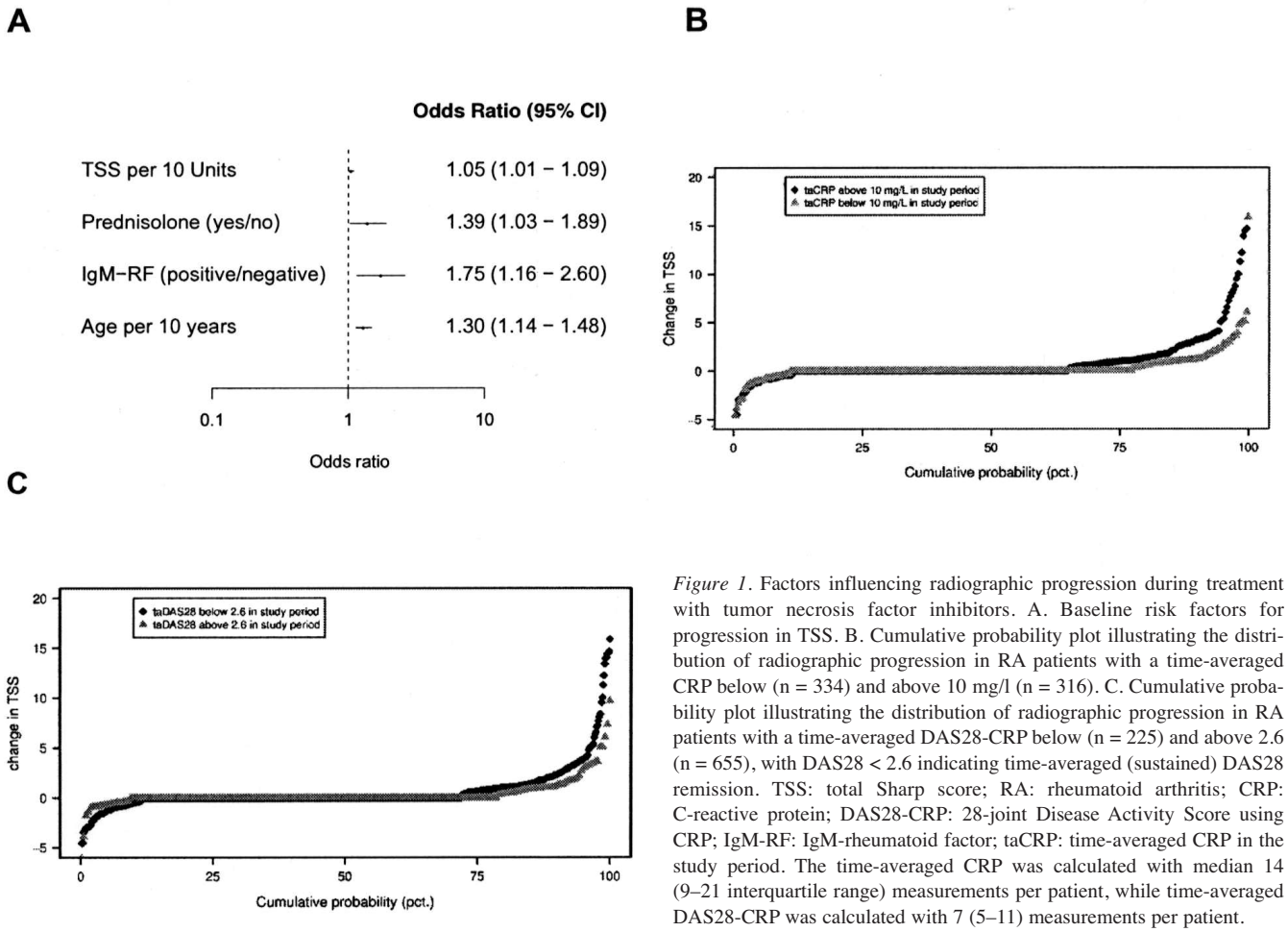

Figure 1. Factors influencing radiographic progression during treatment with tumor necrosis factor inhibitors. A. Baseline risk factors for progression in TSS. B. Cumulative probability plot illustrating the distribution of radiographic progression in RA patients with a time-averaged CRP below (n = 334) and above 10 mg/l (n = 316). C. Cumulative probability plot illustrating the distribution of radiographic progression in RA patients with a time-averaged DAS28-CRP below (n = 225) and above 2.6 (n = 655), with DAS28 < 2.6 indicating time-averaged (sustained) DAS28 remission. TSS: total Sharp score; RA: rheumatoid arthritis; CRP: C-reactive protein; DAS28-CRP: 28-joint Disease Activity Score using CRP; IgM-RF: IgM-rheumatoid factor; taCRP: time-averaged CRP in the study period. The time-averaged CRP was calculated with median 14 (9–21 interquartile range) measurements per patient, while time-averaged DAS28-CRP was calculated with 7 (5–11) measurements per patient.

the initial anti-TNF (p = 0.59, Kruskal-Wallis test, p = 0.56, ANOVA).

Interestingly, we found in a secondary analysis that patients who had daily received more than 2.5 mg, 5 mg, or 7.5 mg prednisolone during the 2 years prior to baseline had an increased risk of radiographic progression during followup (OR 1.5, 1.8, and 2.0, respectively, p < 0.01). For 1.25 mg of prednisolone, OR was 1.15 (not statistically significant).

Followup variables associated with radiographic progression. Figure 1B illustrates in a probability plot radiographic progression stratified by time-averaged CRP < or ≥ 10 mg/l while Figure 1C illustrates radiographic progression in patients with a time-averaged DAS28-CRP < or > 2.6. OR was 1.02 (1.01–1.03) per mg/l increase in time-averaged CRP. Similarly, an OR of 1.3 (1.14–1.50) per unit increase in time-averaged DAS28-CRP was found (both p < 0.0001). Similar associations were found when analyses were performed in subgroups of patients with a disease duration ≥ 3 years and < 3 years (time-averaged DAS28-CRP OR 1.34 vs 1.45 per unit increase, time-averaged CRP OR 1.02 vs 1.02 per mg/l increase, all p < 0.01). Time-averaged SJC, TJC, MTX, and prednisolone dosage were not associated with radiographic progression. For time-averaged VAS global, OR was 1.1 (1.03–1.17) per 10-mm increase (p = 0.008).

Effect of discontinuation of first anti-TNF on radiographic progression. Patients who switched biological treatment or withdrew from biological treatment during followup had a higher risk of radiographic progression than did patients who continued the initial anti-TNF (OR 1.62, 95% CI 1.17–2.22, p = 0.003; and OR 1.75, 95% CI 1.08–2.78; p = 0.02, respectively). In a model that included both the baseline factors and time-averaged CRP, we found that both switching and withdrawal from biological treatment remained independent risk factors (OR 1.68 and 2.06, respectively, p < 0.001).

Patients who continued treatment had an annual progression rate of median (IQR)/mean (SD) 0 (0–0)/0.3 (1.6) units/year. This was lower than in patients who switched treatment [0 (0–0.8), p < 0.001 (Mann-Whitney U test)/1 (3.6), p = 0.002 (2-sample t test)] or stopped treat-

ment [0 (0–1), p = 0.006 (Mann-Whitney U test)/0.8 (2.0), p = 0.02 (2-sample t-test)]. In patients who were treated the entire followup period, we observed a lower percentage of progressors than in the patients who switched or withdrew from treatment (23% vs 34% and 33%, respectively, p < 0.001, chi-square). Baseline disease activity and demographic characteristics were similar between the 3 subgroups of patients, in particular IgM-RF status, age, percentage of prednisolone users, and TSS at baseline. Patients who continued treatment during followup had lower time-averaged DAS28-CRP than did patients who switched or withdrew from biological treatment (3.1 vs 3.9 and 3.7, respectively, p < 0.001, Mann-Whitney U test).

Patients who were receiving active biological treatment (including switches) 100% of followup time were less likely to experience radiographic progression than were patients who were treated 1% of followup time (OR 0.34, 95% CI 0.21–0.72, p = 0.003). Similarly, patients who were treated more than 50% of followup time had a reduced risk of radiographic progression compared with patients who were receiving active biological treatment < 50% of followup time (OR 0.54, 95% CI 0.31–0.79, p = 0.02).

DISCUSSION

This is the first study searching for factors associated with radiographic progression in patients with RA treated with anti-TNF in clinical practice, to our knowledge. In this large cohort of patients treated with anti-TNF because of failure of prior DMARD treatment, very few patients experienced progression. This is a great clinical achievement with the incidental effect of limiting statistical power to identify such factors.

Our main finding was that older age, IgM-RF positivity, structural damage, and concomitant treatment with prednisolone at baseline were independently associated with radiographic progression 2 years after initiation of the first anti-TNF.

In a posthoc analysis of the Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE) trial, older age was associated with radiographic progression. In contrast to our finding, baseline radiographic damage was inversely associated with radiographic progression during treatment[27]. Modeling the probability of rapid radiographic progression (change in TSS > 5 units/yr) in ASPIRE[13] identified IgM-RF positivity as an important factor. In ASPIRE, baseline disease activity (28-joint SJC and CRP) was associated with rapid radiographic progression but not with radiographic progression *per se*. Similarly, we found that baseline CRP was independently associated with rapid radiographic progression but not with radiographic progression. In the BeSt study (*Behandel Strategieen*, i.e., Treatment Strategies Study), baseline erosion score, CRP, and IgM-RF/anti-CCP were independently associated with rapid radiographic progression in a cohort of DMARD-treated and anti-TNF-treated patients[12]. Our findings are consistent with numerous studies from the pre-anti-TNF era, when baseline radiographic damage and IgM-RF positivity were associated with severe radiographic outcome irrespective of treatment[28,29].

Of the baseline factors associated with radiographic progression identified in our study, age and concomitant prednisolone have been found to be inversely associated with a clinical response in the DANBIO registry[7]. The Italian LORHEN registry also found that concomitant prednisolone (> 5 mg/day) was associated with a clinical nonresponse[11]. In the present observational study of patients with primarily established RA, we interpret baseline concomitant prednisolone as a surrogate marker of previous high disease activity. It is notable that, to our knowledge, no association between IgM-RF positivity and clinical response has been published, while both RCT and our observational study report a strong association between IgM-RF positivity and radiographic progression. This confirms that the pathways leading to joint inflammation and joint damage are not identical. In accordance with this, studies have shown different clinical effectiveness for the 3 anti-TNF[7,30,31,32] while type of anti-TNF had no association with radiographic progression in our study.

It is a strength of our study that the generalizability is high because it included the largest published anti-TNF-treated RA cohort with radiographic data from clinical practice. The data completeness in the DANBIO registry is generally high and because of review of all patient files, missing data were kept to a minimum.

However, using registry data has several inherent limitations, most importantly the varying length of followup and the absence of variables known to be associated with radiographic progression in other settings, e.g., bone marrow edema by magnetic resonance imaging[33]. Levels of IgM-RF and anti-CCP may have provided additional information. Anti-CCP data were available in only half the patients as a result of the historical nature of the study cohort. However, in analyses of the 432 patients with anti-CCP data, the prognostic value of anti-CCP was not superior to that of IgM-RF. In addition to factors known to influence radiographic progression, unmeasured confounders such as comorbidities and socioeconomic status may have influenced our findings.

The fraction of variation explained by our model was low. This could partly be explained by the lack of information on known — and unknown — associated factors. We observed radiographic progression in 27% of patients and rapid radiographic progression in only 4%. In our study, only hand and wrist radiographs were evaluated owing to few available foot radiographs, and this might have led to an underestimation of the frequency of radiographic progression. Knevel, *et al* report that omitting foot radiographs

leads to misclassification of 20%–30% of patients as being nonerosive in an RA cohort observed for 2 years[34]. The statistical power of future studies could benefit from the inclusion of foot radiographs.

In this cohort, inflammation in the study period (assessed by time-averaged CRP and DAS28-CRP) and radiographic progression were strongly associated, which highlights the importance of inflammatory control achieved during treatment. When stratifying the cohort for disease duration (≥ 3 yrs vs < 3 yrs), similar associations were found. Thus, a key implication of our findings for the clinician is the importance of a treatment strategy in routine care settings aiming at remission with tight clinical monitoring including regular radiographs of all anti-TNF-treated patients, especially of patients with prognostic factors indicating severe radiographic outcome identified by our model to ensure that adjustment of treatment is not delayed if either the clinical or the radiographical response is unsatisfactory.

The Danish Health and Medicines Authority requires registration of all Danish patients with RA in the DANBIO database, which promotes a treat-to-target strategy. The low radiographic progression rates observed in our cohort of DANBIO-registered patients are comparable to rates observed in RCT, and only 4% of our cohort experienced rapid radiographic progression, i.e., an annual change in TSS above the SDC. These findings emphasize the potential for improving treatment outcomes by routine registration and tight control aiming at remission for all patients with early RA.

We found that the rate of radiographic progression during 2 years of followup in our cohort of 930 anti-TNF-treated patients with RA from clinical practice was very low. Factors independently associated with radiographic progression were previous radiographic structural damage, higher age, IgM-RF positivity, and concomitant prednisolone at the initiation of treatment with anti-TNF. High disease activity during treatment, and switching and withdrawal from anti-TNF treatment increased the risk of radiographic progression, while we found no association between type of anti-TNF and radiographic progression.

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