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Original article

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Impact of different infliximab dose regimens on treatment response and drug survival in 462 patients with psoriatic arthritis: results from the nationwide registries DANBIO and ICEBIO

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Abstract

Objective. The aim of this study was to describe dose regimens, dose escalation and clinical outcomes in TNF-α inhibitor (TNFi)–naive patients with PsA treated with infliximab in routine rheumatology care.

Methods. We conducted an observational cohort study based on the nationwide Danish Rheumatologic Database (DANBIO) and Center for Rheumatology Research (ICEBIO) registries. Stratified by country, characteristics of patients treated with ⩽3 mg infliximab/kg body weight, 3–5 mg/kg or ⩾5 mg/kg every 8 weeks were described. Outcomes were evaluated by ACR 20%, 50% and 70% (ACR20/50/70) responses and European League Against Rheumatism good response after 6 months, disease activity after 12 months, Kaplan–Meier plots and regression analyses.

Results. Four hundred and sixty-two patients (376 Danish, 86 Icelandic) received treatment with infliximab. In Danish patients, the starting dose was ⩽3 mg/kg in 110 patients (29%), 3–5 mg/kg in 157 (42%), ⩾5 mg/kg in 38 (10%) and unregistered in 71 (19%). In Icelandic patients, corresponding numbers were 64 (74%), 17 (27%), 0 (0%) and 5 (6%). Patients with a higher body weight received lower doses per kilogram. Danish patients received higher doses than Icelandic patients at baseline [median 3.1 (interquartile range 3.0–3.8) *vs* 2.3 (2.1–2.9) mg/kg, $P < 0.05$] and after 12 months [3.3 (3.0–4.5) *vs* 2.9 (2.2–3.5) mg/kg, $P < 0.0001$]. After 12 months, 58% of Danish and 66% of Icelandic patients maintained treatment. Danish patients had shorter drug survival than Icelandic patients (1183 *vs* 483 days). In univariate analyses stratified by country, time until dose escalation, response rates, drug survival and 1-year's disease activity were independent of starting dose. Drug survival was shorter among patients not receiving concomitant MTX.

Conclusion. In clinical practice, >70% of Icelandic and Danish PsA patients treated with infliximab received sustained doses below the 5 mg/kg every 8 weeks recommended in international guidelines. Lower starting doses did not affect drug survival or response.

Key words: PsA, outcome, drug survival, biological treatment, infliximab, routine care, clinical registry.

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CLINICAL SCIENCE

Introduction

Therapy with TNF-α inhibitors (TNFis) has improved treatment outcome in patients with PsA who have failed treatment with conventional synthetic DMARDs (csDMARDs) [1–8]. B

By March 2013, four TNFis were marketed in Denmark and Iceland to treat PsA: adalimumab, etanercept, golimumab and infliximab [7, 9–12]. The recommended dose regimens for adalimumab, etanercept and golimumab in PsA are equal to the regimens in RA, i.e. fixed dosage independent of the patient's body weight. For infliximab, patients with PsA are recommended higher doses than patients with RA, i.e. 5 *vs* 3 mg/kg body weight every 8 weeks [13–16]. This recommendation is based on data from randomized placebo-controlled clinical trials [4, 6, 17, 18]. Data on the effectiveness of lower infliximab doses in PsA are, however, scarce [19–23].

The Danish nationwide DANBIO registry now includes >10 years of prospective follow-up of patients with inflammatory arthritis treated with biologics in routine care [24, 25]. Similarly, Icelandic patients have been registered and followed in the ICEBIO registry since 2007 [26].

Based on data from DANBIO and ICEBIO we aimed to describe the following: (i) the infliximab dose regimens used in clinical practice, (ii) dose escalation and (iii) whether the starting dose regimen affected (a) treatment response and (b) drug survival in TNFi-naive patients with PsA receiving their first infliximab treatment course.

Patients and methods

The nationwide Danish DANBIO registry commenced in 2000 and covers >90% of Danish adults treated with biologics due to rheumatic disease in routine care [27–29]. Prospective data registration in the Icelandic ICEBIO registry started in 2007. Biologic treatment courses, which were started in Iceland before 2007, have been registered retrospectively. Currently ICEBIO covers >95% of all biologic treatment given in Iceland in patients with rheumatic disorders (B. Gudbjorsson, 2013, personal communication). According to Danish legislation, the registration and publication of data from clinical registries does not require patient consent or approval by an ethics committee. In Iceland, this study was approved by the National Bioethics Committee (VSNb201310035/03.15) and the Data Protection Authority (2012080907HGK).

In Iceland, local hospital guidelines in PsA recommend infliximab doses of 200 mg every 8 weeks, irrespective of the patient's body weight. In cases of insufficient response, doses are increased stepwise to 300, 400 or 500 mg [26, 30]. In Denmark, no national treatment guidelines existed during the study period.

By March 2013, 4966 patients with a diagnosis of PsA according to the treating physician had been registered (4742 patients in DANBIO, 224 in ICEBIO). Among these, 3237 patients were treated only with csDMARDs. The remaining 1729 patients were treated with biologic DMARDs (bDMARDs): 462 patients received infliximab as the first bDMARD, 705 adalimumab, 371 etanercept, 51 golimumab and 19 received other biologic drugs. We excluded 82 patients treated with bDMARDs as part of clinical trials and 39 patients with insufficient data on their first TNFi treatment course. Only the 462 patients who received infliximab as the first bDMARD were included in the present study.

DANBIO and ICEBIO use a common web-based system (www.danbio-online.dk) [31]. Baseline demographics include age, gender, body weight, height, disease duration, previous or current treatment with MTX or other csDMARDs. Functional status and peripheral disease activity are monitored prospectively by the Health HAQ [32], the 28-joint DAS (DAS28) [33], CRP level (normal range ⩽10 mg/l) and visual analogue scales (VASs) for pain, patient's global assessment and fatigue. It is not explicitly registered whether a patient has spinal disease. Data registration is recommended to occur at least biannually, or when the medical treatment is changed [24].

Infliximab dose regimens

The infliximab dose per infusion was reported as (i) the total dose per infusion (in mg) and (ii) the dose measured in milligrams per kilogram of body weight. The patients were treated at weeks 0 (baseline), 2 and 6 and thereafter at regular intervals (typically every 8 weeks). Arbitrarily patients were divided into three categories according to dose per kilogram of body weight at the baseline visit: ⩽3 , 3–5 , ⩾5 mg/kg. Dose escalation was defined as increased dose and/or reduced time intervals between infusions compared with baseline.

Data quality

Queries were sent to the departments regarding treatment series with incomplete data (infliximab dose regimens and/or body weight) and the registries were corrected accordingly.

Treatment duration

Treatment duration was the number of days individual patients maintained infliximab treatment. The start date was the date the first dose was given and the stop date was the date of the first missed dose. Temporary treatment interruptions of ⩽3 months were allowed. All observations were censored by 15 March 2013. Among patients with no follow-up since 15 November 2012, data were censored according to the last visit registered.

The reasons for drug discontinuation are registered in DANBIO/ICEBIO in pre-specified categories: lack of treatment effect (LOE), adverse events (AEs), disease remission, pregnancy, surgery, cancer, death, infections, loss to follow-up and other reasons. In the following, reasons for discontinuation are divided into three categories: AEs (including infection, death or cancer), LOE and other (including pregnancy, surgery, loss to follow-up, remission or multiple reasons for discontinuation).

Treatment response

Disease activity and physical function were evaluated at baseline and after 3, 6 and 12 months of therapy. The

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baseline visit was defined as the time window from 30 days before until 6 days after the initiation of therapy. For the 3-month visit the time window was 10–17 weeks, for the 6-month visit it was 18–32 weeks and for the 12-month visit it was 46–64 weeks after initiation of treatment. If more than one registration occurred within a given time window, the one closest to the given time point was selected for analysis. If a patient had no registrations within a given time window, data were registered as missing for the given visit.

In the analyses of the 12-month outcome, the last observation carried forward (LOCF) method was used among patients with missing data at the 12-month visit and among patients who had stopped treatment within the first year. All other calculations were based on observed data with no imputation of missing data.

Clinical response was evaluated as achievement of ACR 20%, 50% or 70% response (ACR20/50/70) [34] or the European League Against Rheumatism (EULAR) good response [35]. We classified patients as responders if they achieved clinical response (yes/no) at both the 3- and 6-month visits compared with baseline. In case of missing data at either the 3- or 6-month visit, one registration of clinical response was sufficient to characterize the patient as a responder. Patients who had stopped treatment within the first 10 weeks of therapy were considered non-responders (non-responder imputation, $n = 44$).

Statistics

Statistical analyses were performed using SPSS version 16.0 (SPSS, Chicago, IL, USA) and SAS version 9.0 (SAS Institute, Cary, NC, USA) software. Demographic and descriptive data are presented as median [interquartile range (IQR)]. Groups were compared by non-parametric tests (chi-squared, Mann–Whitney, Wilcoxon signed rank test). A P-value of < 0.05 was considered statistically significant.

Kaplan–Meier plots and log-rank tests were performed for infliximab drug survival analyses and to analyse time until dose escalation. Univariate and multivariate Cox regression analyses with hazard ratios (HRs) were used to identify the impact of baseline infliximab dose on drug survival. In the subanalysis of time to discontinuation due to AEs, discontinuations due to ineffectiveness were censored. Similarly, discontinuations due to AEs were censored in the analysis of discontinuation due to ineffectiveness. Logistic regression analyses and odds ratios were calculated to identify the impact of baseline infliximab dose on clinical response. Baseline infliximab dose was included in all analyses as a categorical variable ($\leqslant 3$, 3–5, $\geqslant 5$ mg/kg). Additional sensitivity analyses were performed with the baseline dose (in mg/kg) as a continuous variable.

All multivariate analyses were performed stratified by country to avoid statistical interaction. The following baseline variables were considered *a priori* confounders and included in all multivariate analyses: gender, MTX use (yes/no), patient age, time interval between infusions (weeks), disease duration (years), HAQ and DAS28. Calendar year of starting treatment and body weight were considered intermediate variables potentially influenced by the starting dose of infliximab and were not included.

Results

A total of 462 infliximab-treated patients (376 Danish, 86 Icelandic) were included. Baseline demographics for Danish and Icelandic patients are shown in Table 1 and Table 2, respectively. The median starting infliximab dose was 3.1 mg/kg (IQR 3.0–3.8) for Danish patients and 2.3 mg/kg (2.1–2.9) for Icelandic patients ($P < 0.0001$). After up-titration, 94% of patients received infliximab at 8-week intervals. Danish patients had lower body weight [80 kg (IQR 68–94) *vs* 87 (77–97), $P = 0.001$], lower BMI [27 kg/m^2 (IQR 24–30) *vs* 29 (26–32), $P = 0.001$], higher DAS28 [4.7 (IQR 3.8–5.5) *vs* 4.2 (3.3–4.9), $P = 0.009$] and higher tender joint count (TJC) [6 (IQR 2–11) *vs* 4 (2–6), $P = 0.006$] compared with Icelandic patients upon initiation of therapy, whereas other baseline characteristics [age, gender distribution, height, disease duration, MTX use, VAS score, swollen joint count (SJC) and CRP] were similar (all $P > 0.05$).

At baseline, Danish patients treated with $\geqslant 5$ mg/kg infliximab had lower SJC and lower VAS physician score compared with Danish patients on lower doses, whereas other measures of disease activity were similar (Table 1). Doses >5 mg/kg were more often started in the later years and in women (Table 1). Among Icelandic patients there was a tendency towards higher VAS physician score and TJC among patients starting treatment with >3 mg/kg, and no patients started on doses $\geqslant 5$ mg/kg (Table 2). In both Denmark and Iceland, patients with higher body weight and BMI received lower doses per kilogram (Table 1 and Table 2).

At 12 months median infliximab doses for Danish and Icelandic patients were 3.3 mg/kg (IQR 3.0–4.5) and 2.9 (2.2–3.5) ($P < 0.0001$) every 8 (8–8) weeks, respectively. The median dose per infusion was 300 mg (IQR 200–300) and 200 (200–300) ($P < 0.01$), respectively. Danish patients had similar disease activity irrespective of the baseline infliximab dose (LOCF, Kruskal–Wallis test; Table 3). Similar results were found in Icelandic patients (data not shown, all $P > 0.05$). There were no differences in DAS28, VAS score, SJC, TJC or HAQ after 12 months between Danish and Icelandic patients (Mann–Whitney, all $P > 0.05$, data not shown).

At the latest registered visit, 247 patients (53%) received infliximab in unaltered or reduced regimens, whereas 145 patients (31%) (53% of Icelandic and 26% of Danish patients) had an increased dose due to either increased dose per infusion [65 patients, median dose increase/kg 1.2 mg/kg (IQR 0.8–1.8)], shortening of the time interval between infusions (32 patients) or both (48 patients). In 2% of patients the infliximab dose was increased but the time intervals were prolonged or vice versa. Data were missing in 13% of patients. Danish patients on increased infliximab dose regimens had longer treatment duration [median 819 days (IQR 321–1723)]

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Table 1 Baseline demographics and disease activity for Danish patients registered in DANBIO according to infliximab dose at the baseline visit

	Total	Infliximab dose/kg ($n = 305$ [a])			*P*-value[b]
		⩽3 mg	3–5 mg	⩾ 5 mg	
Patients, *n*	376	110	157	38	
Infliximab dose, mg	290 (200–300)	200 (200–293)	300 (200–300)	403 (400–500)	<0.0001
Female, *n* (%)	204 (54)	50 (45)	96 (61)	23 (61)	0.03
Dosing interval, weeks	8 (8–8)	8 (8–8)	8 (8–8)	8 (8–8)	0.04
Year starting TNFi, *n* (%)					
2000–2	20 (5)	6 (5)	5 (3)	0 (0)	<0.001
2003–5	104 (28)	30 (27)	31 (18)	6 (15)	
2006–8	145 (39)	54 (49)	69 (44)	4 (11)	
2009–12	107 (28)	20 (18)	52 (33)	28 (74)	
Concomitant MTX, *n* (%)	260 (69)	82 (75)	111	22	0.2
Disease duration, years	7 (3–13)	9 (3–17)	7 (3–14)	6 (4–11)	0.6
Age, years	48 (40–56)	46 (40–55)	50 (40–58)	47 (41–54)	0.2
Body weight, kg	80 (68–94)	82 (71–100)	80 (65–90)	80 (70–90)	0.01
Body height, cm	172 (165–178)	172 (166–180)	172 (165–178)	176 (167–182)	0.2
BMI, kg/m^2	27 (24–30)	28 (25–32)	26 (23–30)	26 (23–29)	0.006
HAQ	1.1 (0.8–1.6)	1.1 (0.6–1.6)	1.1 (0.8–1.6)	1.0 (0.6–1.8)	1.0
DAS28	4.7 (3.8–5.5)	4.9 (3.7–5.6)	4.7 (3.8–5.5)	4.0 (3.3–5.3)	0.1
CRP, mg/l	10 (4–25)	10 (5–24)	10 (4–26)	5 (2–12)	0.07
SJC, *n* (range)	2 (1–6)	3 (0–7)	2 (1–5)	1 (0–2)	0.02
TJC, *n* (range)	6 (2–11)	6 (2–14)	6 (2–11)	4 (1–9)	0.3
VAS physician, score (range)	37 (23–55)	38 (26–57)	39 (22–52)	25 (17–39)	0.02
VAS global, mm	69 (51–84)	67 (50–84)	68 (49–87)	72 (52–90)	0.9
VAS fatigue, mm	68 (47–83)	69 (45–77)	70 (49–86)	68 (42–90)	0.4
VAS pain, mm	62 (43–76)	65 (45–78)	62 (37–75)	58 (34–81)	0.8

Data are presented as median (interquartile range) unless stated otherwise. [a]Missing data on baseline infliximab dose in 71 patients. [b]*P*-value in Kruskal–Wallis test. TNFi: TNF-α inhibitor; DAS28: 28-joint DAS; SJC: swollen joint count; TJC: tender joint count; VAS: visual analogue scale.

compared with the patients receiving unaltered/reduced doses [371 days (159–1249)] ($P < 0.001$). Similar results were found in Icelandic patients [1207 days (432–2139) *vs* 307 (120–757), $P < 0.001$].

The numbers of Danish and Icelandic patients receiving starting doses of ⩽3, 3–5 or ⩾5 mg/kg are shown in Fig. 1. Among patients with available data and who were treated for >100 days, 77% (205/265) of Danish and 96% (69/72) of Icelandic patients received sustained infliximab doses <5 mg/kg (Fig. 1).

Data on baseline infliximab dose per kilogram were missing in 71 Danish and 5 Icelandic patients. Danish patients with missing data had similar gender, BMI and age distribution to the 305 patients with available data (all $P > 0.05$), whereas patients with missing data more often started treatment during earlier years ($P < 0.0001$). In Icelandic patients, baseline demographics were similar between patients with available and those with missing data on baseline dose (all $P > 0.05$).

Cumulated follow-up time for Danish and Icelandic patients was 1185 patient-years and the median follow-up time was 550 days (95% CI 383, 317). Overall, 116 patients (25%) stopped treatment due to LOE and 134 (29%) stopped due to AEs. The reasons for stopping treatment were similar for Danish and Icelandic patients ($P = 0.4$). The starting infliximab dose per kilogram was similar between patients who continued treatment [median 3.0 mg/kg (IQR 2.6–3.8)] and patients who stopped due to LOE [3.1 mg/kg (2.7–3.6)] or AEs [3.1 mg/kg (2.9–3.5)] ($P = 0.2$). At the latest visit, patients who stopped treatment due to LOE received higher infliximab doses compared with patients who stopped due to AEs [median 3.5 mg/kg (IQR 3.0–4.7) *vs* 3.1 (2.9–3.7), $P = 0.002$].

After 12 months, 58% of Danish and 66% of Icelandic patients were still on the drug. Drug survival was significantly shorter among Danish compared with Icelandic patients [median 483 days (95% CI 372, 594) *vs* 1183 (470–1896), log rank 7.7, $P = 0.005$] (Fig. 2A). The starting infliximab dose did not affect survival (Danish patients: Fig. 2B; Icelandic patients: Fig. 2C). For Danish patients, drug survival was shorter in patients not receiving concomitant MTX (Fig. 2D) and when treatment was started in later years (Fig. 2E). Similar results were found when Kaplan–Meier analyses were performed among Icelandic patients (MTX use, $P = 0.1$; treatment start year, $P = 0.003$). The start dose did not affect the time until dose escalation ($P = 0.9$). The median number of days until dose escalation was similar for Danish and Icelandic patients [266 days (IQR 131–560) *vs* 290 (182–559), $P = 0.2$].

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Table 2 Baseline demographics and disease activity for Icelandic patients registered in ICEBIO according to infliximab dose at the baseline visit

	Total	Infliximab dose/kg ($n = 81$[a])			*P*-value[b]
		⩽3 mg	3–5 mg	⩾5 mg	
Patients, *n*	86	64	17	0	
Infliximab dose, mg	200 (200–200)	200 (200–200)	200 (200–350)	—	<0.0001
Female, *n* (%)	48 (56)	35 (54)	12 (71)	—	0.2
Dosing interval, weeks	8 (8–8)	8 (8–8)	8 (8–8)	—	1.0
Year starting TNFi, *n* (%)				—	
2000–2	5 (6)	5 (8)	0 (0)	—	0.9
2003–5	15 (17)	10 (16)	2 (12)	—	
2006–8	25 (29)	16 (25)	8 (47)	—	
2009–12	41 (48)	33 (52)	7 (41)	—	
Concomitant MTX, *n* (%)	53 (61)	40 (63)	10 (59)	—	0.8
Disease duration, years	8 (3–17)	7 (3–17)	7 (2–35)	—	0.8
Age, years	48 (36–54)	49 (37–55)	43 (35–62)	—	0.8
Body weight, kg	87 (77–97)	92 (80–99)	65 (61–86)	—	<0.001
Body height, cm	172 (166–182)	174 (167–182)	167 (162–169)	—	0.002
BMI, kg/m^2	29 (26–32)	30 (27–33)	24 (21–30)	—	0.006
HAQ	0.8 (0.3–1.1)	0.8 (0.3–1.0)	1.4 (0.2–2.1)	—	0.3
DAS28	4.2 (3.3–4.9)	4.2 (3.3–4.9)	4.8 (4.4–6.0)	—	0.1
CRP, mg/l	8 (5–19)	9 (4–19)	9 (6–39)	—	0.7
SJC, *n* (range)	3 (1–5)	3 (1–5)	5 (1–8)	—	0.6
TJC, *n* (range)	4 (2–6)	4 (2–6)	6 (5–17)	—	0.08
VAS physician, score (range)	55 (42–67)	51 (40–64)	72 (56–89)	—	0.05
VAS global, mm	35 (37–81)	64 (38–80)	89 (47–97)	—	0.1
VAS fatigue, mm	74 (45–80)	72 (49–80)	91 (47–100)	—	0.1
VAS pain, mm	65 (42–81)	63 (45–80)	88 (47–97)	—	0.2

Data are presented as median (interquartile range) unless stated otherwise. [a]Missing data on baseline infliximab dose in five patients. [b]*P*-value in Kruskal–Wallis test. TNFi: TNF-α inhibitor; DAS28: 28-joint DAS; SJC: swollen joint count; TJC: tender joint count; VAS: visual analogue scale.

Table 3 Disease activity at the 1-year visit for Danish patients according to the baseline infliximab dose

	Baseline infliximab dose/kg[a]			*P*-value
	⩽3 mg	3–5 mg	⩾5 mg	
Number still treated after 12 months, *n* (%)	70 (64)	89 (57)	24 (63)	
HAQ	0.8 (0.2–1.3)	0.6 (0.1–1.1)	0.9 (0.2–1.4)	0.8
DAS28	3.0 (2.3–3.9)	3.1 (2.1–4.2)	2.4 (2.1–4.1)	0.3
CRP, mg/l	5 (2–10)	5 (2–11)	4 (1.5–8.5)	0.4
SJC, *n* (range)	0 (0–3)	0 (0–2)	0 (0–1)	0.1
TJC, *n* (range)	1 (0–4)	2 (0–6)	0 (0–6)	0.5
VAS global, mm	33 (13–62)	33 (15–63)	37 (19–84)	0.9
VAS fatigue, mm	47 (16–68)	50 (25–76)	63 (25–83)	0.6
VAS pain, mm	27 (13–59)	32 (10–56)	36 (16–77)	0.2

Data are presented as median (interquartile range), unless stated otherwise. [a]Missing data on baseline dose, $n = 39$ (16%). Last observation carried forward (LOCF) method. DAS28: 28-joint DAS; VAS: visual analogue scale; SJC: swollen joint count; TJC: tender joint count.

In multivariate Cox regression analysis among Danish patients, infliximab starting dose as a categorical value did not affect drug survival ($P = 0.5$). In a similar analysis with starting dose as a continuous variable, patients on a lower dose had shorter drug survival [HR 0.7/mg/kg (95% CI 0.55, 0.95), $P = 0.02$]. The same pattern was observed when looking only at patients who withdrew due to AEs [HR 0.7/mg/kg (95% CI

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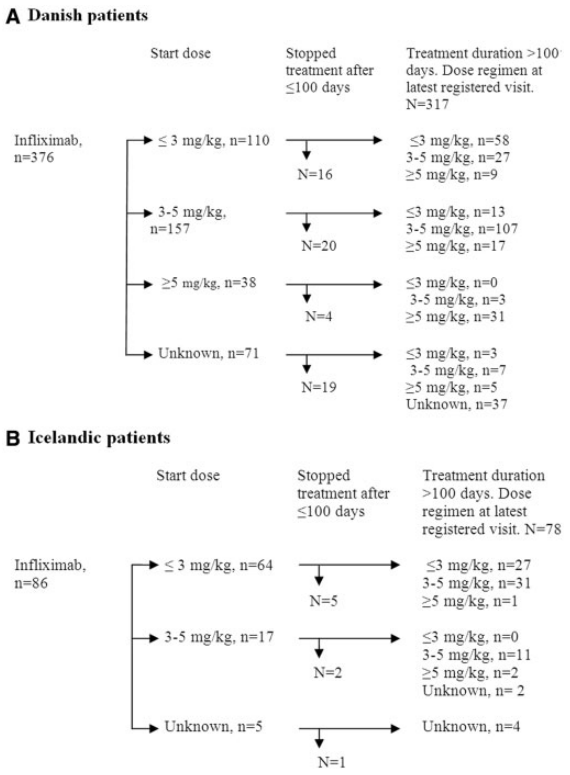
Fig. 1 Study flow chart of infliximab dose according to treatment duration, stratified by country



0.4, 1.1), $P = 0.06$] or LOE [HR 0.7 (95% CI 0.5, 1.0), $P = 0.07$].

In multivariate Cox regression analysis of Icelandic patients, those who started treatment with doses $\leqslant 3$ mg/kg had longer drug survival than patients starting on higher doses [$\leqslant 3$ *vs* 3–5 mg/kg, HR 0.2 (95% CI 0.001, 0.5), $P = 0.02$)]. In a similar analysis with infliximab starting dose as a continuous variable, the starting dose was not statistically significant ($P = 0.6$). Stratified analyses according to the cause of treatment termination were not performed in Icelandic patients due to few events.

In Danish patients, EULAR good response and ACR20/50/70 response rates after 6 months were 33%, 38%, 23% and 10%, respectively. EULAR and ACR response data were available in 54% and 63% of patients, respectively, with no systematic differences between patients with complete and incomplete data, except for more patients with missing ACR response data during earlier years. The response rates were not associated with baseline dose (as categorical or continuous variable) in either univariate or multivariate analyses. In Icelandic patients, EULAR good response and ACR20/50/70 response rates after 6 months were 39%, 27%, 17% and 11%, respectively. Response data were available in 38% of patients. There were no statistically significant differences in response rate between Danish and Icelandic patients (all $P > 0.05$).

Discussion

In this observational study of 376 Danish and 86 Icelandic patients with PsA treated with infliximab in routine care, the majority of patients received continuous treatment with doses below the 5 mg/kg recommended in international guidelines. The starting infliximab dose did not affect the time until dose increase, drug effectiveness or drug survival. Icelandic patients received lower doses than Danish patients but had similar response rates and longer drug survival.

In RA, treatment with infliximab doses at 3 mg/kg with gradual dose escalation according to clinical response is a well-known treatment strategy [36–38]. The recommended infliximab dose regimen in PsA is 5 mg/kg every 8 weeks [13, 16] based on data from randomized controlled trials (RCTs) [4, 6, 17, 18]. Few data are available on the effectiveness of lower doses [39] and originate mainly from small observational studies of $\leqslant 10$ patients [19, 21] or case reports [20]. No randomized trials on dose escalation have been performed.

Infliximab starting doses in patients with PsA treated in routine care vary across countries [40–42]. In Sweden, patients with PsA routinely receive a starting dose of 3 mg/kg [43, 44]. In the current study, Danish patients received a median starting dose of 3.1 mg/kg, which was independent of baseline disease activity. The more frequent use of a 5 mg/kg starting dose after year 2008 might reflect that RA dose regimens were copied in the earlier years and that adherence to international guidelines for PsA [13, 16] was higher in the later years. In Iceland, the treating physicians complied with national Icelandic treatment guidelines with a median starting dose of 2.3 mg/kg and no patients started treatment with doses $\geqslant 5$ mg/kg.

Despite dose escalation in 53% of Icelandic and 26% of Danish patients, the majority of patients received sustained treatment with doses <5 mg/kg. This is in contrast to observational data on 32 patients with PsA followed for 2 years by the South Swedish Arthritis Treatment Group (SSATG). In the Swedish study, 72% of the patients needed dose escalation [23]. The SSATG has previously reported the average infliximab dose among 114 patients with PsA to be $\sim$5 mg/kg every 8 weeks after 6 months of treatment [43]. The Swedish patients apparently had similar baseline disease activity and demographics as the Danish and Icelandic populations [23]. The Swedish studies provide no data on infliximab response rates and survival [23, 43], so we do not know whether the different regimens affected outcome.

Drug survival may be perceived as a measure of treatment effectiveness [45]. In Danish patients, drug survival was longer among patients who received higher baseline infliximab doses, thus indicating a positive effect of higher doses. However, the infliximab dose only affected drug survival in multivariate and not univariate analyses. In Icelandic patients, the picture was less clear, perhaps due to limited statistical power. The different treatment strategies in Denmark *vs* Iceland might have an impact on the results. In Iceland, patients had lower disease

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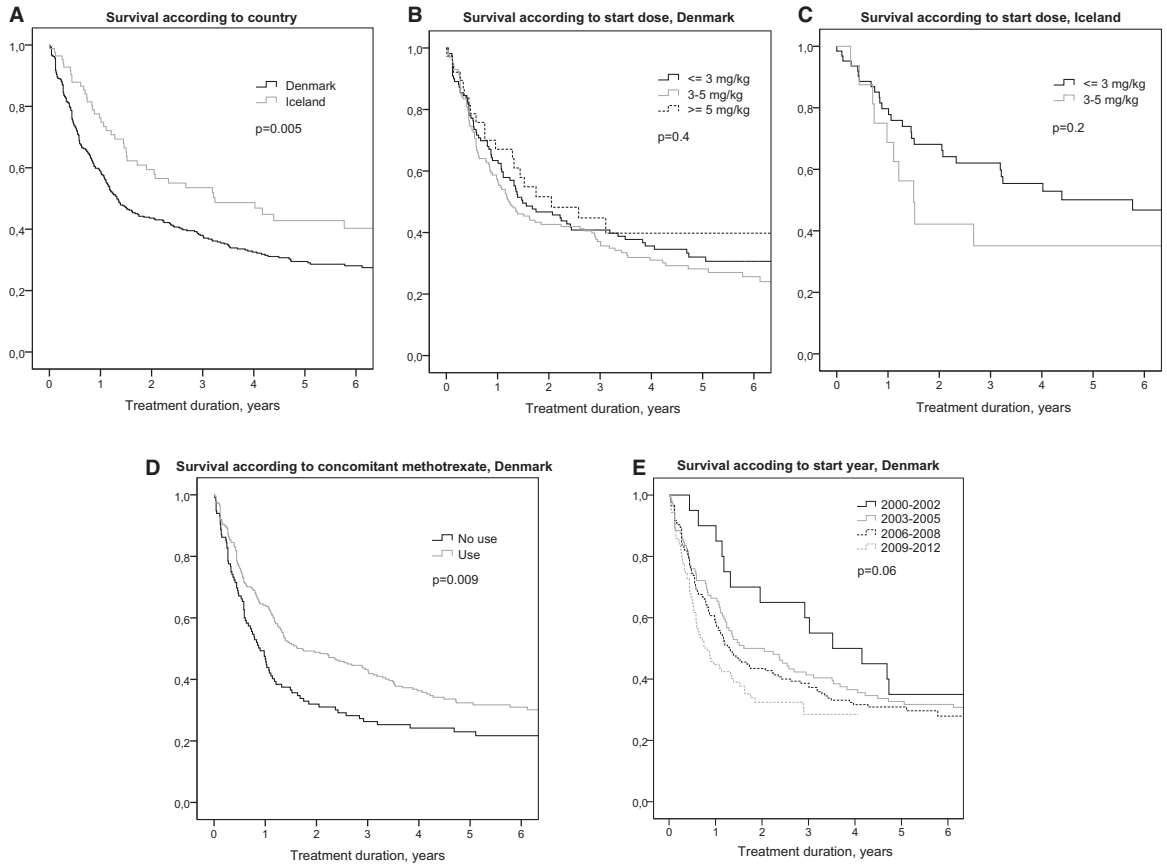
Fig. 2 Kaplan–Meier drug survival curves



Infliximab drug survival (Kaplan–Meier) according to (**A**) country; (**B**) starting dose, Danish patients; (**C**) starting dose, Icelandic patients; (**D**) concomitant MTX, Danish patients and (**E**) start year, Danish patients.

activity at treatment start and the majority of patients received a fixed starting dose of 200 mg. In Denmark, the starting dose was chosen according to the preference of the treating physician. Thus confounding by indication or channelling bias cannot be ruled out and differences in disease severity, co-morbidities or other psoriatic disease manifestations might have affected drug effectiveness as judged by drug survival.

Observational and registry studies provide a valuable supplement to RCTs regarding prescription practice and treatment outcome when drugs are used in routine care [29, 46]. In real life, with more liberal treatment criteria than in RCTs, drug retention rates, and thus effectiveness, are often lower. In addition, patients who stopped treatment within 3 months were classified as non-responders in the present study. As expected, we found the effectiveness of infliximab in routine care to be lower than drug efficacy in RCTs. Thus RCTs of infliximab in PsA have reported drug efficacy (ACR20/50/70 response rates) to be approximately 50%, 35% and 20%, respectively [6, 47]. We did not find effectiveness to be associated with the baseline dose of infliximab. The current study demonstrated that the clinical use of infliximab and adherence to national and international guidelines varied between Denmark and Iceland. This illustrates that extrapolation of outcome data across countries must be done with caution and that publication of clinical data from various countries is of importance.

We found that concomitant MTX improved infliximab drug survival. This is in accordance with previous studies regarding TNFi treatment in PsA [25, 43, 48–51]. The possible beneficial effect of MTX combination therapy in PsA might be reduced formation of anti-chimeric antibodies [23, 51, 52].

Drug survival was shorter among patients who started treatment during the later years. This might illustrate a change in prescription practice with initiation of TNFi treatment among less ill patients with poorer treatment outcomes [53]. Also, the availability of more TNFis might lead to early switching [12]. This could also explain why many patients stopped infliximab treatment due to LOE although they only received a lower infliximab dose;

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alternatively, economic considerations or fear of AEs might have affected this decision.

This study has limitations to consider. Few patients started treatment with infliximab $\geqslant 5$ mg/kg and a lack of power to detect potential beneficial effects of higher doses cannot be excluded. Similarly, the patients who stopped treatment due to LOE while receiving doses <5 mg/kg might have experienced an effect on higher doses. Response data were only available in approximately half of the patients, and this might have affected our results. Although ACR and EULAR responses were originally developed to monitor treatment effect in RA, they have been widely used in PsA [54, 55]. However, these measures do not include data on all joints potentially affected in PsA, e.g. hips, DIP joints of the hand or ankles and joints of the feet. This may be of importance when these response measures are used in a clinical setting and may cause an underestimation of disease activity [56]. This might perhaps explain the relatively low median SJC upon initiation of infliximab therapy seen in the present study. Spinal disease might affect the starting dose: perhaps patients with symptoms of spinal disease more frequently received higher doses in accordance with the guidelines for AS. Furthermore, enthesitis, dactylitis or other psoriatic disease manifestations are potential confounders, but we did not have data to investigate this. To address these issues further, a future randomized clinical trial comparing low *vs* traditional infliximab doses in PsA would be of relevance. Preferably such a trial should include data on not only 68-joint disease activity, but also skin and other psoriatic disease domains.

In conclusion, this observational study from two countries demonstrated that infliximab doses below the recommended 5 mg/kg were widely used in PsA in routine care. A low starting dose with subsequent step-up therapy seemed an effective strategy. Concomitant use of MTX was associated with improved drug survival.

Rheumatology key messages

- In Denmark and Iceland, infliximab doses < 5 mg/kg are widely used in routine treatment of PsA.
- A low infliximab starting dose with subsequent step up therapy seems effective in PsA.

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