Patient-reported outcomes and PRO remission rates in 12,262 biologic-naïve patients with psoriatic arthritis treated with TNF-inhibitors in routine care

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ABSTRACT

Objectives: To evaluate patient-reported outcomes (PROs) after initiation of tumor necrosis factor-inhibitor (TNFi) treatment in European real-world patients with psoriatic arthritis (PsA). Further, to investigate PRO remission rates across treatment courses, registries, disease duration, sex and age at disease onset.

Methods: Visual-analogue-scale or Numerical Rating Scale scores for pain, fatigue, patient global, and Health Assessment Questionnaire disability index (HAQ) from 12,262 PsA patients initiating a TNFi in 13 registries were pooled. PRO remission rates (pain ≤1, fatigue ≤2, patient global ≤2, HAQ ≤0.5) were calculated for patients still on drug.

Results: For the 1st TNFi, median pain score was reduced by ≈50% (baseline/6/12/24 months: 6/3/3/2) as were fatigue (6/4/4/3), patient global (6/3/3/2) and HAQ scores (0.9/0.5/0.5/0.4). Six-months' LUNDEX-adjusted remission rates for pain/fatigue/patient global/HAQ were 24%/31%/36%/43% (1st TNFi), 14%/19%/23%/29% (2nd TNFi) and (9%/14%/17%/20% (3rd TNFi).

For bio-naïve patients with disease duration <5 years, 6-months LUNDEX-adjusted remission rates for pain/fatigue/patient global/HAQ were 22%/28%/33%/42%. Corresponding rates for patients with disease duration >10 years were 27%/32%/41%/43%. Remission rates were 33%/40%/45%/56% for men and 17%/23%/24%/32% for women. For patients <45 years at diagnosis, 6-months LUNDEX-adjusted remission rate for pain was 28% vs. 18% for patients ≥45 years.

Conclusions: In 12,262 biologic-naïve PsA patients, 6 months treatment with TNFi reduced pain by approximately 50%. Marked differences in PRO remission rates across treatment courses, registries, disease duration, sex and age at onset of disease were observed, emphasizing the potential influence of other factors than disease activity on PROs.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic immune-mediated inflammatory disease, causing widespread inflammation, pain, fatigue, physical disability and reduced quality of life (1). In addition to musculoskeletal manifestations and psoriasis, psoriatic arthritis is associated with extra-musculoskeletal manifestations such as uveitis and inflammatory bowel disease, and comorbidities including obesity, diabetes, hypertension, cardiovascular disease and depression(1).

PsA is initially treated with non-steroidal inflammatory drugs, local corticosteroids and / or conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), such as methotrexate. For PsA patients with an insufficient response to these treatments, biologic DMARDs, including tumor necrosis factor inhibitors (TNFi) and other biologics (interleukin (IL)-17 inhibitors, IL-12/23 or IL-23 inhibitors), are recommended (2,3).

Patient-reported outcomes (PROs) are important tools for the assessment of symptoms experienced by PsA patients, such as pain, fatigue and functional status, thereby supplementing the clinical examination (4–6). Until now, the effect of TNFi treatment on PROs in PsA patients has mainly been investigated in smaller real-world studies (7–9) and in randomized clinical trials (10–13) with focus on treatment response assessed at group level, whereas larger real-world studies investigating PROs and PRO remission rates, i.e. the proportion of individual patients who achieved very low scores of PROs (≤1 for pain, ≤2 for fatigue and patient global and ≤0.5 for HAQ) during TNFi treatment, are missing. Also, while previous studies suggest varying response to TNFi between patients stratified by sex and treatment courses, knowledge on TNFi effect on PROs in sub-groups of PsA patients are lacking (8,14).

In 2017, the European Spondyloarthritis (EuroSpA) Research Collaboration Network was established allowing secondary use of real-world data from existing registries (15) The present study was based on such data and aimed to 1) investigate the effects of TNFi treatment on PROs in

PsA patients and 2) to explore differences in PRO remission rates across treatment courses, registries, disease duration, sex and early vs later onset of disease.

METHODS

The EuroSpA Research Collaboration Network

The present study was based on data from the EuroSpA Research Collaboration Network, which includes data on PsA patients from the following 13 registries (country; year of registry start): ATTRA (Czech Republic; 2002), DANBIO (Denmark; 2000), ROB-FIN (Finland; 1999), ICEBIO (Iceland; 2007), GISEA (Italy; 2008), NOR-DMARD (Norway; 2000), Reuma.pt (Portugal; 2008), RRBR (Romania; 2015), Biorx.si (Slovenia; 2008), BIOBADASER (Spain; 2000), SRQ (Sweden; 1999), SCQM (Switzerland; 2006) and TURKBIO (Turkey; 2011) (16–28). Data were collected prospectively by the individual registries according to their respective protocols, either in a routine care environment or within a specific research context (29). Thus, number of PROs assessed and follow-up schedules differed between registries. The process of data transfer from the registries to the research collaboration network included three steps: 1) data managers in each of the 13 registries received a list of variables that were predefined in the study protocol and created pseudonymized datasets, 2) datasets were securely uploaded to the EuroSpA server, 3) datasets were harmonized and pooled to one dataset at the EuroSpA Coordinating Center.

Study population

Inclusion criteria for the present study were an initial clinical diagnosis of PsA at age 18 years or older, initiation of a TNFi as first biological treatment in the period January 1, 2009, to December 31, 2018 and at least one visit (baseline, 6, 12 or 24 months) with a registered PRO while being treated with a TNFi. Patients who switched from a 1st to 2nd TNFi and from a 2nd to 3rd TNFi, without non-TNFi biological or targeted synthetic DMARD treatments in between, were included in

the analyses of 2nd and 3rd TNFi, respectively. Treatment switches from originator to biosimilar or between biosimilar TNFi were disregarded. Data collection ended on November 4, 2019, which allowed all patients to have a minimum 10 months of follow-up after starting their 1st TNFi treatment.

Data collection

At baseline for each TNFi, the following variables were extracted: age, years since diagnosis, sex, body mass index (BMI), smoking status (current, previous, never), physician global assessment, joint counts, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and composite disease activity indices (table 1). The following four PROs of interest were collected, if available, at baseline and at 6, 12 and 24 months of follow-up for 1st, 2nd and 3rd TNFi treatments in patients who were still treated: patient's assessment of pain, fatigue (30), and patient's global assessment of disease activity (patient global) (31), as well as the Health Assessment Questionnaire disability index (HAQ) score (32). Three registries (RRBR, biorx.si and SCQM) used a 0-10 Numeric Rating Scale (NRS) for pain, fatigue, patient global and physician global, while the remaining registries used a Visual Analogue Scale (VAS) 0-100 scale. Scores on a VAS 0-100 scale were converted to 0-10 by dividing with 10 and rounding to nearest integer and therefore scores were harmonised on a common 0-10 scale. HAQ was collected on a 0-3 scale. The 6, 12 and 24 months visits were defined as registered visits in the periods 90 to 270 days, 271 to 545 days and 546 to 910 days after baseline, respectively. If more than one visit was available in a period, the visit with registration of most PROs was preferred. If similar number of PROs were available, the visit closest in time to 6, 12 and 24 months was selected. Only medians for PROs reported by ≥50 patients were included in tables and figures.

Definition of PRO remission

There is no international consensus on cut-off values for PRO remission in PsA patients. However, a study by Coates et al. defined minimal disease activity (MDA) as patients fulfilling 5 out of 7 criteria selected by an expert group (33). Three of these criteria were VAS score for pain ≤15 mm, patient's global assessment ≤20 mm and HAQ-score ≤0.5. Based on these definitions of MDA, we defined PRO remission for each PRO as follows: pain ≤1, fatigue ≤2, patient global ≤2 and HAQ ≤0.5.

Ethics

The study was approved by the respective national Data Protection Agencies and Research Ethical Committees according to legal regulatory requirements in the participating countries and was performed in accordance with the Declaration of Helsinki.

The present study followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (34).

Statistical analyses

Descriptive statistics (medians with interquartile ranges) were applied for PRO scores and changes in PROs from baseline to 6, 12 and 24 months. For PRO remission, we report crude and LUNDEX-adjusted rates(35). The LUNDEX adjusted rate integrates clinical response with treatment retention by use of the equation: (Fraction of starters still in the study at time T) x (Fraction responding at time T). Drug retention rates were calculated with Kaplan Meier estimation. In addition, meta-analyses across registries were performed for median PRO scores and crude PRO remission rates in registries with ≥ 20 patients with available data for the PRO and timepoint. No imputation of missing data was performed. All statistical analyses were performed in R version 3.6.1.

RESULTS

Patients

We included data on 12,262 biologic-naïve PsA patients starting treatment with a 1st TNFi in a real-world setting between January 1, 2009, and December 31, 2018. Among these patients, 4239 patients later initiated a 2nd TNFi and 1240 patients a 3rd TNFi. Considering the 1st TNFi treatment course, etanercept was the most frequently prescribed drug (35% of patients), followed by adalimumab (30%), infliximab (17%), golimumab (13%) and certolizumab pegol (7%). Similar prescription patterns were seen across treatment courses (table 1).

The following median PRO scores were observed at baseline for 1st TNFi treatment: pain: 6 (IQR: 4-8), fatigue: 6 (4-8), patient global: 6 (4-8) and HAQ: 0.9 (0.5-1.4). PRO scores at baseline were similar across 1st, 2nd and 3rd treatment courses (pain: 6/6/7, fatigue: 6/7/7, patient global: 6/6/7, HAQ: 0.9/1.0/1.0) (table 1). Baseline values for physician reported outcomes, joint counts, blood tests and composite disease activity indices were also comparable across treatment courses (table 1).

PROs and changes from baseline at 6, 12 and 24 months of 1st, 2nd and 3rd TNFi treatment

Figure 1 shows the median scores for pain, fatigue, patient global and HAQ scores at baseline and at 6, 12 and 24 months after start of 1st, 2nd and 3rd TNFi treatment in the overall cohort. For patients receiving their 1st TNFi treatment there was a marked improvement in median PRO scores from baseline to 6 months. Median pain score decreased from 6 to 3, while fatigue score decreased from 6 to 4 and patient global score from 6 to 3. Improvements were also seen for patients receiving their 2nd and 3rd TNFi treatments, but to a smaller degree. Similarly, larger changes in individual patients in PROs from baseline were observed for 1st TNFi treatment compared to later line treatment courses; most markedly in pain scores (online supplementary figure 1).

The distribution of individual pain scores changed markedly from baseline to 6 months after start of a 1st TNFi treatment, while distributions at 12 and 24 months were similar to those at 6 months (figure 2 (upper figures)). Figure 2 (lower figures) shows that 12% of patients who reported high pain at baseline (9-10) also reported high pain at 6 months. Conversely, in patients who reported pain at baseline in the range 6-7, ≤2% reported high pain (9-10) at 6 months (figure 2, lower figures). Similar patterns were seen for fatigue, patient global and HAQ (online supplementary figures S2 a-c).

PRO remission rates after 6, 12 and 24 months of 1st, 2nd and 3rd TNFi treatment

After 6 months of a 1st TNFi treatment, the crude remission rate for pain score (i.e. pain score ≤1) was 29% in the overall cohort. The estimated remission rate (95% CI) based on meta-analysis was 30% (26-34), while the LUNDEX-adjusted remission rate was 24%. Six-month crude remission rate for fatigue (fatigue score ≤2) was 37%, while the meta-analysis based rate was 43% (32-54) and the LUNDEX adjusted remission rate was 31%. For patient global remission (patient global ≤2), the crude 6-month remission rate was 43%, the meta-analysis based estimate 45%5 (39-51) and the LUNDEX adjusted remission rate 36%. Crude 6-month HAQ remission rate (HAQ ≤0.5) was 52%, the meta-analysis based estimate 54% (46-62)) and the LUNDEX adjusted remission rate 43%. After 12 and 24 months of a 1st TNFi, the crude remission rates increased slightly, while the LUNDEX-adjusted PRO remission rates had decreased (online supplementary figure S3, table 2). Crude and LUNDEX-adjusted remission rates were lower for the 2nd and 3rd TNFi (online supplementary figure S3) as were the estimates based on meta-analysis (data not shown).

PROs across registries

Across the 13 registries, PRO registration varied considerably. Twelve registries had registrations of two or more PROs and 6 registries had registrations of all four PROs of interest. Also, variations in both patient characteristics, baseline disease activity and PROs were observed. The median age at start of TNFi treatment ranged from 41 to52 years, and age at PsA diagnosis ranged between 36 and49 years, while median pain scores ranged from 5 (NOR-DMARD) to 8 (TURKBIO) (online supplementary tables S1 and S2). Figure 3 shows PROs per registry for the 1st TNFi treatment at baseline and at 6, 12 and 24 months. For all 13 registries an improvement in PROs was seen after the start of a 1st TNFi treatment when compared to baseline, however, the magnitude of the improvements differed between registries. Similarly, PRO remission rates differed, exemplified by LUNDEX-adjusted pain remission rates at 6 months ranging from 13% (GISEA) to 31% (TURKBIO).

PRO remission rates across disease duration, sex and age at disease onset

To explore differences in PRO remission rates, the overall cohort was stratified according to a) disease duration (≤5 years, 6-10 years, > 10 years), b) sex (men, women) and c) age at disease onset (<45 years, ≥45 years).

Patients with medium and long disease duration (6-10 and >10 years) at start of 1st TNFi had numerically higher LUNDEX-adjusted pain remission rates than patients with short disease duration (28%/27% vs 22% at 6 months); this pattern was also seen for fatigue and patient global, while HAQ remission rates seemed similar across disease duration (42%,45%,43%). Similar findings were present for 2nd and 3rd TNFi (figure 4, table 2, online supplementary tables S3, S4 and S5).

Men had numerically higher LUNDEX-adjusted PRO remission rates than women for all PROs after 6, 12 and 24 months of a 1st TNFi (figure 4, table 2). A similar pattern was seen for 2nd and 3rd TNFi courses (online supplementary table S3, S4 and S5).

In patients with early onset of disease (<45 years at diagnosis) the LUNDEX-adjusted pain remission rate was higher than in patients with later onset of disease (34% vs 22% at 6 months after start of 1st TNFi; this pattern was seen for all four PRO measures in 1st, 2nd and 3rd TNFi courses (figure 4, table 2, online supplementary tables S3, S4 and S5).

Drug retention rates

Retention rates for the overall cohort decreased with increasing number of TNFi treatment courses, while retention rates in the stratified cohort displayed the same trend as observed for PRO remission rates with lower retention in women, patients with short disease duration and later onset of disease (online supplementary table S6).

DISCUSSION

Based on prospectively collected PROs from more than 12,000 PsA patients treated across Europe, the present study reports, for the first time, the impact of TNFi on PROs and PRO remission rates in a large real-world cohort. At baseline, PRO values were high, demonstrating a large disease burden. We observed that 6 months of a 1st TNFi reduced the pain score by approximately 50% and led to the remission of pain (defined as pain score ≤1 on a 0-10 scale) in about 25% of patients. Similar treatment responses and remission rates were seen for fatigue, patient global and HAQ scores. Interestingly, we observed marked differences in all PROs and PRO remission rates across treatment courses, registries, disease duration, sex and age at onset of disease suggesting that PRO values are influenced by multiple factors.

While pain and fatigue are recognized as the most disabling symptoms by patients with PsA (36) surprisingly few studies have addressed the impact of treatment on the individual PROs outside of randomized controlled trials (RCTs). In RCTs, benefit of TNFi treatment on PROs in PsA has been

shown (10–13,37), but concern has been raised about the extrapolation of results from RCTs to real world patients due to the strict inclusion and exclusion criteria applied in RCTs (38,39). Here we provide evidence from a large multinational cohort of patients treated in routine care registries, that improvement in PROs can be expected during TNFi treatment, which is in accordance with the few smaller studies on real world data (7–9)

We found that the effects of a 2nd and 3rd TNFi drug on PRO scores were smaller than those observed for the 1st TNFi treatment. This finding was expected since patients switching to a 2nd or 3rd TNFi is a selected group of patients with poor initial response or secondary loss of response to a 1st TNFi and probably a poorer response to TNFi treatment in general (8,40). Our finding is in accordance with the results of a real-world study from the UK including 141 PsA patients treated with TNFi and a follow-up period of ≥3 years, which also showed that patients with poor response to the 1st TNFi experienced less benefit and more adverse events in the following TNFi treatment course (8).

We observed that patients with a high pain score (≥9) at baseline had a lower PRO response to the 1st TNFi treatment after 6 months (12% reported pain ≥9 at 6 months) than in patients with a baseline pain score <7 (≤2% reported pain ≥9 at 6 months). A similar observation has been made in axial spondyloarthritis, where patients with extremely high PRO scores had poorer response to TNFi than patients with more favorable PRO scores at baseline (41,42). We hypothesize, that these observations are due to comorbidities such as chronic widespread pain or fibromyalgia, which are known to be frequent in PsA patients and diminish treatment response (43,44). It is one of the limitations of our study, that no data on comorbidities was available for analyses. An additional limitation is the differences between registries in number of PROs assessed and follow-up schedules

that caused substantial variation in the number of patients that could be included in the analyses across PRO and follow-up visit. Linde et al. have recently published details on the organisation, inclusion criteria and data collection across registries participating in the EuroSpA collaboration (29). Registry differences add to the inherent limitation of missing outcome data in registry research, which is also evident in our study as pain assessment after 6 months of 1st TNFi was available in 68% of patients with decreasing data availability as follow-up increased (12 months: 60%, 24 months 42%). This may lead to a bias towards lower PROs if patients with a good response to TNFi treatment are overrepresented in our study due to a higher motivation to comply with their physician appointments. However, a bias in the opposite direction could also have been introduced as patients with disease flares in need of treatment intensification would be more likely to have a hospital visit scheduled. Differences in treatment outcomes in PsA patients across countries have been documented in several previous papers from the EuroSpA Collaboration and other groups (15,45,46). Country specific guidelines and recommendations for TNFi treatment of PsA patients may have influenced our results and contributed to the observed differences between registries. Of specific importance to PROs, differences in the exact wording of the questions, including the recall period used, may also have contributed to the observed differences between registries.

To our knowledge, there is no consensus for the definition of PRO remission; and ideally the definition of PRO remission should be based on a validated combination of PRO measures describing the most important disease features seen from the patients' perspective (47). Lacking

validated PRO remission cut-offs, we based our definitions on those previously reported for minimal disease activity in PsA patients (33).

With the applied definitions of PRO remission, the majority of PsA patients in the present study did not reach PRO remission during treatment with a TNFi, which suggests an unmet need for further treatment options from the patient perspective. Of note, the crude rates reported are based on patients who were receiving treatment at the time of assessment. This implies that despite PRO scores larger than 2 on 0-10 scale, the treating rheumatologist generally found the treatment effect satisfactory, since the TNFi was continued in most cases. Thus, the low PRO remission rates could also point to a need for better strategies to cope with pain and disease impact in patients suffering from this complex disease.

Our finding of higher PRO remission rates in men is in accordance with a European study showing that women were less likely to reach the treatment target according to Disease Activity in Psoriatic Arthritis (DAPSA) (48). In contrast, the higher PRO remission rates among patients with medium and long disease duration (>5 year) at initiation of TNFi treatment, when compared to patients with shorter disease duration, was an unexpected finding, as a previous study reported better treatment outcomes with regards to PROs for patients treated at an early point in their disease (49). We observed that patients diagnosed prior to 45 years of age were more likely to reach PRO remission after 6 months of a 1st TNFi treatment when compared to patients older than 45 years at diagnosis. This finding adds to studies describing different phenotypes of PsA according to age at onset of disease (50,51). Currently, very limited data on treatment outcomes in these phenotypes is available and our findings suggest worse treatment outcomes in later onset PsA.

Overall, striking differences in PRO remission rates across treatment courses, registries, gender, disease duration and age at onset of disease were seen. This may suggest that disease control i.e. suppression of inflammation is achieved to a lesser degree in certain groups of patients, but may also be interpreted in light of the emerging distinction between disease impact as experienced by the patient and measured with PROs, and disease activity caused by inflammation and measured by joint counts and inflammatory markers (52).

In conclusion, this study showed a marked improvement in PROs in more than 12,000 patients with PsA during TNFi treatment. While large improvements at the group level were seen, only one quarter of patients reached pain remission, pointing to an unmet need for improvements in treatment and pain management from the patient perspective. In addition, female sex, shorter disease duration and older age at diagnosis were associated with lower PRO remission rates.

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DATA AVAILABILITY STATEMENT: The data in this article was collected in the individual registries and made available for secondary use through the EuroSpA Research Collaboration Network [https://eurospa.eu/#registries]

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FIGURE LEGENDS

FIGURE 1. RADAR CHARTS ILLUSTRATING THE MEDIAN SCORES FOR PATIENT-REPORTED OUTCOMES AT BASELINE AND AT 6, 12 AND 24 MONTHS AFTER START OF 1ST TUMOR NECROSIS FACTOR ALPHA INHIBITOR (TNFI) (BASELINE, N=12626), 2ND TNFI (BASELINE, N=4329) and 3RD TNFI (BASELINE, N=1240)

Patient global: Patient's global assessment of disease activity, HAQ: Health Assessment Questionnaire disability index.
*HAQ was scored on a scale ranging from 0-3.

FIGURE 2. PAIN, 1st TNFI TREATMENT

Upper figure: Three-dimensional bar chart of the relative frequency (y-axis) of pain (mm given on x-axis) among all PsA patients at baseline, 6, 12 and 24 months after start of 1st TNFi treatment (z-axis). Lower figure: Stacked bar chart showing the distribution of PsA patients' pain scores at 6 months dependent on how the same patients scored at start of TNFi treatment (baseline). Table: Percentages as illustrated in stacked bar chart.

FIGURE 3. PAIN, FATIGUE, PATIENT GLOBAL AND HAQ BY REGISTRY FOR PSA PATIENTS AT BASELINE AND 6,12 AND 24 MONTHS AFTER START OF 1ST TNFI TREATMENT

For BIOBADASER, pain and HAQ were not collected. For ROB-FIN, GISEA, reuma.pt, RRBR, Biorx.si and BIOBADASER fatigue was not collected; the remaining missing median PROs were not calculated due PRO data for <50 patients.
Patient global: Patient's global assessment of disease activity, HAQ: Health Assessment Questionnaire disability index.
Three registries (RRBR, biorx.si and SCQM) used a 0-10 numeric rating scale (NRS) for pain, fatigue, patient global and physician global, while the remaining registries used a 0-100 scale. Scores on a 0-100 scale were converted to 0-10 by dividing with 10 and rounding to nearest integer. *HAQ was scored on a scale ranging from 0-3. HAQ scores were multiplied by 3.3 to fit the 0-100 scale in this figure.

FIGURE 4. PRO REMISSION RATES (%) AT 6, 12 and 24 MONTHS AFTER 1ST TNFI TREATMENT START ACROSS SEX, TIME SINCE DIAGNOSIS AND AGE AT DIAGNOSIS

Left panel: crude remission rates; right panel: LUNDEX-adjusted remission rates. Definitions of remission: pain score ≤1, fatigue score ≤2, patient global score ≤2, HAQ score ≤0.5.Patient global: Patient's global assessment of disease activity, HAQ: Health Assessment Questionnaire disability index.

Table 1. Baseline characteristics of psoriatic arthritis patients starting a 1st TNFi treatment between January 1, 2009, and December 31, 2018[a]

	1st TNFi treatment (n=12262)		2nd TNFi treatment (n=4329)		3rd TNFi treatment (n=1240)	
Characteristic	**No. of patients with available data**	**Median (IQR) or n (%)**	**No. of patients with available data**	**Median (IQR) or n (%)**	**No. of patients with available data**	**Median (IQR) or n (%)**
Age at TNFi treatment start, years	12262	49 (40-58)	4329	51 (41-59)	1240	50 (41-59)
Men	12262	5663 (48%)	4329	1736 (40%)	1240	434 (35%)
Years since diagnosis	9498	3 (1-8)	3234	5 (2-9)	875	6 (3-10)
≤5	9498	6072 (64%)	3234	1840 (57%)	875	437 (50%)
6-10		1656 (17%)		699 (22%)		242 (28%)
>10		1770 (19%)		695 (22%)		196 (22%)
Age at diagnosis, years	9498	43 (33-52)	3234	43 (34-52)	875	42 (33-51)
<45	0498	5224 (55%)	3234	1772 (55%)	875	490 (56%)
≥45		4274 (45%)		1462 (45%)		385 (44%)
BMI, kg/m^2	4578	27 (24-30)	1381	27 (24-31)	397	27 (24-31)
Current smokers	10358	1758 (17%)	3583	624 (17%)	1054	196 (19%)
1st TNFi drug (year of EMA approval)	12262		4329		1240	
- Infliximab (1999)		2107 (17%)		481 (11%)		204 (16%)
- Etanercept (2000)		4182 (35%)		1566 (37%)		330 (27%)
- Adalimumab (2003)		3629 (30%)		1360 (31%)		315 (25%)
- Certolizumab (2009)		811 (7%)		319 (7%)		138 (11%)
- Golimumab (2009)		1533 (13%)		603 (14%)		253 (20%)
1st TNFi start, year	12262		4329		1240	
- 2009-2014		7017 (57%)		2042 (47%)		560 (45%)
- 2015-2018		5245 (43%)		2287 (53%)		680 (55%)
Patient-reported outcomes[b]						
- Pain	9000	6 (4-8)	3053	6 (4-8)	896	7 (5-8)
- Fatigue	4748	6 (4-8)	2007	7 (4-8)	634	7 (5-8)
- Patient global	9577	6 (4-8)	3194	6 (5-8)	914	7 (5-8)
- HAQ	8484	0.9 (0.5-1.4)	2885	1.0 (0.5-1.5)	834	1.0 (0.6-1.5)
Physician reported outcomes						
- Physician global	5956	4 (2-6)	1946	3 (2-5)	551	3 (2-5)
Joint counts						
- 28SJC	9189	2 (0-5)	3087	1 (0-4)	880	1 (0-3)
- 28TJC	9201	4 (1-9)	3090	4 (1-8)	880	4 (1-8)
- 66SJC	5377	3 (1-7)	1834	2 (0-5)	536	2 (0-5)
- 68TJC	5456	7 (3-13)	1871	6 (2-12)	549	6 (2-12)
Blood tests						
- CRP, mg/l	8052	6 (3-14)	2742	4 (2-11)	798	4 (2-10)
- ESR, mm/hr	7458	15 (7-29)	2263	12 (6-25)	612	13 (6-27)
Composite indices						
- DAS28-CRP	7144	4.2 (3.3-5.0)	2430	3.9 (3.0-4.8)	704	4.0 (3.0-4.8)
- DAS28-ESR	6342	4.3 (3.3-5.3)	1915	4.0 (3.0-5.0)	513	4.1 (3.0-5.1)
- DAPSA28	6878	25 (17-37)	2361	23 (14-34)	698	24 (16-35)
- DAPSA68	3853	25 (17-35)	1383	22 (15-32)	403	23 (16-34)

IQR: Interquartile Range; BMI: Body Mass Index; EMA: European Medicines Agency; TNFi: Tumor Necrosis Factor alpha Inhibitor; VAS: Visual Analogue Scale; HAQ: Health Assessment Questionnaire disability index; SJC: Swollen Joint Count; TJC: Tender Joint Count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS: Disease Activity Score; DAPSA: Disease Activity in Psoriatic Arthritis.

[a]By 2009 all relevant TNFi products were marketed and the patients included in this cohort had the same treatment options as patients treated today, however, after 2009 other biologic treatment options, which can replace TNFi drugs, have been marketed.

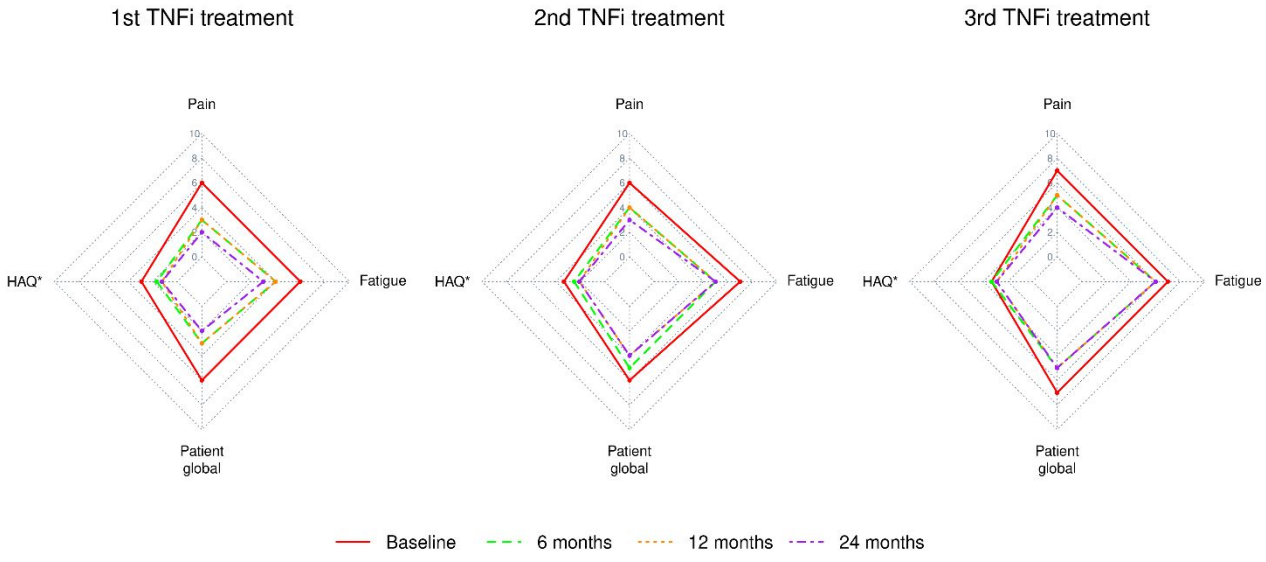
[b]The scales for the PROs and physician global were 0-10, except for the HAQ scale which was from 0-3.

Three registries (RRBR, biorx.si and SCQM) used a 0-10 numeric rating scale (NRS) for pain, fatigue, patient global and physician global, while the remaining registries used a 0-100 scale. Scores on a 0-100 scale were converted to 0-10 by dividing with 10 and rounding to nearest integer.

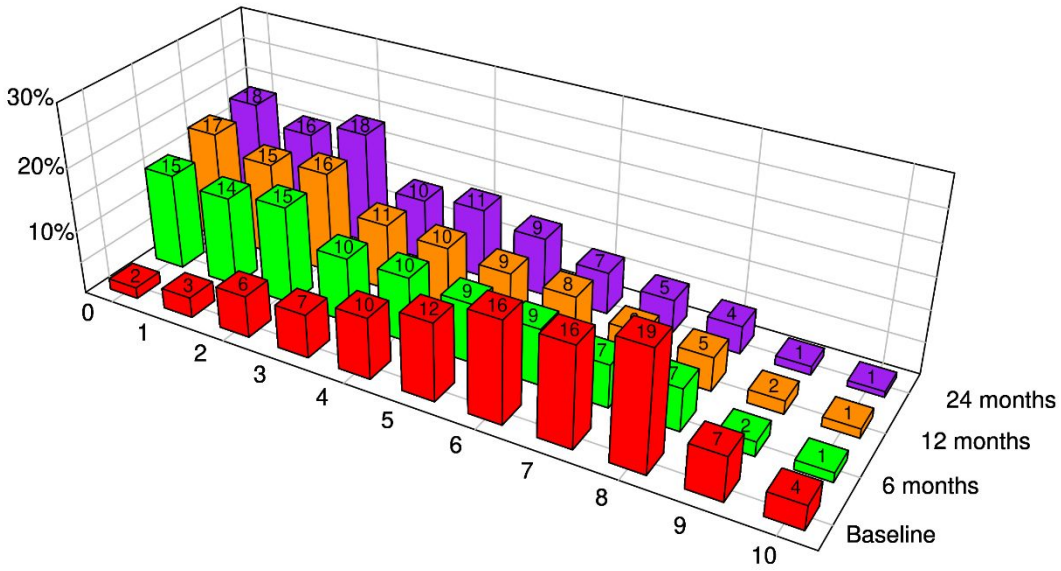
Table 2. LUNDEX-adjusted PRO remission rates (%) at 6, 12 and 24 months after 1st TNFi treatment start across time since diagnosis, sex, and age at diagnosis.

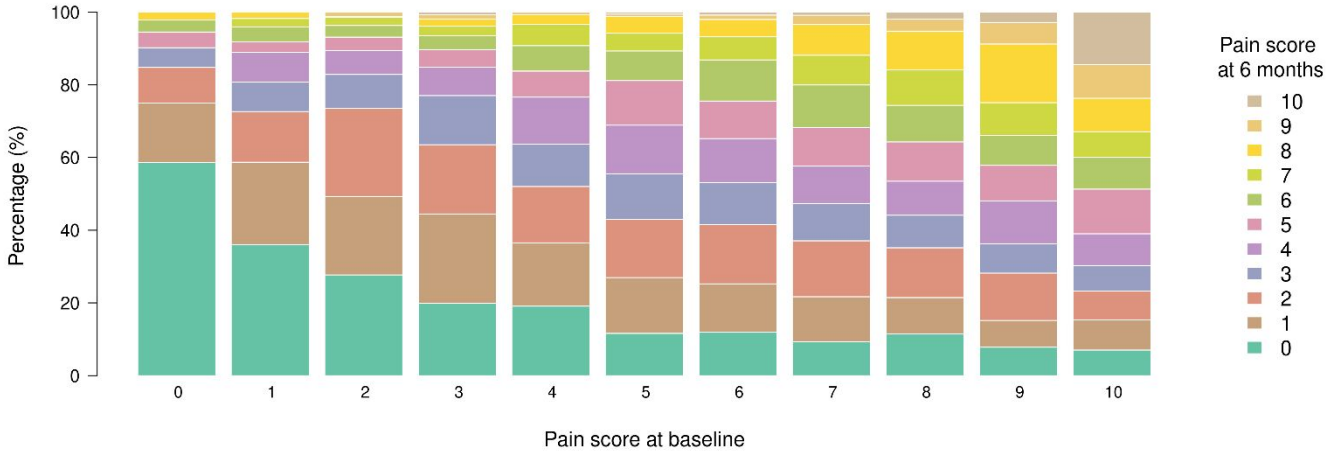
Months treated		**6**	**12**	**24**
Pain remission (≤1)		**no. of patients in remission (LUNDEX adjusted rate %)**		
All	N =12262	2297 (24)%	1839 (22%)	978 (18%)
Sex	**Men** N=5863	1436 (33%)	1164 (32%)	621 (25%)
	Women N = 6399	861 (17%)	675 (16%)	357 (12%)
Years since diagnosis (years)	**≤5** N=6072	1022 (22%)	813 (20%)	534 (18%)
	6-10 N=1656	323 (28%)	292 (27%)	188 (21%)
	>10 N=1770	355 (27%)	285 (24%)	170 (19%)
Age at diagnosis (years)	**<45** N=5224	1130 (29%)	927 (27%)	588 (22%)
	≥45 N=4274	570 (18%)	463 (16%)	304 (14%)
Fatigue remission (≤2)		**no. of patients in remission (LUNDEX adjusted rate %)**		
All	N =12262	1736 (31%)	13264 (27%)	557 (23%)
Sex	**Men** N=5863	1030 (40%)	803 (36%)	355 (32%)
	Women N = 6399	706 (23%)	461 (19%)	202 (15%)
Years since diagnosis (years)	**≤5** N=6072	838 (28%)	576 (25%)	302 (22%)
	6-10 N=1656	221 (33%)	187 (31%)	97 (26%)
	>10 N=1770	235 (32%)	163 (31%)	97 (26%)
Age at diagnosis (years)	**<45** N=5224	803 (34%)	578 (30%)	309 (26%)
	≥45 N=4274	491 (22%)	348 (22%)	175 (20%)
Patient global remission (≤2)		**no. of patients in remission (LUNDEX adjusted rate %)**		
All	N =12262	3507 (36%)	2842 (32%)	1636 (28%)
Sex	**Men** N=5863	2041 (45%)	1732 (41%)	986 (36%)
	Women N = 6399	1466 (24%)	1119 (24%)	651 (20%)
Years since diagnosis (years)	**≤5** N=6072	1587 (33%)	1310 (30%)	867 (26%)
	6-10 N=1656	507 (40%)	461 (37%)	331 (33%)
	>10 N=1770	559 (41%)	458 (36%)	309 (32%)
Age at diagnosis (years)	**<45** N=5224	1694 (41%)	1429 (38%)	953 (32%)
	≥45 N=4274	959 (28%)	800 (25%)	554 (23%)
HAQ remission (≤0.5)		**no. of patients in remission (LUNDEX adjusted rate %)**		
All	N =12262	3895 (43%)	3029 (38%)	1627 (31%)
Sex	**Men** N=5863	2330 (56%)	1896 (51%)	1013 (42%)
	Women N = 6399	1565 (32%)	1133 (27%)	614 (22%)
Years since diagnosis (years)	**≤5** N=6072	1863 (42%)	1446 (37%)	891 (30%)
	6-10 N=1656	520 (45%)	443 (41%)	312 (35%)

	>10 N=1770	541 (43%)	429 (38%)	252 (30%)
Age at diagnosis (years)	**<45** N=5224	1890 (50%)	1507 (45%)	959 (37%)
	≥45 N=4274	1034 (34%)	811 (29%)	496 (23%)
N: number of patients in cohort; HAQ: Health Assessment Questionnaire				

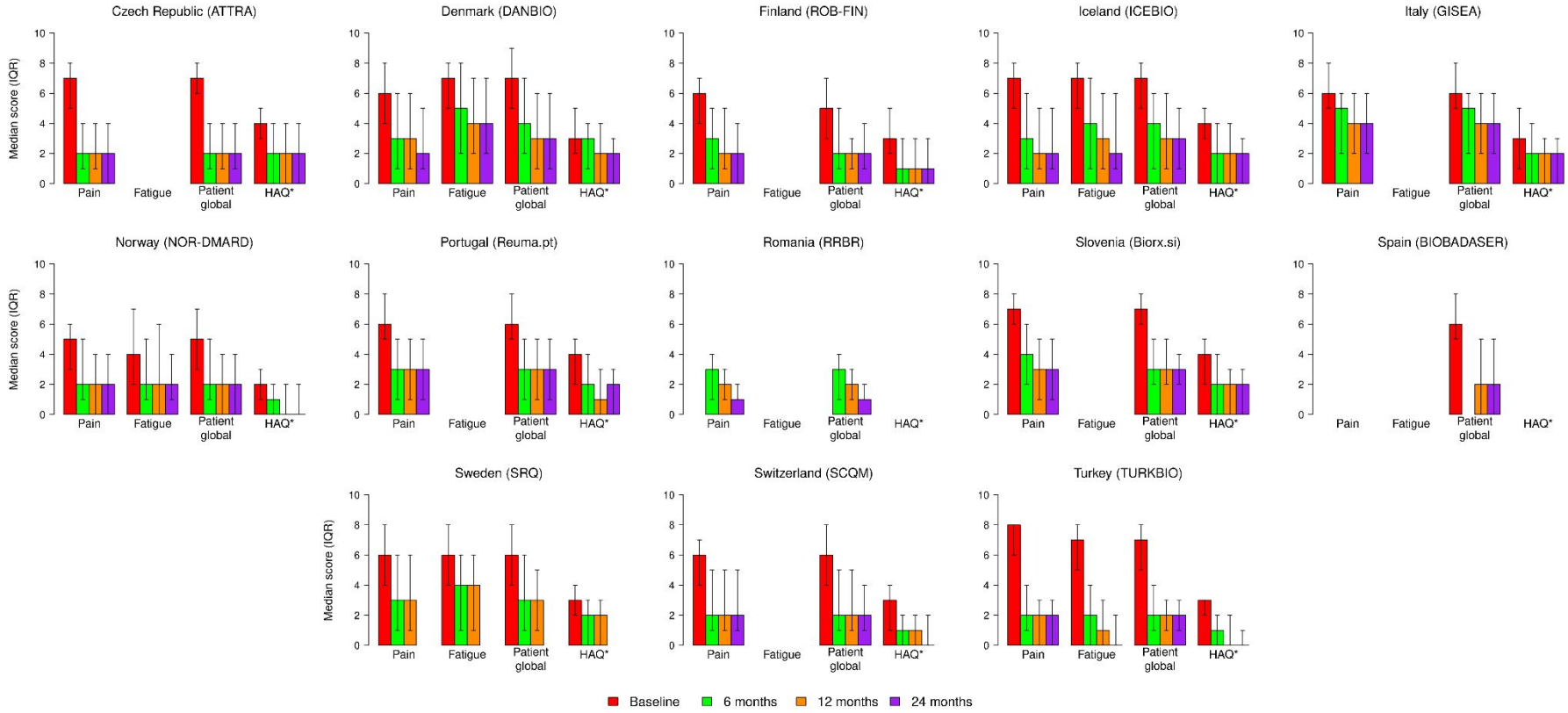


Pain scores, 1st TNFi treatment

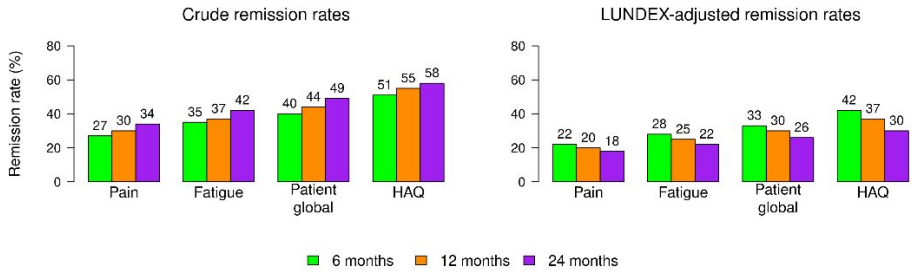




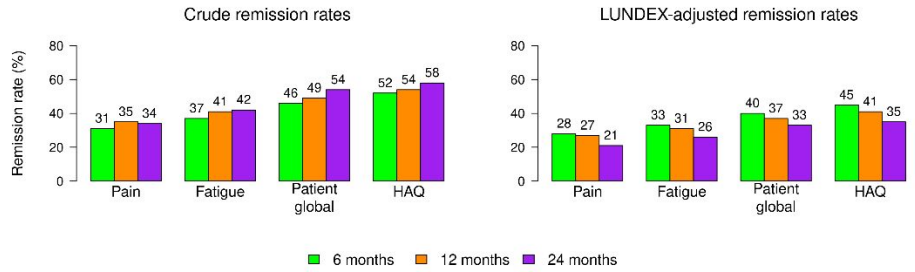
Pain scores at baseline	Pain scores at 6 months after start of 1st TNFi treatment										
	0	1	2	3	4	5	6	7	8	9	10
0	59%	16%	10%	5%	0%	4%	3%	0%	2%	0%	0%
1	36%	23%	14%	8%	8%	3%	4%	2%	2%	0%	0%
2	28%	22%	24%	9%	7%	4%	3%	2%	0%	1%	0%
3	20%	25%	19%	14%	8%	5%	4%	3%	2%	1%	1%
4	19%	17%	16%	12%	13%	7%	7%	6%	3%	1%	0%
5	12%	15%	16%	13%	13%	12%	8%	5%	5%	1%	1%
6	12%	13%	16%	12%	12%	10%	11%	6%	5%	1%	1%
7	9%	12%	15%	10%	10%	11%	12%	8%	8%	3%	1%
8	11%	10%	14%	9%	9%	11%	10%	10%	11%	3%	2%
9	8%	7%	13%	8%	12%	10%	8%	9%	16%	6%	3%
10	7%	8%	8%	7%	9%	12%	9%	7%	9%	9%	14%



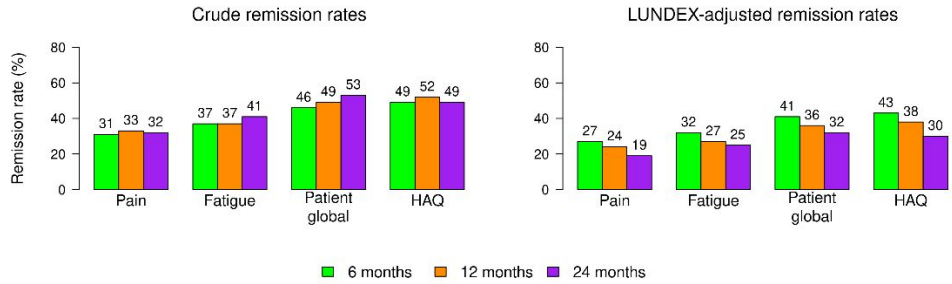
5 or fewer years since diagnosis



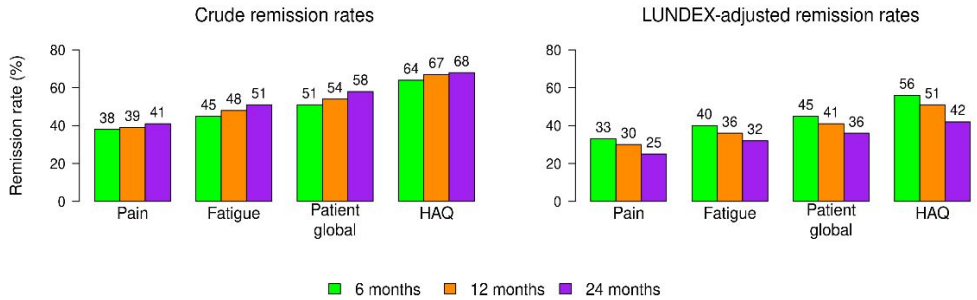
Between 6 and 10 years since diagnosis



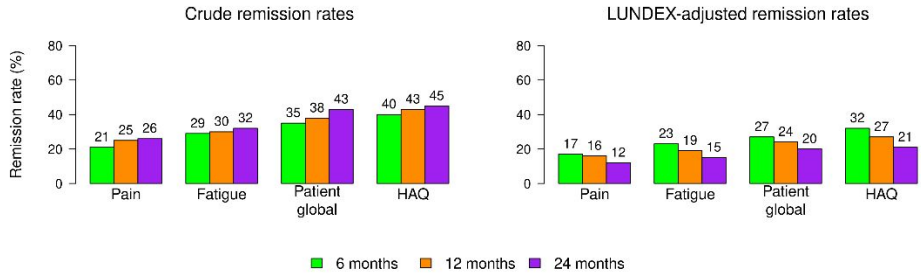
More than 10 years since diagnosis



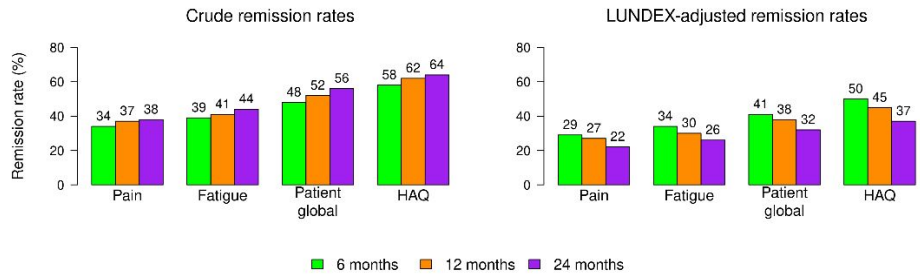
Men



Women



Less than 45 years old at time of diagnosis



More than 45 years old at time of diagnosis