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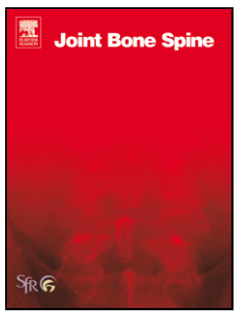

Drug effectiveness of 2nd and 3rd TNF inhibitors in psoriatic arthritis – does it depend on the reason for withdrawal from the previous treatment?

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Drug effectiveness of 2nd and 3rd TNF inhibitors in psoriatic arthritis – does it depend on the reason for withdrawal from the previous treatment?

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Highlights

- Effectiveness of a 2nd and 3rd TNFi treatment in PsA patients was lower than what has previously been reported for the 1st TNFi treatment.

- Initiation of a 2nd or 3rd TNFi treatment in clinical practice led to DAS28 remission in a substantial number of PsA patients.

- Similar drug effectiveness was observed in patients who stopped the previous TNFi due to AE compared to overall LOE, while better drug effectiveness was found in patients who had stopped the previous TNF due to secondary LOE compared to primary LOE.

ABSTRACT

Objective. To investigate real-world retention and remission rates in PsA patients initiating a 2nd or 3rd TNFi and the association with reason for discontinuation from the previous TNFi-treatment.

Methods. Prospectively collected routine care data from 12 European registries were pooled. Retention rates (Kaplan-Meier estimation) and crude/LUNDEX-adjusted rates of Disease Activity Score 28 and Disease Activity index for PSoriatic Arthritis (DAS28 and DAPSA28) remission were calculated and compared with adjusted cox regression analyses and Chi-squared test, respectively).

Results. We included 5233 (2nd TNFi) and 1906 (3rd TNFi) patients. Twelve-month retention rates for the 2nd and 3rd TNFi were 68% (95%CI: 67-70%) and 66% (64-68%), respectively. Patients who stopped the previous TNFi due to AE/LOE had 12-month retention rates of 66%/65% (2nd TNFi), and 65%/63% (3rd TNFi), respectively. Patients who stopped the previous TNFi due to LOE after less vs more than 24 weeks had 12-month retention rates of 54%/69% (2nd TNFi), and 58%/65% (3rd TNFi).

Six-month crude/LUNDEX-adjusted DAS28 remission rates were 48%/35% and 38%/27%, and DAPSA28 remission rates were 19%/14% and 14%/10%, for the 2nd and 3rd TNFi.

Conclusion. Two-thirds of patients remained on TNFi at 12 months for both the 2nd and 3rd TNFi, while one-third and one-quarter of patients were in DAS28 remission after 6 months on the 2nd and 3rd TNFi. While drug effectiveness was similar in patients who stopped the previous TNFi due to AE compared to overall LOE, drug effectiveness was better in patients who had stopped the previous TNF due to secondary LOE compared to primary LOE. .

Keywords

Psoriatic arthritis; TNF-inhibitors; epidemiology; treatment withdrawal

INTRODUCTION

Tumour necrosis factor inhibitors (TNFi) have demonstrated efficacy in the treatment of patients with psoriatic arthritis (PsA), but 30-40% of patients withdraw from the first (1st) TNFi in the first 12 months, mainly due to lack or loss of effect (LOE) or adverse events (AE) [1–3]. Current evidence available on the effectiveness of switching to a second (2nd) or third (3rd) TNFi is based on smaller studies with varying outcomes evaluated and mixed findings. Only a few of these studies investigated the potential impact of reason for discontinuation of the previous TNFi[4–7]. While the studies from British and Portuguese registries found similar effectiveness for the 2nd TNFi regardless of the reason for switching, a Danish study showed withdrawal from the 1st TNFi due to adverse event to be associated with a lower chance of response to the 2nd TNFi [6–8]. To date, no studies have investigated whether effectiveness of a 3rd TNFi depend on withdrawal reason from the 2nd TNFi in PsA patients, nor has the impact of an early vs. late withdrawal due to LOE been investigated. In contrast, a study from the Swiss registry demonstrated that patients with axial spondyloarthritis (axSpA), who withdrew before 6 months of treatment due to LOE or discontinued due to AE on their first TNFi had lower response rates to their 2nd TNF [9,10].

A research network of European registries, the European Spondyloarthritis (EuroSpA) Research Collaboration, aims to strengthen research on real-world data in patients with spondyloarthritis (SpA), including PsA, based on secondary use of data from European clinical registries in rheumatology [11,12].

In this study, we aimed to determine retention and remission rates in PsA patients initiating the 2nd and 3rd TNFi treatment in clinical practice across Europe. In addition, we aimed to investigate whether the outcomes were associated with the reason for withdrawal from the previous TNFi treatment. We hypothesized that treatment effectiveness (retention rates and remission rates) would be higher for the 2nd than for the 3rd TNFi and lower in patients who had withdrawn from the

previous treatment due to LOE, especially in the first 6 months after start, than in patients who withdrew due to AE.

METHODS

Patients

Anonymized data from 12 registries in the EuroSpA Research Collaboration were extracted based on a pre-specified variable list and uploaded through a secured Virtual Private Network server and pooled: SRQ (Sweden), DANBIO (Denmark), SCQM (Switzerland), NOR-DMARD (Norway), ATTRA (Czech Republic), Reuma.pt (Portugal), BIOBADASER (Spain), ROB-FIN (Finland), biorx.si (Slovenia), ICEBIO (Iceland), TURKBIO (Turkey) and RRBR (Romania). Ahead of pooling, the individual data uploads were screened and if inconsistencies were found a query was sent to the registry data manager and if relevant a new data set was uploaded. The data were collected between 1999 and 2018. This study included secondary use of data on patients with a diagnosis of PsA according to the treating rheumatologist, who were diagnosed after the age of 18. Included patients had been followed in a registry since initiation of the 1st TNFi and provided data from treatment with the 2nd and, if available, also the 3rd TNFi. Analyses were conducted separately for patients initiating their 2nd and 3rd TNFi. Further, analyses were performed stratified by reason for withdrawal from the previous TNFi (AE vs LOE) and in patients withdrawn from the previous TNFi due to LOE, additional stratification in primary and secondary LOE was done. Primary LOE (i.e. lack of effect) was defined as withdrawal before 24 weeks of treatment) vs. secondary LOE (i.e. loss of effect) defined as withdrawal after 24 or more weeks of treatment). The cut-off at 24 weeks was a pragmatic choice to distinguish between lack vs loss of effect based on the assumption that a treatment will only continue after 24 weeks in case of an initial response.

Clinical assessment

Treatment start date ("baseline") of 1st, 2nd and 3rd TNFi treatment and, if relevant, corresponding stops date were retrieved from each registry. Baseline data was retrieved for each treatment and included age at treatment initiation, gender, body mass index (BMI), previous and current treatment with conventional synthetic Disease Modifying Anti Rheumatic Drugs (csDMARDs), time since diagnosis, smoking status and name of TNFi. Disease activity was assessed by Disease Activity Score based on CRP (DAS28), Disease Activity Index or PSoriatic Arthritis (DAPSA) and the modified Disease Activity index for PSoriatic Arthritis (DAPSA28) (DAPSA28=(28TJCx1.6)+(28SJCx1.6)+patient's global assessment [0-10 VAS]+patient's pain assessment [0-10 VAS]+CRP [mg/dL]) [13] at baseline, 6, 12 and, 24 month follow-up in patients still treated at these timepoints.

Retention rates

Time on drug was defined as the number of weeks that individual patients continued treatment (from start to stop date). For treatments with no stop date, the drug was assumed to have been discontinued if a new biologic DMARD (bDMARD) was recorded in the registry and the stop date was then defined as the date of next bDMARD start. If no new bDMARD was registered, treatments were censored by the date of data extraction, date of death, or end of registry follow-up, whichever came first. If the same drug was re-started within 3 months of the recorded treatment stop date, with no other bDMARD recorded in-between, the treatment periods were considered as one period. Drug withdrawal reason was assessed in prespecified categories (LOE and AE). If both LOE and AE were registered as withdrawal reasons, LOE was selected over AE. Patients who withdrew due to remission, other reasons or who had no registered withdrawal reason were censored at the stop date.

Clinical remission

Clinical remission was assessed by DAS28 remission (DAS28<2.6), DAPSA remission (DAPSA≤4) and DAPSA28 remission (DAPSA28≤4).

Study endpoints

The primary endpoints were the overall 12-month TNFi retention rates and 6-month remission rates for the 2nd and 3rd TNFi. Secondary endpoints were overall 6- and 24-month retention rates and 12- and 24-month DAS28, DAPSA and DAPSA28 remission rates. Additional secondary endpoints were: 1) retention rates at 12 months and remission rates at 6 months in the individual registries, 2) retention rates and remission rates stratified by reason for withdrawal (AE or LOE) from the previous TNFi and 3) retention and remission rates in patients withdrawn from previous TNFi due to primary vs. secondary LOE.

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.

Statistical analysis

Statistical analyses were performed according to a predefined statistical analysis plan using R version 3.4.3. All calculations were based on observed data; no imputation of missing data was performed. Descriptive statistics (median, interquartile range (IQR) for categorical variables and/or percentage with 95% confidence intervals (95% CI)) were calculated for patient characteristics and outcomes.

Kaplan-Meier estimation was used to investigate TNFi retention rates, including 95% confidence intervals (CI). Cox regression analyses with adjustment for age, gender and registry were used to compare 12 month retention rates across groups. As sensitivity analyses, cox regression models with further adjustment for smoking status and BMI were performed in patients with available data. Remission rates (crude and LUNDEX adjusted [14]) for DAS28 remission and DAPSA28 remission were calculated. Chi-squared tests were used to compare remission rates across groups.

RESULTS

Patient characteristics

We included data on 5233 PsA patients initiating a 2nd TNFi treatment, and 1906 PsA patients initiating a 3rd TNFi treatment (**Table 1**). We identified 1190 and 2790 patients who initiated a 2nd TNFi, and 383 and 1021 patients initiating a 3rd TNFi because of AE and LOE on the 1st, and the 2nd TNFi treatment, respectively. The remaining 1253/502 patients who stopped the 1st /2nd TNFi had registered other reasons for withdrawal (i.e., remission, pregnancy wish, etc.) (n=1122/468) or missing registration of stop reason (n=131/34) respectively.

Patients initiating a 2nd and 3rd TNFi had a median (IQR) time since diagnosis of 5 (2-11) and 7 (4-13) years, respectively, whereas the baseline DAS28 was 4.0 (3.1-4.9) and 4.1 (3.2-5.0), and

DAPSA28 was 24.6 (15.3-36.7) and 25.4 (16.3-38.5), respectively. See Table 1 for additional baseline characteristics at the start of the 2nd and 3rd TNFi, respectively. The patient characteristics at the start of 1st TNFi of the study cohort are presented in Table 1 as reference [7].

Baseline characteristics from the individual registries are shown in **Table S1** (2nd TNFi) and **Table S2** (3rd TNFi) demonstrating marked differences in both demographic characteristics and disease activity measures across registries.

Switching patterns

In the cohort of patients initiating a 3rd TNFi, 31% had received etanercept as their first treatment, while 29% and 31% had received adalimumab and infliximab, respectively. Certolizumab and golimumab was the first treatment in 3% and 6 % of patients. In the patients failing a monoclonal antibody (adalimumab, infliximab, certolizumab or golimumab), etanercept was chosen as the 2nd TNFi in 58%, 47%, 33% and 43% of patients, respectively. In the 608 patients, who had failed two monoclonal antibodies, 52 % were switched to etanercept, while the remaining 48 % were switched to a third monoclonal antibody. The switching patterns are visualized in Figure S1.

Retention rates

Overall, the 12-month retention rate was 68% (95% CI: 67-70%) for the 2nd TNFi, and 66% (64-68%) for the 3rd TNFi. The corresponding retention rates at 6 months were: 79% (78-80%) and 77% (75-79%) for 2nd and 3rd TNFi treatment, respectively, and at 24 months: 60% (58-61%) and 55% (52-57%) respectively (**Table 2 and Table 3**).

In patients who had stopped the 1st TNFi due to AE, the 12-month retention rate for the 2nd TNFi treatment was 66% (63-68%), which was comparable to the retention rate in patients who stopped the first TNFi treatment due to LOE, where it was 65% (63-67%) (HR 1.02 (95% Confidence interval 0.90-1.1, p = 0.78). Similarly, no difference in 12 month retention rate for the 3rd TNFi was seen between patients who stopped the 2nd TNFi due to AE (65% (60-70%)) or LOE (63% (60-66%)) (HR 1.1 (0.9-1.4), p = 0.3) **(Figure 1).**

Patients who withdrew from the 1st TNFi due to primary LOE had a 12-month lower retention rate on the 2nd TNFi (58% (56-61%) compared to patients who withdrew due to secondary LOE (72% (71-73%), HR 1.6 (1.4-1.8), p = 0.001. Similarly, a lower 12-month retention rate on the 3rd TNF was present in patients who withdrew from the 2nd TNFi due to primary LOE 56% (51-62%) compared to patients who withdrew to secondary LOE on the 2nd TNFi (66% (62-70%), HR = 1.2 (1.1-1.6), p = 0.01. **(Figure 2)**.

Sensitivity analyses in patients who had available baseline data on smoking status and BMI confirmed the findings above (data not shown).

In the individual registries, the 12-month retention rates for the 2nd TNFi ranged from 48% to 85%, and for the 3rd TNFi from 59% to 91% (**Table 2 and Table 3)**

Remission rates

The overall crude (LUNDEX-adjusted) DAS28 remission rates at 6 months were 48% (35%) for patients receiving the 2nd TNFi, and 38% (27%) for patients receiving the 3rd TNFi. Six-month DAPSA remission rates were 18% (13%) for the 2nd TNFi and 10% (7%) for the 3rd TNFi. DAPSA28 remission rates were 19% (14%) and 13% (9%), respectively (**Table 4**).

Patients were stratified based on whether they had stopped the previous TNFi due to AE or LOE. In patients receiving their 2nd TNFi, the crude (LUNDEX-adjusted) DAS28 remission rates at 6 months were 48% (33%) and 43% (31%) for those who had stopped the previous TNFi due to AE and LOE, respectively (p=0.08 andp=0.41)). Corresponding crude (LUNDEX-adjusted) DAPSA remission rates were 17% (12%) and 14% (10%) (p = 0.6 and p = 0.7, respectively), while DAPSA28 remission rates at 6 months were 18% (13%) and 14% (10%), (p=0.03 and p=0.15, respectively). In patients receiving the 3rd TNFi, crude (LUNDEX-adjusted) DAS28 remission rates at 6 months were 39% (27%) and 36% (25%), for those who had stopped the previous TNFi due to AE or LOE, respectively (p=0.6 and p=0.6). Corresponding DAPSA remission rates were 11% (8%) and 10% (7%), (p = 0.9 and p = 0.9)). DAPSA28 remission rates at 6 months were 14% (10%) and 11% (8%) (p=0.6 and p=0.5)) (**Table 4**).

The 6-month remission rates on a 2nd TNFi were lower among patients who had withdrawn from 1st TNFi due to primary LOE compared to those that had withdrawn due to secondary LOE. For these patients, the DAS28 remission at 6 months (crude/LUNDEX) was 42/27% vs 50/38% (p=0.21/0.01), and the DAPSA28 remission 10/6% vs. 15/11% (p=0.09/0.04

In the individual participating registries, the median 6-month LUNDEX adjusted DAS28 remission rates for 2nd TNFi ranged from 21% to 57%, and for 3rd TNFi from 22% to 55% (**Table 4**).

DISCUSSION

This study investigated real-world effectiveness of the 2nd and 3rd TNFi in patients with PsA, based on data from 12 registries in the EuroSpA research collaboration. One-year retention rates for 2nd and 3rd TNFi were similar (68% and 66%), while higher remission rates for the 2nd TNFi were observed.

Previous studies investigating retention rates in real-world data for PsA patients initiating their 2nd TNFi have been performed in single registries. The 12-month drug survival has been reported to be 74% (a British biologics registry), 81% (Spanish BIOBADASER), 76-80% (Finnish ROB-FIN), and 70% (Danish DANBIO), whereas the Norwegian NOR-DMARD registry reported a 36-month drug survival of 36% [15–19]. These are in line with the drug retention rates found for the individual registries in the present dataset. Data regarding routine care retention rates for the 3rd TNFi are limited. A British biologics registry reported 48% 5-year drug-survival for the 3rd TNFi treatment [20]. The Portuguese register "Reuma.pt" found lower retention rates for the 3rd as compared to the 2nd TNFi [6]. These studies all had relatively few patients (111, 50 and 189 patients, respectively). The present multinational study, which included high patient numbers through pooling of data from multiple registries, found very similar retention rates for the 2nd and the 3rd TNFi. Lack of treatment alternatives to TNFi at the time of data collection may, at least in part, have contributed to this finding.

As expected, we found that the remission rates were significantly lower in the patients receiving the 3rd compared to the 2nd TNFi treatment. The NOR-DMARD study [7] found poorer DAS28 remission rates at 3 months to the 2nd TNFi compared to the 1st (28.2% vs 54.1%), and in line with this the Portuguese register also found lower response rates to the 2nd TNFi compared to the 1st [6].

We hypothesized that LOE (primary and secondary LOE combined) to the previous TNFi would be related to poorer retention to the subsequent TNFi, i.e., a drug with a similar mode of action, as compared to switching due to AE. This could, however, not be confirmed. We observed no clinically relevant differences in remission or retention rates between patients who had stopped the previous TNFi treatment due to AE or LOE overall, neither in patients receiving the 2nd nor the 3rd TNFi. In line with our results, studies from the BSRBR-AS and the Reuma.pt likewise

detected no association between the reason for discontinuation of the 1st TNFi and drug retention of the 2nd TNFi [6,7]. No previous studies have to our knowledge investigated if the reason for discontinuation of the 2nd TNFi is associated with remission or retention rates of the 3rd TNFi. However, a study from our group recently demonstrated that discontinuation reason from the 2nd TNFi had no impact on effectiveness of the 3rd TNFi in axSpA patients [21].

Interestingly, we observed higher retention and remission rates for the subsequent TNFi treatment in patients who switched due to LOE after more than 24 weeks on the previous TNFi. This finding supports a clinical relevance of primary vs. secondary LOE, as implemented in the recent ACR guidelines for PsA [22,23], where it is suggested to consider switching to an alternative mode of action if a patient has had a primary failure to TNFi. It should be noted that while retention was indeed higher in patients who switched due to secondary LOE (72%), our data also demonstrated an acceptable 12-month retention of 58% in patients who stopped the previous TNFi due to primary LOE. Thus our data also support the current clinical practice to consider switching to a 2nd TNFi in case of failure to the 1st TNFi – regardless of reason for discontinuation.

Across registries, we found that both retention rates and remission rates differed markedly with 12-month retention rates varying from 48% in Norway to 85% in Finland for the 2nd TNFi and from 59% in Denmark to 78% in Spain for the 3rd TNFi. Considerable heterogeneity in number of patients included, baseline characteristics and disease activity, was observed, and may have contributed to the differences in outcomes. Overall, a trend towards higher retention rates in countries with fewer socioeconomic resources was present, which could be explained by stricter criteria for treatment initiation and a higher threshold for switching from one TNFi to another in these countries. However, we also observed differences in retention rates between the Scandinavian registries, which suggests an impact of additional factors such as different national treatment guidelines [24].

Future studies should investigate whether inter-country differences in outcomes can be explained by differences in demographic, clinical, imaging, or biochemical patient characteristics, and factors of predictive value for remission and drug retention should be explored. Detailed information on national treatment recommendations and guidelines and access to biological drugs should be collected to investigate their influence on patient characteristics, retention, and remission rates. For instance, it could be speculated that higher accessibility to treatment may lead to more rapid treatment switching with less disease activity at treatment start and lower TNFi retention rates.

Strengths of this study include the high number of patients with at least 2 years of follow-up, which was made possible through secondary use of data from 12 registries across Europe. This enabled us to stratify for the reason for discontinuation of the previous TNFi in patients receiving 2nd and 3rd TNFi. Limitations include limited data availability with regards to 66/68 joint counts, and the lack of available information regarding other PsA domains than joints, such as axial involvement, dactylitis, enthesitis and skin involvement, since these data were not collected in the participating registries. Due to this we were only able to analyse effectiveness in the joint domain of PsA. Thus, the outcome measures applied in the present study may overlook residual disease activity in other domains. Selection bias based on data availability cannot be ruled out. Subjects that are compliant may visit their rheumatologist more regularly and therefore have more complete registry data. This could potentially lead to overestimation of remission rates, but this bias would affect 2nd and 3rd TNFi to a similar degree. All data were collected prospectively in the individual countries, independently of the current research study.

In conclusion, this EuroSpA study of pooled data from 12 European registries found that 12-month retention rates were 68% for the 2nd TNFi and 65% for the 3rd TNFi. Approximately

one third and one quarter of patients who started 2nd or 3rd TNFi, respectively, were in DAS28 remission at 6-month follow-up.

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AUTHOR CONTRIBUTION

Study leads were LØ, CHB, LL, MØ and MLH. All authors took part in discussions around setting up the collaboration and planning this study. The study analysis plan was drafted by LØ, CHB, MØ and MLH and all authors gave input and approved it. Data cleaning was performed by NSK, LØ, CHB and overseen by MØ and MLH. Data analyses were conducted by NSK, CHB and LØ. The manuscript was drafted by LØ, CHB, LL, MØ and MLH and the final version of the manuscript was revised and approved by all authors, who also approved submission. See Credit statement for details (Doc S1)

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]. Relevant

patient level data may be made available on reasonable request to the corresponding author but will require approval from all contributing registries.

CONFLICT OF INTERESTS

Lykke M. Ørnbjerg: Novartis; **Cecilie H. Brahe**: Novartis**; Louise Linde:** Novartis: **Lennart Jacobsen**: none; **Michael Nissen**: Lilly, Pfizer, Novartis; **Eirik Klami Kristianslund**: none; **Herman Mann**: AbbVie, MSD, Novartis, Pfizer, Sanofi; **Maria José Santos**: AbbVie, Biogen, Lilly, Pfizer, Novartis; **Manuel Pombo Suarez**: none; **Dan Nordström**: AbbVie, BMS, Lilly, MSD, Novartis, Pfizer, Roche, Sandoz, UCB; **Ziga Rotar**: Abbvie, Celgene, MSD, Novartis, Pfizer, **Bjorn Gudbjornsson**: Amgen, Novartis, Pfizer; **Fatos Onen**: Abbvie, Novartis, Pfizer, Roche, UCB; **Catalin Codreanu**: AbbVie, Amgen, Angellini, Astra Zeneca, BMS, Egis, MSD, Pfizer, Richter, Roche, Sanofi, Servier, Teva, UCB, Zentiva; **Ulf Lindström**: none; **Burkhard Möller**: none; **Tore K Kvien**: AbbVie, BMS, Amgen, Celltrion, Galapagos, Gilead, Grünenthal, Novartis, Pfizer, Sandoz, UCB: **Karel Pavelka**: AbbVie, Roche, Pfizer, Amgen, Sanofi, Egis, BMS, UCB, MSD, Lilly; **Anabela Barcelos**: Amgen, Novartis, Abbvie, Janssen; **Carlos Sánchez-Piedra**: none; **Kari K. Eklund**: none; **Matija Tomšič**: none; **Thorvardur Jon Love**: none; **Gercek Can**: none; **Ruxandra Ionescu**: none; **Anne Gitte Loft**: Novartis, AbbVie, MSD, Lilly, Roche; **I.E. van der Horst-Bruinsma**: AbbVie, MSD, Novartis, Pfizer, Lilly, UCB; **Gary J. Macfarlane**: Pfizer, Abbvie, UCB; **Florenzo Iannone**: BMS, Pfizer, Abbvie, UCB, Roche, Celgene, Lilly, Hospira, Janssen, Merck; **Lise Hejl Hyldstrup**: Novartis; **Niels Steen Krogh:** none; **Mikkel Østergaard**: Abbvie, BMS, Boehringer-Ingelheim, Celgene, Eli-Lilly, Galapagos, Gilead, Hospira, Janssen, MEDAC, Merck, Novartis, Novo, Orion, Pfizer, Regeneron, Roche, Sandoz, Sanofi and UCB; **Merete Lund Hetland**: Abbvie, Biogen, BMS, CellTrion, MSD, Novartis, Orion, Pfizer, Samsung, UCB

Online material. Supplementary data

Supplementary data associated with this article can be found in the online version at …

REFERENCES

1. Callhoff J, Sieper J, Weiß A, et al. Efficacy of TNFα blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: A meta-analysis. *Ann Rheum Dis* 2015;74:1241–8.

2. Ash Z, Gaujoux-Viala C, Gossec L, et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: Current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis* 2012;71:319–26.

3. Saad AA, Ashcroft DM, Watson KD, et al. Efficacy and safety of anti-TNF therapies in psoriatic arthritis: an observational study from the British Society for Rheumatology Biologics Register. *Rheumatology (Oxford) 2010;49:607-705*

4. Reddy SM, Crean S, Martin AL, et al. Real-world effectiveness of anti-TNF switching in psoriatic arthritis: a systematic review of the literature. *Clin Rheumatol* 2016;35:2955-2966

5. Gülfe A, Kristensen LE, Saxne T, et al. Utility-based outcomes made easy: the number needed per quality-adjusted life year gained. An observational cohort study of tumor necrosis factor blockade in inflammatory arthritis from Southern Sweden. *Arthritis Care Res* 2010;62:1399–406

6. Vieira-Sousa E, Eusébio M, Ávila-Ribeiro P, et al. Real-world Longterm Effectiveness of Tumor Necrosis Factor Inhibitors in Psoriatic Arthritis Patients from the Rheumatic Diseases Portuguese Register. *J Rheumatol* 2020;47:690–700.

7. Fagerli KM, Kearsley-Fleet L, Watson KD, et al. Long-term persistence of TNF-inhibitor treatment in patients with psoriatic arthritis. Data from the British Society for Rheumatology Biologics Register. *RMD Open* 2018;4:596.

8. Glintborg B, Østergaard M, Krogh NS, et al. Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor α inhibitor therapy: Results from the danish nationwide DANBIO registry. *Arthritis Rheum*2013;65:1213–23.

9. Ciurea A, Exer P, Weber U, et al. Does the reason for discontinuation of a first TNF inhibitor influence the effectiveness of a second TNF inhibitor in axial spondyloarthritis? Results from the Swiss Clinical Quality Management Cohort. Arthritis Res Ther 2016; 22;18:71.

10. Deodhar A, Yu D. Switching tumor necrosis factor inhibitors in the treatment of axial spondyloarthritis. *Semin Arthritis Rheum* 2017;47:343–50.

11. Ørnbjerg LM, Brahe CH, Askling J, et al. Treatment response and drug retention rates in 24 195 biologic-naïve patients with axial spondyloarthritis initiating TNFi treatment: routine care data from 12 registries in the EuroSpA collaboration. *Ann Rheum Dis* 2019;78:1536–44.

12. Brahe CH, Ørnbjerg LM, Jacobsson L, et al. Retention and response rates in 14 261 PsA patients starting TNF inhibitor treatment-results from 12 countries in EuroSpA. *Rheumatology (Oxford)* 2020;59:1640-50.

13. Michelsen B, Sexton J, Smolen JS, et al. Can disease activity in patients with psoriatic arthritis be adequately assessed by a modified Disease Activity index for PSoriatic Arthritis (DAPSA) based on 28 joints? *Ann Rheum Dis* 2018;77:1736–41.

14. Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: Results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in Southern Sweden. *Arthritis Rheum* 2006;54:600–6.

15. Saad AA, Ashcroft DM, Watson KD, et al. Persistence with anti-tumour necrosis factor therapies in patients with psoriatic arthritis: Observational study from the British Society of Rheumatology Biologics Register. *Arthritis Res Ther* 2009;11:52.

16. Carmona L, Gómez-Reino JJ. Survival of TNF antagonists in spondylarthritis is better than in rheumatoid arthritis. Data from the Spanish registry BIOBADASER. *Arthritis Res Ther* 2006;8(3):72.

17. Glintborg B, Østergaard M, Dreyer L, et al. Treatment response, drug survival, and predictors thereof in 764 patients with psoriatic arthritis treated with anti-tumor necrosis factor α therapy: Results from the nationwide Danish DANBIO registry. *Arthritis Rheum* 2011;63:382–90.

18. Fagerli KM, Lie E, Van Der Heijde D, et al. Switching between TNF inhibitors in psoriatic arthritis: Data from the NOR-DMARD study. *Ann Rheum Dis* 2013;72:1840–4.

19. Aaltonen K, Heinonen A, Joensuu J, et al. Effectiveness and drug survival of TNF-inhibitors in the treatment of psoriatic arthritis: A prospective cohort study. *Semin Arthritis Rheum* 2017;46:732–9.

20. Fagerli KM, Kearsley-Fleet L, Watson KD, et al. Long-term persistence of TNF-inhibitor treatment in patients with psoriatic arthritis. Data from the British Society for Rheumatology Biologics Register. *RMD Open* 2018;4:596.

21. Linde L, Ørnbjerg LM, Heegaard Brahe C, et al. Second and third TNF inhibitors in European patients with axial spondyloarthritis: Effectiveness and impact of the reason for switching. *Rheumatology (Oxford) Epub ahead of print* doi: 10.1093/rheumatology/kead494

22. Singh JA, Guyatt G, Ogdie A, et al. Special Article: 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. *Arthritis Rheum 2019:5–32*.

23. Ogdie A, Coates LC, Gladman DD. Treatment guidelines in psoriatic arthritis. *Rheumatology (Oxford*,59:i37-i46.

24. Michelsen B, Østergaard M, Nissen MJ, et al. Differences and similarities between the EULAR/ASAS-EULAR and national recommendations for treatment of patients with psoriatic arthritis and axial spondyloarthritis across Europe. *Lancet Reg Health Eur. 2023 Aug 4;33:100706*

Table 1
Baseline characteristics of PsA patients at start of 1st, 2nd and 3rd TNFi treatment

	1st TNFi (n=14691)*	2nd TNFi (n=5233)**	3rd TNFi (n=1906)***
Fulfilling CASPAR criteria	75%	75 %	73%
Age, years	49 (40-57)	50 (41-59)	51 (42-59)
Male	49 %	42 %	38 %
Concomitant csDMARD	60 %	54 %	52 %
Prior csDMARD	81 %	81 %	84 %
Time since diagnosis, years	4 (1-9)	5 (2-11)	7 (4-13)
Current smoking	16 %	17 %	18 %
Infliximab	22 %	12 %	17 %
Etanercept	34 %	38 %	27 %
Adalimumab	31 %	33 %	28 %
Certolizumab	4 %	6 %	9 %
Golimumab	11 %	12 %	19 %
Calendar year of treatment start			
Prior to 2009	26%	17 %	12 %
2009-2011	22%	23 %	21 %
2012-2014	25%	31 %	35 %
2015-2017	28%	30 %	32 %
DAS28	4.3 (3.4-5.1)	4 (3.1-4.9)	4.1 (3.2-5.0)
DAPSA	24.8 (17.3-35.0)	23.5 (15.1-33)	23.6 (15.5-34.4)
DAPSA28	26.7 (17.6-39.2)	24.6 (15.3-36.7)	25.4 (16.3-38.5)
CRP, mg/L	7 (3-17)	5 (2-13)	5 (2-14)

SJC (0-28)	3 (1-6)	2 (0-4)	2 (0-4)
TJC (0-28)	5 (2-9)	4 (1-9)	4 (1-10)
SJC (0-66)	4 (1-7)	2 (0-6)	2 (0-6)
TJC (0-68)	8 (4-14)	6 (2-12)	6 (2-12)
Pain score (VAS 0-100 mm)	62 (42-75)	63 (40-78)	65 (42-80)
Fatigue score (VAS 0-100 mm)	64 (40-80)	68 (45-81)	70 (48-83)

Data are as observed, median (IQR) or percentage; PsA: Psoriatic Arthritis; CASPAR: ClASsification criteria for Psoriatic Arthritis; csDMARD: conventional synthetic Disease Modifying Anti Rheumatic Drug; TNFi: tumor necrosis factor inhibitor; SJC: swollen joint count; TJC: tender joint count;

VAS: visual analogue scale; CRP: C-Reactive Protein; DAS28: Disease Activity Score 28 joint-count; DAPSA28: Disease Activity index for Psoriatic Arthritis 28 joint-count * number of patients with available data varied from: 3228-14691

number of patients with available data varied from n: 1025-5233; * number of patients with available data varied from n: 342-1906

Table 2
Retention rates after 6, 12 and 24 months in cohorts of PsA patients initiating a 2nd TNF inhibitor

Cohort	No. of patients	6 months (95% CI)	12 months (95% CI)	24 months (95% CI)
All patients	5233	79 % (78-80%)	68 % (67-70%)	60 % (58-61%)
AE on 1st TNFi	1190	75% (73-78%)	66% (63-68%)	57% (54-60%)
LOE on 1st TNFI	2790	78% (76-80%)	65% (63-67%)	56% (54-58%)
Primary LOE on 1st TNFi	653	68% (65-72%)	54% (50-58%)	47% (43-51%)
Secondary LOE on 1st TNFi	2137	81% (79-83%)	69% (67-71%)	59% (57-61%)
SRQ	2370	79%(78-81%)	69% (67-71%)	60% (58-63%)
BIOBADASER	174	83% (77-88%)	72% (65-79%)	64% (56-72%)
Biorx.si	106	85(%78-92%)	68% (59-77%)	62% (53-72%)
DANBIO	1060	73% (70-76%)	60% (57-63%)	52% (49-55%)
ICEBIO	144	82% (76-89%)	72% (64-80%)	64% (56-73%)
NOR-DMARD	197	62% (56-70%)	48% (42-56%)	38% (31-46%)
reuma.pt	139	89% (84-95%)	74% (67-82%)	69% (61-78%)
ROB-FIN	150	89% (84-94%)	85% (79-91%)	81% (75-88%)
RRBR	16	-	-	-
SCQM	514	84% (81-87%)	73% (69-77%)	63% (58-67%)
TURKBIO	129	87% (81-93%)	79% (72-86%)	66% (58-75%)
ATTRA	234	86% (81-90%)	76% (70-82%)	68% (62-75%)

TNFi: tumor necrosis factor inhibitor; AE: adverse event; LOE: lack of effect. Only rates calculated with > 50 patients are presented.

Table 3
Retention rates after 6, 12 and 24 months in cohorts of PsA patients initiating a 3rd TNF inhibitor

Cohort	No. of patients	6 months (95% CI)	12 months (95% CI)	24 months (95% CI)
All patients	1906	77 % (75-79%)	66 % (64-68%)	55 % (52-57%)
AE on 2nd TNFi	383	75% (71-80%)	65% (60-70%)	54% (49-60%)
LOE on 2nd TNFI	1021	75% (73-78%)	63% (60-66%)	50% (47-54%)
Primary LOE on 2nd TNFi	325	69% (64-74%)	56% (51-62%)	43% (37-49%)
Secondary LOE on 2nd TNFi	696	78%(75-82%)	66% (62-70%)	54% (50-58%)
SRQ	906	78% (75-80%)	66% (63-69%)	53% (50-57%)
BIOBADASER	66	89% (81-97%)	-	-
Biorx.si	30	-	-	-
DANBIO	407	69% (65-74%)	59% (54-64%)	51% (46-56%)
ICEBIO	55	-	-	-
NOR-DMARD	42	-	-	-
reuma.pt	37	-	-	-
ROB-FIN	35	-	-	-
RRBR	1	-	-	-
SCQM	202	79% (73-85%)	67% (61-74%)	55% (48-63%)
TURKBIO	50	-	-	-
ATTRA	75	85% (77-93%)	-	-

TNFi: tumor necrosis factor inhibitor; AE: adverse event; LOE: lack of effect. Only rates calculated with > 50 patients are presented.

Table 4
Remission rates after 6, 12 and 24 months in cohorts of PsA patients initiating a 2nd or 3rd TNF inhibitor

	2nd TNF inhibitor						3rd TNF inhibitor					
	DAS28 remission		DAPSA28 remission		DAPSA remission		DAS28 remission		DAPSA28 remission		DAPSA remission	
	Rate at 6/12/24 month		Rate at 6/12/24 month		Rate at 6/12/24 month		Rate at 6/12/24 month		Rate at 6/12/24 month		Rate at 6/12/24 month	
	Crude*	LUNDEX-adjusted**	Crude*	LUNDEX-adjusted**	Crude*	LUNDEX-adjusted**	Crude*	LUNDEX-adjusted**	Crude*	LUNDEX-adjusted**	Crude*	LUNDEX-adjusted**
All patients	48/51/55	35/29/22	19/20/23	14/12/9	18/20/23	13/11/9	38/40/48	27/22/17	13/15/18	9/8/6	10/15/17	7/8/6
AE on 1st TNFi	48/53/56	33/30/22	18/18/23	13/10/9	17/19/23	12/10/9	39/44/56	27/24/21	14/13/22	10/7/8	11/8/19	8/4/7
LOE on 1st TNFI	43/47/51	31/26/20	14/16/21	10/9/8	14/16/19	10/9/7	36/39/49	25/20/18	11/14/14	8/7/5	10/15/17	7/8/6
Primary LOE on 1st TNFi	39/43/46	25/19/14	10/15/17	7/7/5	9/10/22	6/5/7	37/42/44	24/20/13	13/13/18	9/6/5	17/12/21	11/12/6
Secondary LOE on 1st TNFi	44/48/52	33/28/22	15/17/22	11/10/9	15/17/18	12/10/8	35/37/51	26/21/20	10/14/13	8/8/5	8/16/15	6/9/6
SRQ	47/46/52	34/26/21	17/17/21	12/9/9	-	-	34/34/42	24/18/14	10/11/15	7/6/5	-	-
BIOBADASER	-	-	-	-	-	-	-	-	-	-	-	-
Biorx.si	49/47/-	42/29/-	19/22/33	16/14/16	-	-	-	-	-	-	-	-
DANBIO	45/53/54	31/28/19	18/22/24	12/11/9	17/26/-	12/14/-	34/36/52	22/18/17	11/16/16	7/6/5	-	-
ICEBIO	29/50/-	21/30/-	10/-/-	8/-/-	-	-	-	-	-	-	-	-
NOR-DMARD	52/43/-	32/18/-	22/22/-	13/9/-	-	-	-	-	-	-	-	-
reuma.pt	44/59/-	37/39/-	15/13/-	12/8/-	-	-	-	-	-	-	-	-
ROB-FIN	-	-	-	-	-	-	-	-	-	-	-	-
RRBR	-	-	-	-	-	-	-	-	-	-	-	-
SCQM	54/56/63	43/36/28	24/22/30	19/13/19	24/22/27	19/14/12	-	-	-	-	-	-
TURKBIO	-	-	-	-	-	-	-	-	-	-	-	-
ATTRA	62/65/63	49/38/28	29/31/23	22/18/10	-	-	-	-	-	-	-	-

Data are as observed, median (IQR) or percentage; DAS28: Disease Activity Score 28 joint-count; DAPSA28: Disease Activity index for Psoriatic Arthritis 28 joint-count; TNFi: tumor necrosis factor inhibitor; AE – adverse event; LOE -lack of effect.

Details on numbers of patients with available data at the relevant timepoints are found in Table S3 and S4. Only rates calculated with > 50 patients are presented** Crude rate: the fraction responding of those still on drug at 6,12 and 24 months with available assessment, respectively. ***Lundex adjusted rate: crude rate adjusted for drug retention.

FIGURE LEGENDS

Figure 1 Kaplan-Meier curves (top) showing drug retention rates up to 24 months. Panel A: 2nd TNFi stratified by discontinuation reason from the 1st TNFi (LOE or AE). Panel B: 3rd TNFI stratified by discontinuation reason from the 2nd TNFi (LOE or AE).

The table (bottom) shows the number of patients who were still being treated at the corresponding time points.

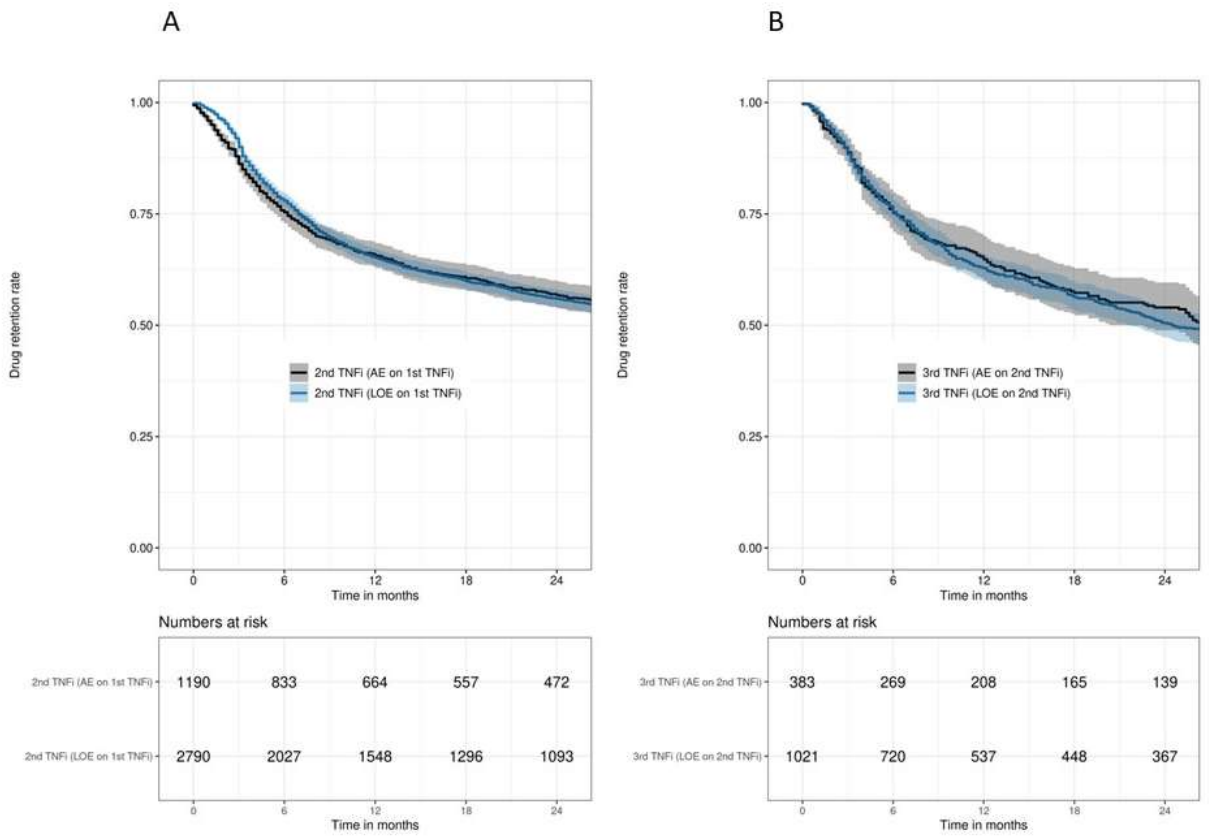
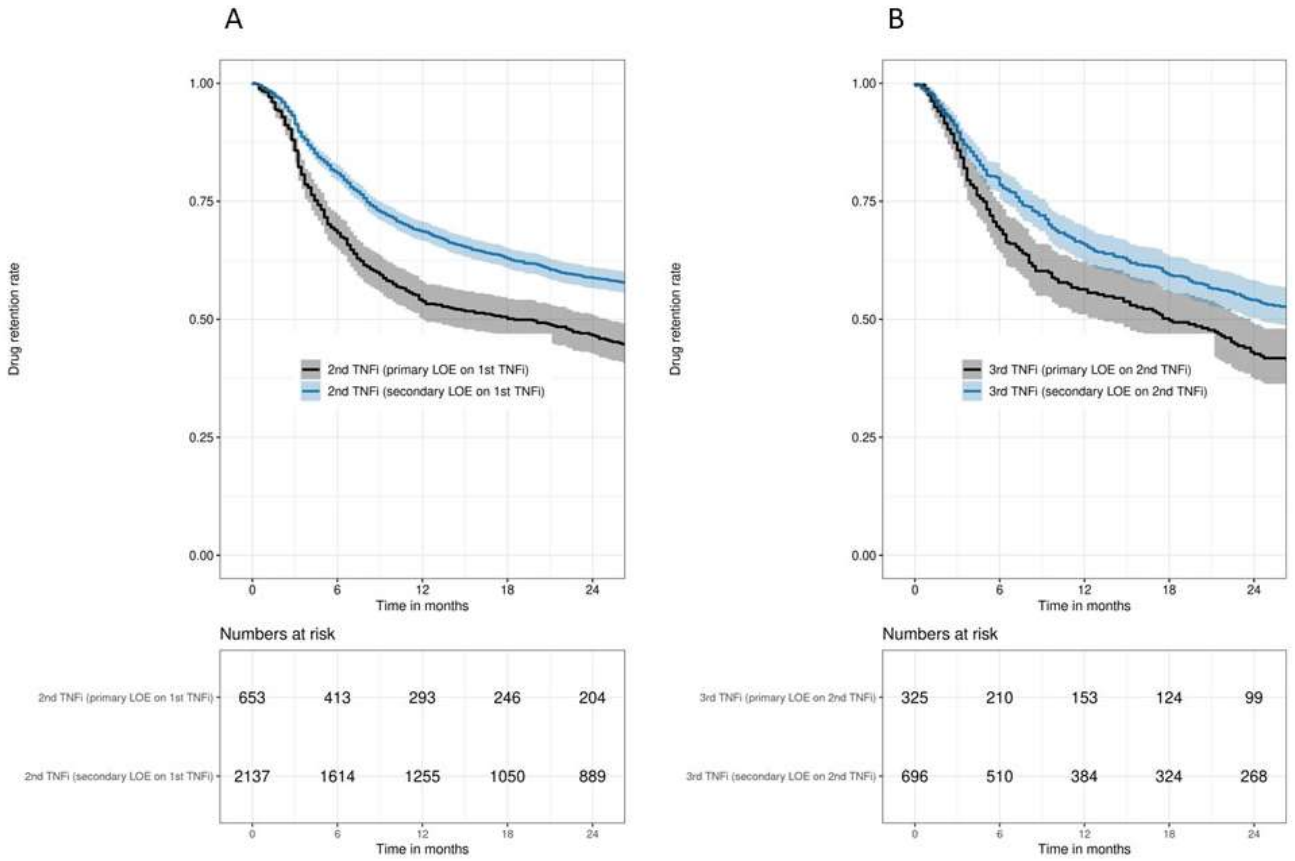

A
B
Drug retention rate
1.00
0.75
0.50
0.25
0.00
2nd TNFi (AE on 1st TNFi)
2nd TNFi (LOE on 1st TNFi)
3rd TNFi (AE on 2nd TNFi)
3rd TNFi (LOE on 2nd TNFi)
0
6
12
18
24
Time in months
Numbers at risk
2nd TNFi (AE on 1st TNFi) 1190 833 664 557 472
2nd TNFi (LOE on 1st TNFi) 2790 2027 1548 1296 1093
3rd TNFi (AE on 2nd TNFi) 383 269 208 165 139
3rd TNFi (LOE on 2nd TNFi) 1021 720 537 448 367

Figure 2 Kaplan-Meier curves (top) showing drug retention rates up to 24 months. Panel A: 2nd TNFi stratified by discontinuation reason from the 1st TNFi (primary LOE or secondary LOE). Panel : 3rd TNFi stratified by discontinuation reason from the 2nd TNFi (primary LOE or secondary LOE).

The table (bottom) shows the number of patients who were still being treated at the corresponding time points.


A
Drug retention rate
1.00
0.75
0.50
0.25
0.00
2nd TNFi (primary LOE on 1st TNFi)
2nd TNFi (secondary LOE on 1st TNFi)
0
6
12
18
24
Time in months
Numbers at risk
2nd TNFi (primary LOE on 1st TNFi) 653 413 293 246 204
2nd TNFi (secondary LOE on 1st TNFi) 2137 1614 1255 1050 889
Time in months
B
Drug retention rate
3rd TNFi (primary LOE on 2nd TNFi)
3rd TNFi (secondary LOE on 2nd TNFi)
Time in months
Numbers at risk
3rd TNFi (primary LOE on 2nd TNFi) 325 210 153 124 99
3rd TNFi (secondary LOE on 2nd TNFi) 696 510 384 324 268
Time in months