One-Year Treatment Outcomes of Secukinumab Versus Tumor Necrosis Factor Inhibitors in Spondyloarthritis : Results From Five Nordic Biologic Registries Including More Than 10,000 Treatment Courses

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One-year treatment outcomes of secukinumab versus tumor necrosis factor inhibitors in Spondyloarthritis.

Results from 5 Nordic biologic registries including >10.000 treatment courses

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Abstract

Objective

To describe baseline characteristics and to compare treatment effectiveness of secukinumab versus tumor necrosis factor inhibitors (TNFi), in patients with spondyloarthritis (SpA) using adalimumab as the main comparator.

Methods

Observational, prospective cohort study. Patients with SpA (clinical ankylosing spondylitis/non-radiographic axial SpA/undifferentiated SpA) starting secukinumab or a TNFi during 2015-2018 were identified from five Nordic clinical rheumatology registries. Comorbidities and extra-articular manifestations (psoriasis/uveitis/inflammatory bowel disease) were captured from national registries (data available in 94% of patients) and included in multivariable analyses. We assessed 1-year treatment retention (crude survival curves, adjusted hazard ratios (HR) for treatment discontinuation) and 6-months' response-rates (ASDAS<2.1/BASDAI<40mm, crude/LUNDEX-adjusted, adjusted logistic-regression analyses with odds-ratio(OR)), stratified by line of biological treatment (1^{st}/2^{nd}/3^{rd}+).

Results

In total, 10,853 treatment courses (842 secukinumab/10,011 TNFi whereof 1,977 adalimumab) were included. The proportion treated with secukinumab during 1^{st}/2^{nd}/3^{rd}+ was 1%/6%/22%). Extra-articular manifestations varied across treatments, while other baseline characteristics were largely similar.

Secukinumab had a one-year retention comparable to adalimumab as 1^{st} or 2^{nd}, but poorer as 3^{rd}+ line of therapy (secukinumab 56% (51%-61%) versus adalimumab 70% (64%-75%)), adjusted HR 1.43 (1.12-1.81). Across treatment lines, secukinumab had poorer estimates for 6-months response rates than adalimumab, statistically significantly so only for 3^{rd}+ line (adjusted analyses: ASDAS<2.1 OR=0.56 (0.35-0.90), BASDAI<40mm OR=0.62 (0.41-0.95)). Treatment outcomes varied across the five TNFi.

Conclusion

Secukinumab was mainly used in biologically experienced SpA patients. Secukinumab and adalimumab performed similar in patients who had failed a first biological, although with increasing prior biological exposure, adalimumab was superior.

Significance and Innovations

- In spondylarthritis, secukinumab is mainly prescribed in biological experienced patients and not as first line biological
- Outcomes in difficult-to-treat patients that have failed more than two prior biologics are generally poor
- Our data did not support that secukinumab was superior to adalimumab or other tumor necrosis factor inhibitor (TNFi) after failing a previous TNFi

The effect of tumor necrosis factor inhibitors (TNFi) for treatment of spondyloarthrtitis (SpA) is well established.(1) Inhibition of the interleukin (IL)-17 signaling pathway represents a newer mode of action. In 2015 the first IL-17-inhibitor (secukinumab) was approved in ankylosing spondylitis based on phase III studies performed on bio-naïve and previously TNFi-treated patients (MEASURE Trials).(2-4)

Currently, the optimal treatment strategy for SpA in routine care remains to be established,(5;6) and randomized head-to-head comparisons of secukinumab versus individual TNFi are awaited.(7) Recent recommendations acknowledge these evidence gaps - but state that treatment with TNFi should be preferred before secukinumab as first line biologic due do familiarity with long-term safety. However, in case of TNFi failure due to lack of effect, secukinumab should be favored.(5) Studies applying indirect comparisons based on data acquired from phase III trials of the respective drugs found similar or superior effectiveness of secukinumab versus adalimumab.(8)

Many patients treated with biological in routine care would never be eligible for inclusion in a randomized trial due to atypical disease presentation, low disease activity, comorbidity, high age etc.(9) Thus, observational studies contribute a valuable supplement to results from randomized trials (RCT).(10;11) A recent Swizz real-life study including 106 secukinumab treated biologic experienced patients with axial SpA reported similar 1-year treatment effectiveness compared to TNFi.(12) The study included no comparisons for secukinumab versus the individual TNFi, although TNFi treatment effectiveness is known to vary across individual TNFi drugs.(13;14) Furthermore, concomitant extra-articular manifestations might affect TNFi prescription patterns and the observed outcomes.

We have previously described a Nordic epidemiologic research collaboration within inflammatory arthritis aiming to investigate rare exposures or outcomes based on combined datasets from five prospective biologic registries enriched with data from national registries.(15-17) Within this collaboration, we aimed to explore the following in patients with SpA treated with secukinumab versus TNFi (mainly adalimumab) and followed in routine care in the Nordic countries: a) patient characteristics at treatment start, and b) retention to treatment during the first year including reasons for withdrawal, and c) 6 month's treatment response.

Materials and methods

Observational cohort study based on five Nordic biological registries: DANBIO (Denmark), SRQ/ARTIS (Sweden), ROB-FIN (Finland), NOR-DMARD (Norway) and ICEBIO (Iceland).(15) In these registries, patients are followed prospectively in routine care with monitoring of treatment and outcomes as previously described.(15)

Population and treatments

Each registry identified adult patients (≥18 years) with SpA starting a TNFi (infliximab, etanercept, adalimumab, golimumab and certolizumab pegol) or secukinumab between January 1st 2015 and December 31st 2018, regardless of previous biological (bDMARD) treatment. SpA was defined as a clinical diagnosis of: AS, undifferentiated SpA, non-radiographic axial SpA, axial-SpA, or by ICD10-codes: M45, M46.0, M46.1, M46.8, M46.9 and M07.2.

Treatments with other biologicals (e.g. ixekizumab) or JAK inhibitors were excluded due to few treatment courses, but each patient could contribute with more than one bDMARD treatment course.

Patient characteristics

Patient characteristics upon start of individual bDMARDs (=baseline) were retrieved from the biologic registries and included gender, age, disease duration and concomitant treatment with conventional synthetic (cs)DMARDs (e.g. methotrexate, sulfasalazine). Concomitant treatment with non-steroid anti-inflammatory drugs is not routinely registered and will not be reported.

For each treatment course, comorbidities 0-5 years prior to baseline (**Supplementary Table 1**, main or contributory diagnoses) were identified as previous hospital contacts (in- or outpatient care) through linkage to the National Patient Registry of individual countries. The following 8 comorbidities were included: malignancy, infection, congestive heart disease, chronic obstructive or interstitial pulmonary disease, chronic kidney disease, diabetes, myocardial infarction, hip or knee prosthesis. In the National Patient registries, hospital contacts, including discharge diagnoses, are coded according to the International Classification of Diseases (ICD10). Furthermore, extra-articular SpA manifestations (uveitis, inflammatory bowel disease, psoriasis) were identified.

Not all countries were able to deliver comorbidity linkage data for the full observation period (Iceland: not available, Denmark: until August 2018, Sweden, Norway, Finland: Until data-censoring 31st Dec 2018).

Disease activity and treatment outcomes at 6 months

Each registry extracted individual-level data on disease activity from -60 to +540 days (if available) from start of the respective bDMARD treatment. Exploratory analyses were performed to select the optimal time-windows for baseline and 6-months' follow-up data in order to reduce missingness. Thus, baseline data were captured within the time-window -30 to +14 days, and the 6 months' follow-up visit from within 90 to 270 days. In case more than one visit occurred within a given time-window, the one closest to the given time point was selected. No imputation of missing data was performed. Disease activity was reported as Bath Ankylosing Spondylitis Activity Score (BASDAI, mm), Functional Index (BASFI), Metrology Index (BASMI), C-reactive protein (CRP, mg/L), Disease Activity score (ASDAS), patient's global score on a visual analogue scale (VAS, 0-100 mm), and patient's score for pain on a VAS.

For all treatment courses with secukinumab and each of the TNFi, drug type and start date were retrieved. In case of treatment withdrawal, date of withdrawal and reason for withdrawal (pregnancy/remission/insufficient response/adverse events/death/other) were registered. Switching from originator to corresponding biosimilar bDMARD (etanercept, infliximab, adalimumab) or vice versa was not considered a discontinuation if the respective biosimilar/originator was started within three months. Re-exposure to the same TNFi was counted as a separate treatment course if time interval between stop and start was >3 months.

Statistics

All country specific data were pooled for analyses. Analyses were performed using SAS (version 9.4) and Stata (version 16.1) and followed a pre-defined study protocol approved by all co-authors.

Baseline characteristics

Baseline characteristics were evaluated based on percentages and means (standard deviations) for patients treated with secukinumab and each of the 5 TNFi.

Retention to treatment

Treatment retention (=duration of treatment) and withdrawals stratified by drug type (secukinumab and each of the 5 TNFi) and line of treatment (1^{st}, 2^{nd}, 3^{rd+}) was evaluated with Kaplan-Meier analysis, overall and by gender. Main outcome was treatment withdrawal irrespective of reason. The person-time to calculate retention rates was defined as the number of days from treatment start until treatment withdrawal, death, censoring or 365 days of follow-up, whichever came first.

Similarly, proportional hazard Cox regression analyses for treatment withdrawal within 1 year was performed, crude (with 95% confidence intervals) and adjusted for **A**) age, sex, **B**) model A further adding baseline values for BASDAI, CRP, patient global score, and concomitant csDMARD, **C**) model B further adding extra-articular manifestations (uveitis yes/no, inflammatory bowel disease yes/no, psoriasis yes/no) and number of different comorbidities (maximum 8, as described above, summed as: 0/1/>1). Adalimumab was the reference drug. Analyses were stratified according to line of treatment. Additional adjustment for country did not change the results, thus country was not included in the models.

In the multivariate analyses, age was added as a continuous variable including a quadratic term. The following variables were added as categorical: concomitant csDMARD (yes/no/missing), and based on quartiles of the distribution: BASDAI (≤3.7/ >3.7; ≤5.9/ >5.9; ≤7.5/ >7.5/ missing), CRP (mg/L) (≤2/ >2;≤4.2/ >4.2;≤11/ ≥11/ missing), patient global score (≤45/ >45; ≤65/ >65; ≤80/ >80/ missing).

For model C, only patients with available linkage to national patient registries were included.

In all multivariable models, robust standard errors were used to adjust for patients contributing ≥1 treatment course.

Treatment response at 6 months' follow-up

The proportions of patients with at least 6 months' follow- up and available data who a) were in ASDAS low disease activity (ASDAS<2.1), or b) had BASDAI<40 mm at 6 months were identified. Furthermore, the corresponding LUNDEX corrected response rates (crude) were calculated thus taking early withdrawal (<6 months) into account.(18)

Logistic regression analyses for ASDAS<2.1 and BASDAI<40 mm (yes/no) at 6 months among patients still on treatment were performed adjusted as described for model A, B, C above, with adalimumab as the reference drug.

Sensitivity analyses

The following post hoc analyses were performed : Multivariate analyses (Model C) that a) compared secukinumab versus the combined TNFi group, b) only included the subgroup of patients (2^{nd} or 3^{rd}+ treatment courses) where the reason for termination of prior TNFi was lack of effect, and c) added the exact number of previous bDMARD courses to 3^{rd}+ treatment group as further adjustment factor.

Missing data

In order to assess potential bias due to missing baseline data, additional multivariable Cox regression analyses only including patients with complete data on all covariates were performed (=complete case analyses). Furthermore, baseline characteristics in patients with available versus missing measures of 6 months' treatment response were explored.

Ethical approval

The study was approved by the appropriate ethical committees and/or data protection committees in each country (Denmark: RH-2015-209, I-suite 04145; Finland: 73/13/03/00/2014; Iceland: VSNb2017010049/03.01; Norway: 2011/1339 and 2017/243; Sweden: 2015/1844-31/2). Individual patient consent was not required for the reporting of anonymized registry data for research purposes.

Results

In total, 10,853 treatment courses (842 secukinumab (8%)/10,011 TNFi (92%)) in 8,050 unique patients were included. Country-specific numbers for secukinumab/TNFi were: Sweden 497/5286, Denmark 195/2866, Finland 73/806, Norway 67/796, Iceland 10/257. Secukinumab was mostly used in biologically experienced patients (proportion treated with secukinumab during 1st/2nd/3rd+ treatment course: 1%/6%/22%) (**Table 1**) with similar pattern for all 5 countries (Footnote **Table 1**). History of extra-articular manifestations varied across treatments, with inflammatory bowel disease being more common in patients treated with adalimumab, golimumab or infliximab; adalimumab was favored in patients with a history of anterior uveitis; and secukinumab favored in patients with psoriasis. History of other comorbidities was overall similar across different bDMARD and treatment courses, except for heart disease which was more common in patients starting secukinumab as the 1st treatment course. Other baseline characteristics were largely similar including gender distribution, age, concomitant csDMARDs, disease activity, and number of comorbidities (**Table 1**).

Numbers of patients contributing baseline data are shown in **Supplementary Table S2** and contributing linkage data from national registries (n=10180, 94%) in **Supplementary Table S4**.

Retention to treatment

The one-year treatment retention rates varied across treatments (**Table 2, Figure 1**) with secukinumab displaying a drug-retention comparable to adalimumab as 1st or 2nd, but poorer as 3rd+ line of therapy: secukinumab 56% (95% CI: 51%-61%) versus adalimumab (70% (64%-75%), **Table 2**). Similar results were found in multivariable Cox regression analyses adjusted for comorbidities and extra-articular manifestations (**Table 2 and Supplementary Table S4**).

Reasons for withdrawals within the first year of follow-up were mainly lack of effectiveness or adverse events (**Supplementary Table S3**) with a tendency towards higher secukinumab withdrawal due to lack of effectiveness. Secukinumab contributed few withdrawals during 1st line therapy (n=14), thus these data should be interpreted with caution.

Secukinumab had similar treatment retention compared to the combined TNFi group: 1st line HR 0.78 (0.45-1.36), 2nd line HR 0.94 (0.69-1.28), 3rd+ line HR 1.06 (0.91-1.24), Model C).

Sensitivity analyses restricted to patients failing the prior TNFi due to lack of effect showed results similar to those presented in Table 2. Thus, during the third treatment course, HR for one-year treatment withdrawal was 1.60 (1.14-2.24) (Model C, secukinumab versus adalimumab, details not shown).

Sensitivity analyses adding number of previous bDMARDs did not change results markedly (HR 1.46 (1.14-1.86) secukinumab versus adalimumab, Model C, 3rd+ line).Furthermore, complete case analyses showed similar results (data not shown).

Treatment response at 6 months' follow-up

Treatment response differed between secukinumab and the five TNFi with Lundex adjusted response rates for ASDAS<2.1 being 1st line: 27% for secukinumab versus 27-42% for TNFi, 2nd line: 14% versus 23-31%, 3rd+ line: 12% versus 11-24% (**Figure 2**). Similar rates and similar internal relations between the six evaluated drugs were seen for BASDAI<40 mm (**Figure 2**). Baseline characteristics in patients with available versus unavailable measures of treatment response were similar (**Supplementary table S5**).

In adjusted logistic regression analyses (Model C), secukinumab had poorer 6-months' response rates than adalimumab, but the difference was only statistically significant for 3rd+ line (ASADS<2.1 OR 0.56 (0.35-0.90), BASDAI<40 mm OR 0.62 (0.41-0.95) (**Table 3, Supplementary Table S6).** Results for the comparison of secukinumab versus the combined TNFi group were not statistically significant (model C, 3rd+ treatment course, ASDAS<2.1 OR 0.74 (0.51-1.07), BASDAI<40 mm OR 0.79 (0.58-1.09), details not shown).

Sensitivity analyses restricted to patients failing the prior TNFi due to lack of effect showed similar but not statistically significant results for secukinumab versus adalimumab (Model C, 3rd+ line, ASDAS<2.1 OR 0.68 (0.34-1.37), BASDAI<40mm OR 0.59 (0.31-1.09)).

Sensitivity analyses adding number of previous bDMARDs to 3rd+ line did not markedly change results, ASDAS<2.1 OR 0.55 (0.34-0.89), BASDAI<40mm OR 0.63 (0.41-0.98) for secukinumab versus adalimumab.

Discussion

In this observational study including >10.000 patients with SpA treated in routine care from five prospective Nordic rheumatology registries during 2015-2018, secukinumab was mainly prescribed in biologically experienced patients. Through linkage to national registries, we were able to identify comorbidities and extra-articular manifestations. We found marked differences across treatments - with secukinumab more often used in patients with cardiovascular disease and concomitant psoriasis, and adalimumab when there was a history of uveitis. The 6-months' treatment outcomes and 1-year treatment-retention showed wide variation between the five TNFi – with poorer outcomes for secukinumab compared to adalimumab especially during 3rd line treatment. We were not able to demonstrate any superior outcomes for secukinumab versus adalimumab in patients that had previously failed one or several TNFi – neither overall nor in the subgroup that withdrew from TNFi due to lack of effect.

This study adds important knowledge to the gradually emerging evidence regarding routine care use of secukinumab in patients with SpA. Previous studies have demonstrated secukinumab to perform better in bio-naïve than bio-experienced patients.(19;20) However, in accordance with current guidelines,(5;21) we found that secukinumab was mainly used in TNFi experienced patients, and only 1% of first line treatment courses were secukinumab. Although we demonstrated similar performance of first line secukinumab versus adalimumab, secukinumab exposed patients were too few to draw firm conclusions.

It has been hypothesized that change of mode of action – from TNF-inhibition to e.g. Interleukin (IL)-17 inhibition, may be a favorable strategy in case of treatment failure, especially in patients with lack of effect.(5) To date, only few, minor observational studies (abstracts, mono-center, or <50-100 patients) (19;22-25) and no randomized trials have reported outcomes in SpA patients treated with secukinumab compared with a specific TNFi (reviewed in (26)). A recent Swiss study reported comparable one-year effectiveness of secukinumab versus TNFi in a TNFi-experienced real life cohort, with results based on 106 secukinumab treated patients whereof 55 patients had available 1-year outcomes.(12) The study used a comparison group comprising all TNFi combined. In that respect, it is of interest that we in the current cohort demonstrated considerable variation in effectiveness within the group of TNFi.(13;14) Indeed,

whereas comparisons of secukinumab versus combined TNFi outcomes were not statistically significant, results differed for secukinumab versus adalimumab which for some comparisons were significant. It was beyond our scope to explore within-group variations between the different TNFi further, but our results illustrate that pooling of TNFi may be a too simplistic approach when it comes to disentangling the treatment strategy in SpA.

Our study included 2725 patients that had previously failed at least two TNFi. Difficult-to-treat SpA patients failing numerous biologicals are only sparsely described and usually not favored for the inclusion in randomized comparative trials. Thus, little is known on how to approach this challenging patient group. The MEASURE 2 placebo-controlled study preceding the marketing of secukinumab included 72 patients with ankylosing spondylitis whereof 39% had previously failed one TNFi.(27) In the 3^{rd+} treatment group we found that response rates were generally low (12-25% for ASDAS response at 6 months), regardless of drug. In this situation, secukinumab treated patients had a 50% higher withdrawal rate and 40-45% lower odds for response than adalimumab. However, some important aspects of the study should be considered in the interpretation of our results.

Secukinumab was marketed later than the TNFi. It is possible that channeling occurred, i.e. patients failing numerous TNFi 'ended up' on secukinumab, leading to poorer outcomes. Thus, although baseline disease duration upon treatment start appeared similar across treatments, 25% of secukinumab treated patients had failed 3 or more prior TNFi. In this situation, secukinumab treated patients were observed. However, all models were performed stratified by line of treatment. In the 3^{rd+} line group, adding number of previous biologicals to the multivariate models did not change the results. Furthermore, there is always a risk of misdiagnosis or concomitant fibromyalgia in patient non-responsive to therapy.(28) We had no reason to suspect these challenges to be un-evenly distributed in the secukinumab and adalimumab groups, but secukinumab treated patients tended to have slightly higher pain and global scores at treatment start.

Comorbidities and extra-articular manifestations could have an impact due to risk of confounding. Psoriasis was more frequent in patients treated with secukinumab irrespective of treatment line, most likely since secukinumab was available for psoriasis before it was approved for SpA and due to favorable outcomes in psoriasis.(29) Similarly, adalimumab was more

frequently used among patients with prior uveitis and inflammatory bowel disease – manifestations where the effectiveness of secukinumab is still unclear.(30;31) Potential treatment decisions due to flares in these extraarticular manifestations are not uniformly captured in the registries - and could potentially have affected the results. Although adjustment for these comorbidities in the multivariable analyses did not markedly change results, residual confounding remains a risk.

The observational study design with the inclusion of patients from five different countries might have resulted in heterogeneous disease presentations. We have previously shown that disease presentation and threshold for starting biological treatment vary across the Nordic countries.(32) Although adding country as a covariate in the multivariable analyses did not change the associations under study, residual confounding cannot be ruled out. Furthermore, neither TNFi nor secukinumab doses were uniformly available and use of different doses (e.g. secukinumab 150 mg versus 300 s.c. every 4 weeks) including dose-titration during follow-up might have affected results.

This study has several strengths to consider, first and foremost the high number of treatment courses registered prospectively in routine care and the subsequent linkage to national registries providing valid information on comorbidities. This gave us the possibility to explore prior extra-articular manifestations and other comorbidities as possible confounders and to adjust for these in multivariate analyses. It is a limitation that comorbidities exclusively diagnosed in primary care were not included. Thus, mainly severe comorbid conditions were identified. Assessment of psoriasis-related disease activity (e.g. PASI), uveitis flares and bowel symptoms are not routinely registered in the biologic registries contributing to this study. Thus, we could not evaluate if flares of extraarticular manifestations affected the treatment strategy including the decision to stop treatment early. Furthermore, enthesitis is not routinely registered. Impact of missing data was minimized by adding missingness as a separate category in the multivariable analyses but might still have affected results, although analyses from a complete case scenario provided very similar results. Reassuringly, the baseline characteristics of patients with and without 6 months' outcome data were very similar, indicating no systematic differences.

In conclusion, secukinumab was mainly prescribed in biological experienced SpA patients in this study based on >10.000 treatment courses from five Nordic countries. Outcomes in difficult-to-treat patients that had failed more than two prior biologics were generally poor - and slightly poorer for secukinumab versus adalimumab, but similar to other TNFi. Our data did not support that secukinumab was superior to adalimumab or other TNFi after failing a previous TNFi.

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Table 1. Patient characteristics and disease activity at treatment start* stratified by drug and line of treatment

	First line, n=5325						Second line, n=2803						Third+ line, n=2725					
	ADA	SEC	CZP	ETA	GOL	IFX	ADA	SEC	CZP	ETA	GOL	IFX	ADA	SEC	CZP	ETA	GOL	IFX
N	858	70	396	1720	499	1782	662	160	247	890	304	540	457	612	322	500	372	462
Sex, men (%)	478 (56)	38 (54)	207 (52)	892 (52)	312 (63)	1010 (57)	334 (50)	70 (44)	118 (48)	464 (52)	176 (58)	302 (56)	226 (49)	280 (46)	124 (39)	213 (43)	183 (49)	224 (48)
Age, years	42 (13)	44 (14)	39 (12)	41 (14)	39 (13)	42 (14)	44 (13)	45 (13)	43 (13)	44 (13)	42 (13)	44 (13)	46 (13)	47 (12)	45 (13)	46 (13)	46 (13)	44 (13)
Disease duration, years	12 (12)	12 (11)	10 (10)	12 (12)	11 (11)	11 (11)	15 (12)	15 (12)	14 (11)	15 (12)	14 (11)	15 (11)	19 (12)	18 (12)	18 (12)	18 (12)	18 (12)	16 (11)
HAQ	0.7 (0.6)	0.8 (0.6)	0.9 (0.7)	0.8 (0.5)	0.7 (0.5)	0.8 (0.6)	0.8 (0.6)	0.9 (0.5)	0.8 (0.6)	0.9 (0.6)	0.8 (0.6)	0.9 (0.6)	1.0 (0.6)	1.1 (0.7)	1.0 (0.6)	1.1 (0.6)	1.1 (0.6)	1.0 (0.6)
CRP, mg/L	10 (15)	7 (8)	12 (18)	11 (17)	12 (16)	12 (23)	10 (24)	10 (18)	9 (16)	9 (15)	10 (19)	10 (18)	11 (18)	13 (27)	9 (16)	10 (18)	12 (23)	10 (16)
Pain score, VAS, mm	53 (25)	57 (28)	56 (24)	58 (23)	57 (23)	58 (25)	54 (27)	59 (23)	60 (24)	59 (25)	55 (29)	52 (29)	59 (26)	66 (23)	61 (25)	63 (25)	61 (24)	61 (27)
Global score, VAS, mm	52 (26)	55 (26)	58 (25)	57 (23)	53 (27)	62 (25)	56 (27)	60 (25)	63 (24)	62 (25)	56 (30)	54 (30)	62 (25)	68 (24)	63 (25)	66 (24)	62 (25)	63 (27)
BASDAI, mm	48 (24)	47 (28)	50 (22)	52 (21)	48 (23)	55 (21)	51 (24)	52 (22)	53 (22)	55 (22)	50 (62)	49 (27)	56 (23)	63 (22)	58 (23)	59 (23)	58 (24)	57 (25)
BASMI	11 (16)	22 (23)	25 (21)	13 (16)	18 (18)	20 (19)	18 (20)	14 (22)	22 (19)	22 (21)	22 (24)	27 (22)	26 (22)	25 (19)	20 (20)	25 (22)	23 (24)	25 (23)
BASFI	34 (25)	44 (31)	46 (25)	39 (25)	34 (23)	45 (24)	39 (26)	43 (23)	45 (24)	46 (26)	40 (27)	42 (27)	47 (28)	55 (26)	48 (26)	50 (25)	49 (27)	49 (27)
ASDAS	2.9 (1.0)	3.2 (1.1)	3.1 (1.1)	3.1 (1.0)	3.1 (1.0)	3.3 (1.0)	2.9 (1.1)	3.1 (0.9)	3.1 (1.0)	3.1 (1.0)	3.1 (1.2)	2.9 (1.2)	3.1 (1.1)	3.5 (1.1)	3.3 (1.0)	3.2 (1.1)	3.2 (1.1)	3.2 (1.2)
Swollen joint count (0-28), n	1 (2)	0 (1)	0 (1)	1 (1)	0 (1)	0 (1)	1 (1)	1 (2)	0 (2)	1 (2)	1 (2)	0 (1)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)
Concomitant MTX, %*	6	2	11	4	8	14	7	10	8	6	10	12	5	8	9	8	14	14
Concomitant SSZ, %*	7	2	7	4	10	8	2	5	4	2	4	3	1	3	3	4	3	4
Comorbidities, yes, %**																		
Malignancy	1.9	1.6	1.1	1.5	1.3	1.6	2.0	4.7	1.2	2.7	1.8	2.2	5.1	4.0	4.5	3.9	3.1	4.0
Pulmonary disease	0.1	1.6	1.3	0.6	0.2	1.1	0.7	2.0	1.6	1.5	1.1	0.8	1.5	1.9	1.0	0.9	0.6	0.9
Congestive heart failure	0.1	7.8	0.3	0.7	0.4	0.3	0.3	2.0	0.8	1.0	0.4	1.0	1.0	0.7	0.6	1.1	0.6	1.1
Diabetes	1.7	4.7	1.3	2.4	1.3	1.9	2.0	4.7	2.9	2.4	2.1	2.6	2.4	2.8	4.5	2.4	3.4	3.4
Myocardial infarction	0.6	4.7	0.3	0.5	0.4	0.4	0.8	0.7	0.8	1.2	0.7	1.2	1.0	1.8	1.3	1.1	1.1	0.9

Chronic kidney disease	0.4	1.6	0.5	0.3	0.0	0.6	0.2	0.0	0.0	0.6	1.4	1.4	0.2	0.9	1.0	1.3	1.4	0.9
Knee or hip prosthesis	1.0	4.5	0.0	1.4	0.4	0.8	1.3	2.7	0.4	1.2	1.1	1.6	0.5	2.7	2.6	1.3	2.3	1.6
Any infection	19.4	15.6	14.9	20.3	18.6	16.6	26.6	33.1	23.7	24.6	25.0	18.0	33.5	32.7	31.2	34.2	33.6	31.7
No of comorbidities, %																		
1	19.7	21.9	14.7	21.7	19.4	17.9	27.8	35.1	22.9	27.0	25.7	21.6	32.5	30.9	32.8	35.0	31.6	31.9
≥2	2.6	7.8	2.3	2.7	1.5	2.6	2.6	6.8	3.3	3.6	3.9	3.0	5.5	7.6	5.7	4.9	6.6	5.8
Prior extra articular manifestations**																		
IBD	11.4	1.6	2.5	1.6	4.0	8.6	10.9	2.7	2.5	3.9	11.8	9.1	11.3	3.0	7.3	6.4	10.0	10.1
Psoriasis	5.2	10.9	5.8	4.2	2.9	3.7	6.6	13.5	8.6	8.2	4.6	6.7	8.7	13.4	10.5	9.2	8.3	7.0
Uveitis	28.0	3.1	8.6	8.2	15.5	11.7	21.5	10.1	13.1	9.5	15.7	12.5	25.3	12.5	14.3	12.2	17.1	11.2

Numbers are means (standard deviation) unless otherwise stated

Number of patients starting secukinumab in total (first/second/third+ line) per country were: Sweden 497 (36/106/355), Denmark 195 (18/29/148), Finland 73 (15/18/40), Norway 67 (1/4/62), Iceland 10 (0/3/7)

* Based on patients with baseline visit and available data, ** 0-5 years prior to baseline, for availability, see supplementary table S2 and S4

Abbreviations: ASDAS: ankylosing spondylitis disease activity score, BASDAI: Bath ankylosing spondylitis disease activity index, BASMI: metrology index, BASFI: functional index, csDMARD: conventional synthetic disease modifying anti rheumatic drug, HAQ: health assessment questionnaire, IBD: inflammatory bowel disease, MTX: methotrexate, TNFi: tumor necrosis factor inhibitors, SEC: secukinumab, SSZ: sulfasalazine, VAS: visual analogue scale

Table 2

Treatment withdrawals and -retention after 1 year stratified by drug type and line of treatment

Results from Kaplan-Meier and Cox Regression Analyses (crude and adjusted hazard ratios (HR) for withdrawal)

						Hazard ratios (HR) (95% CI) of withdrawal		
	Drug	**N**	**Number of events, n**	**Person years**	**1-year retention rate (95% CI)**	**Model A**	**Model B**	**Model C**
First line	ADA	858	182	625.58	0.74 (0.70-0.77)	1	1	1
	SEC	70	14	48.71	0.76 (0.63-0.85)	0.93 (0.54-1.61)	0.99 (0.57-1.71)	0.89 (0.50-1.57)
	CLZ	396	126	316.12	0.66 (0.61-0.71)	**1.40 (1.11-1.75)**	**1.33 (1.03-1.70)**	1.27 (0.99-1.64)
	ETN	1720	402	1245.08	0.72 (0.69-0.74)	1.10 (0.92-1.31)	1.08 (0.91-1.30)	1.03 (0.85-1.24)
	GOL	499	93	435.69	0.78 (0.74-0.82)	0.78 (0.61-1.00)	0.79 (0.61-1.02)	0.79 (0.61-1.02)
	IFX	1782	585	1325.62	0.62 (0.59-0.64)	**1.53 (1.29-1.80)**	**1.42 (1.19-1.70)**	**1.39 (1.16-1.67)**
Second line	ADA	662	167	451.61	0.69 (0.64-0.73)	1	1	1
	SEC	160	45	105.24	0.67 (0.58-0.74)	1.08 (0.78-1.50)	1.07 (0.77-1.50)	1.05 (0.75-1.47)
	CLZ	247	101	178.26	0.55 (0.48-0.61)	**1.50 (1.17-1.92)**	**1.39 (1.07-1.80)**	**1.36 (1.05-1.77)**
	ETN	890	288	617.78	0.63 (0.59-0.66)	**1.26 (1.04-1.53)**	**1.21 (1.00-1.47)**	1.18 (0.96-1.44)
	GOL	304	80	243.78	0.69 (0.62-0.74)	0.91 (0.70-1.19)	0.93 (0.71-1.22)	0.89 (0.67-1.17)
	IFX	540	169	414.41	0.64 (0.59-0.68)	1.12 (0.91-1.39)	1.20 (0.96-1.51)	1.18 (0.94-1.49)
Third+ line	ADA	457	107	315.90	0.70 (0.64-0.75)	1	1	1
	SEC	612	214	402.51	0.56 (0.51-0.61)	**1.53 (1.22-1.93)**	**1.47 (1.16-1.86)**	**1.43 (1.12-1.81)**
	CLZ	322	148	203.74	0.47 (0.41-0.53)	**2.11 (1.64-2.72)**	**2.14 (1.66-2.76)**	**2.04 (1.57-2.64)**
	ETN	500	156	349.47	0.62 (0.57-0.67)	**1.30 (1.02-1.66)**	1.27 (0.99-1.63)	1.21 (0.94-1.56)
	GOL	372	117	270.77	0.64 (0.58-0.69)	1.27 (0.98-1.64)	**1.30 (1.00-1.69)**	1.26 (0.97-1.65)
	IFX	462	168	320.77	0.58 (0.53-0.63)	**1.55 (1.21-1.98)**	**1.54 (1.21-1.97)**	**1.41 (1.10-1.82)**

Statistically significant results are marked with bold types

Model A: Adjusted by age and sex

Model B: Adjusted by sex, and baseline: age, CRP, BASDAI, patient global score, concomitant csDMARD

Model C: Model B adding baseline comorbidity/extraarticular manifestations, see suppl Table S4 for details including patient numbers

Abbreviations: ADA: adalimumab, CLZ: certolizumab pegol, ETN: etanercept, GOL: golimumab, HR: hazard ratio, IFX: infliximab, SEC: secukinumab

Table 3

Response after 6-months' treatment, stratified by drug type and line of treatment. Results of crude and adjusted logistic regression analyses

				Adjusted models with Odds Ratios (OR) (95% CI)		
		Drug	N response/total*	Model A	Model B	Model C
ASDAS <2.1	First line	ADA	107 / 242	1	1	1
		CLZ	95 / 234	0.85 (0.58-1.23)	**0.63 (0.41-0.97)**	0.66 (0.43-1.02)
		ETN	323 / 695	1.15 (0.85-1.56)	1.12 (0.82-1.53)	1.18 (0.86-1.64)
		GOL	85 / 185	0.99 (0.66-1.47)	1.04 (0.69-1.56)	1.08 (0.72-1.63)
		IFX	389 / 1065	**0.72 (0.54-0.96)**	0.75 (0.55-1.03)	0.77 (0.56-1.06)
		SEC	4 / 17	0.43 (0.13-1.37)	0.47 (0.14-1.55)	0.57 (0.17-1.88)
	Second line	ADA	76 / 233	1	1	1
		CLZ	33 / 125	0.75 (0.46-1.24)	0.62 (0.36-1.07)	0.65 (0.37-1.13)
		ETN	128 / 428	0.89 (0.63-1.27)	0.84 (0.58-1.22)	0.92 (0.62-1.35)
		GOL	50 / 126	1.24 (0.79-1.97)	1.11 (0.68-1.80)	1.06 (0.64-1.76)
		IFX	113 / 356	0.95 (0.66-1.36)	0.70 (0.46-1.05)	0.69 (0.46-1.06)
		SEC	9 / 49	0.47 (0.22-1.04)	0.51 (0.23-1.16)	0.57 (0.25-1.31)
	Third+ line	ADA	54 / 192	1	1	1
		CLZ	25 / 154	**0.52 (0.30-0.88)**	**0.52 (0.30-0.91)**	**0.54 (0.30-0.96)**
		ETN	56 / 240	0.79 (0.51-1.23)	0.87 (0.55-1.38)	0.91 (0.57-1.46)
		GOL	34 / 155	0.72 (0.44-1.18)	0.70 (0.42-1.15)	0.68 (0.40-1.14)
		IFX	53 / 264	**0.63 (0.41-0.98)**	**0.60 (0.38-0.95)**	0.65 (0.41-1.03)
		SEC	48 / 296	**0.51 (0.33-0.80)**	**0.55 (0.35-0.88)**	**0.56 (0.35-0.90)**
BASDAI <40mm	First line	ADA	199 / 364	1	**1**	1
		CLZ	122 / 275	**0.67 (0.49-0.93)**	**0.57 (0.39-0.82)**	**0.61 (0.42-0.88)**
		ETN	425 / 851	0.88 (0.68-1.13)	0.98 (0.75-1.28)	1.07 (0.81-1.41)
		GOL	169 / 302	1.01 (0.74-1.38)	1.02 (0.73-1.41)	1.07 (0.77-1.49)
		IFX	465 / 1179	**0.54 (0.42-0.69)**	**0.61 (0.47-0.80)**	**0.64 (0.48-0.84)**
		SEC	8 / 24	0.46 (0.19-1.13)	0.56 (0.22-1.44)	0.63 (0.24-1.63)
	Second line	ADA	105 / 283	1	**1**	1
		CLZ	45 / 146	0.76 (0.49-1.18)	0.62 (0.38-1.02)	0.64 (0.39-1.06)
		ETN	157 / 488	0.79 (0.58-1.08)	0.74 (0.53-1.04)	0.80 (0.56-1.13)
		GOL	69 / 154	1.29 (0.86-1.93)	1.10 (0.71-1.72)	1.05 (0.67-1.67)
		IFX	143 / 376	1.01 (0.73-1.39)	0.78 (0.53-1.13)	0.77 (0.52-1.13)

		SEC	22 / 70	0.80 (0.45-1.41)	0.73 (0.40-1.34)	0.85 (0.46-1.59)
	Third+	ADA	67 / 212	1	**1**	1
	line	CLZ	36 / 183	**0.54 (0.34-0.87)**	**0.53 (0.32-0.89)**	**0.55 (0.33-0.93)**
		ETN	66 / 258	0.76 (0.51-1.14)	0.81 (0.53-1.25)	0.86 (0.56-1.34)
		GOL	51 / 187	0.80 (0.51-1.23)	0.76 (0.48-1.20)	0.76 (0.48-1.21)
		IFX	70 / 285	**0.71 (0.47-1.05)**	0.68 (0.45-1.04)	0.74 (0.48-1.13)
		SEC	72 / 344	**0.57 (0.38-0.84)**	**0.59 (0.39-0.89)**	**0.62 (0.41-0.95)**

Statistically significant results are marked with bold types

Model A: Adjusted by age and gender

Model B: Adjusted by sex, and baseline: age, CRP, BASDAI, patient global score, concomitant csDMARD

Model C: Model B adding baseline comorbidity/extraarticular manifestations, see suppl Table S4 for details including patient numbers

*Only patients contributing a response measure (ASDAS or BASDAI) at 6 months were included

Abbreviations: ADA: adalimumab, CLZ: certolizumab pegol, ETN: etanercept, GOL: golimumab, HR: hazard ratio, IFX: infliximab, SEC: secukinumab

Figure legends

Figure 1

Survival probability curves for secukinumab and each of the five TNFi. Stratified by line of treatment

Figure 2

Treatment response after 6 months' treatment stratified by line of treatment and drug type.

Numbers are percentage of patients with response, crude with 95% CI (black) and Lundex adjusted (grey)

Figure 1

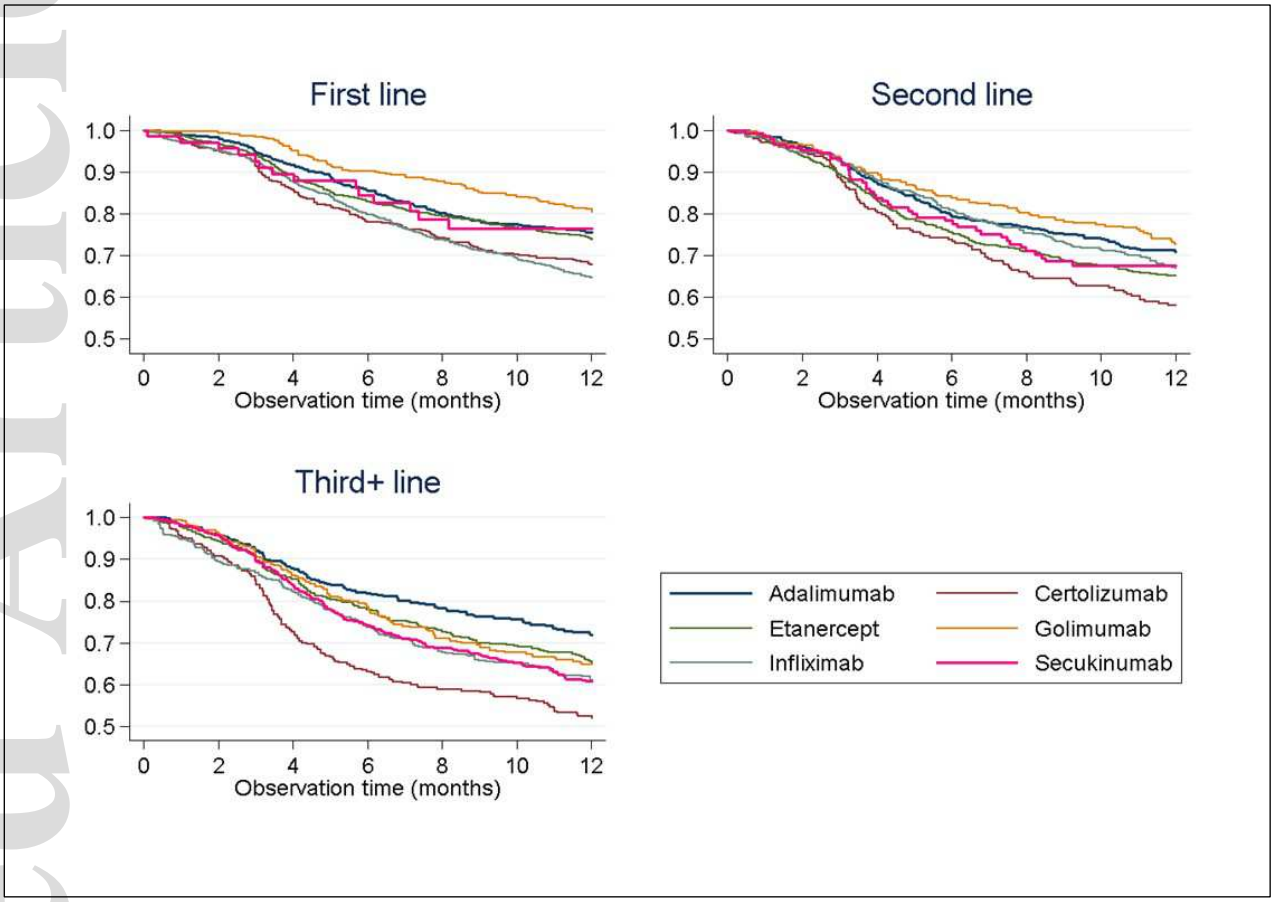
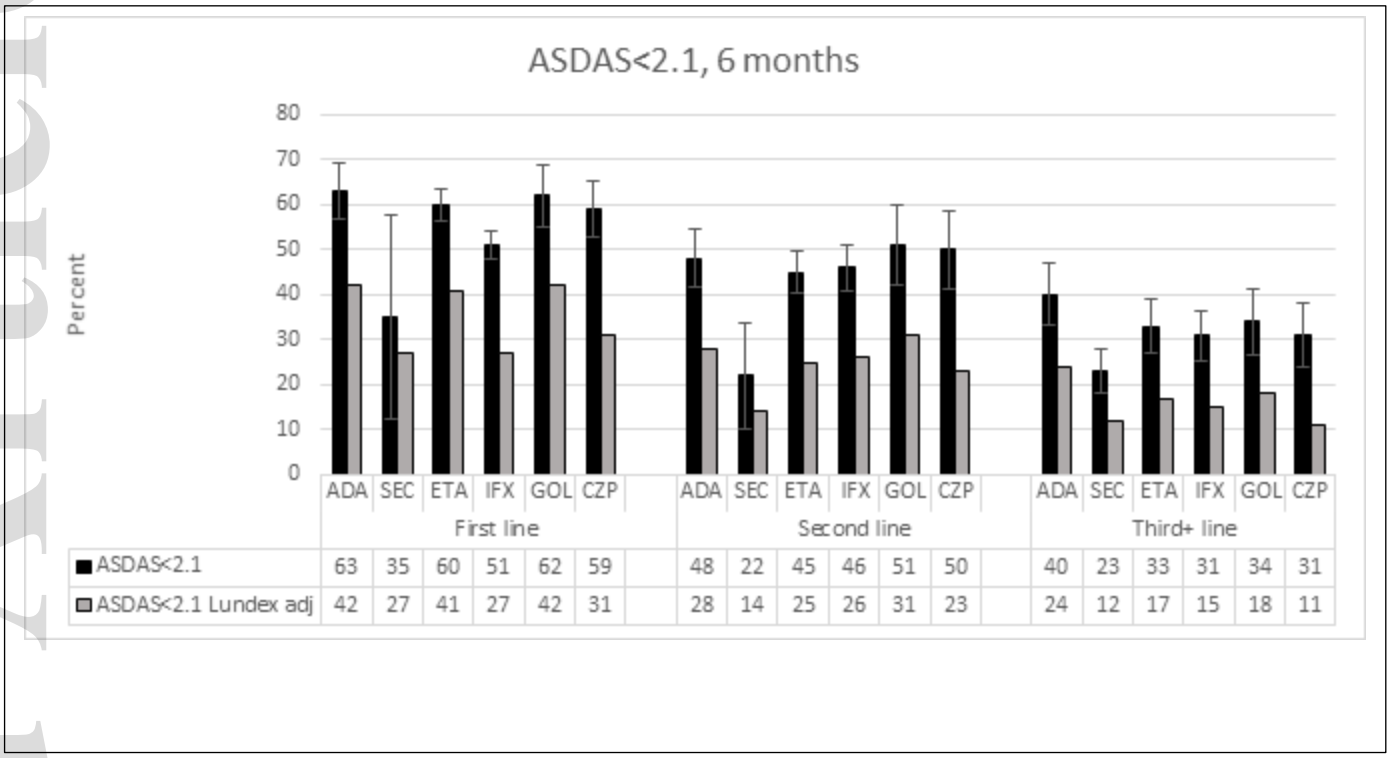
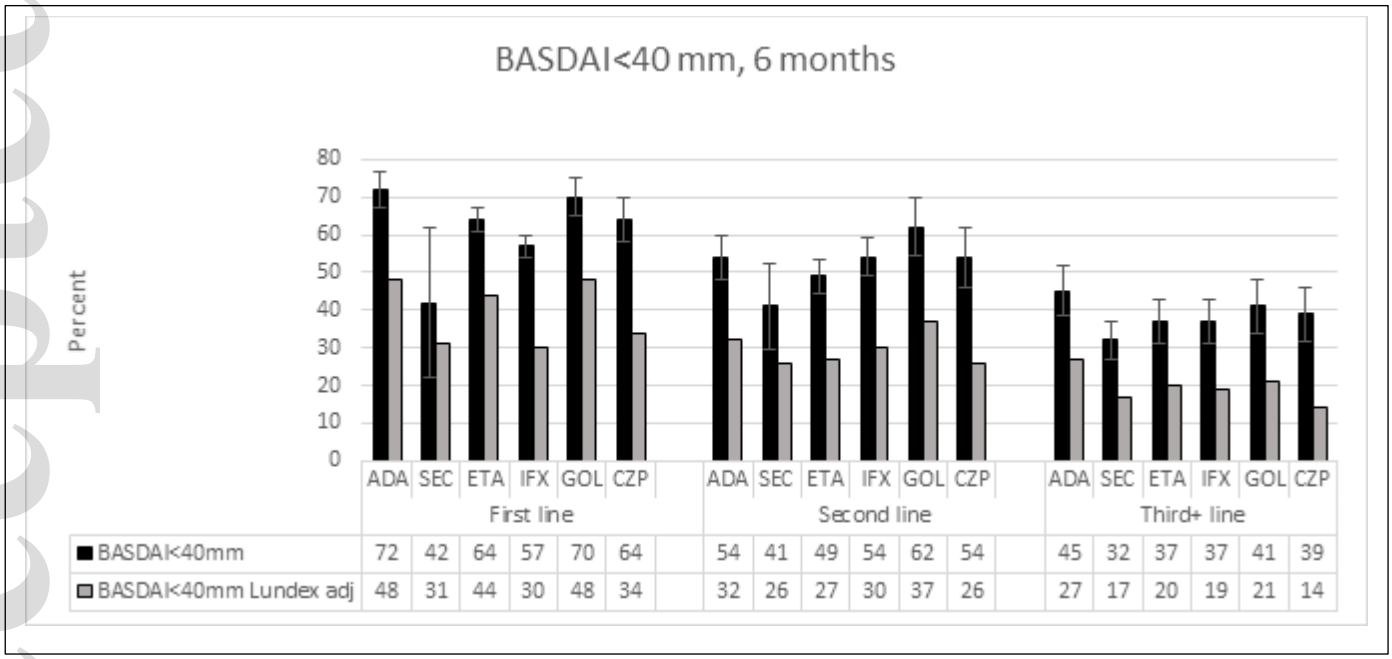


Figure 2



	First line						Second line						Third+ line					
	ADA	SEC	ETA	IFX	GOL	CZP	ADA	SEC	ETA	IFX	GOL	CZP	ADA	SEC	ETA	IFX	GOL	CZP
ASDAS<2.1	63	35	60	51	62	59	48	22	45	46	51	50	40	23	33	31	34	31
ASDAS<2.1 Lundex adj	42	27	41	27	42	31	28	14	25	26	31	23	24	12	17	15	18	11



	First line						Second line						Third+ line					
	ADA	SEC	ETA	IFX	GOL	CZP	ADA	SEC	ETA	IFX	GOL	CZP	ADA	SEC	ETA	IFX	GOL	CZP
BASDAI<40mm	72	42	64	57	70	64	54	41	49	54	62	54	45	32	37	37	41	39
BASDAI<40mm Lundex adj	48	31	44	30	48	34	32	26	27	30	37	26	27	17	20	19	21	14