Rapid and sustained health utility gain in anti-TNF treated inflammatory arthritis. Observational data during seven years in southern Sweden.

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Rapid and sustained health utility gain in anti-TNF treated inflammatory arthritis. Observational data during seven years in southern Sweden.

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Abstract

Background. Rheumatoid arthritis (RA), psoriatic arthritis (PsA), and other spondylarthritides (SpA) impose great impact on the individual in addition to the costs on society, which may be reduced by effective pharmacological treatment. Industry independent health economic studies should complement studies sponsored by industry.

Objective. To study secular trends in baseline health utilities in patients commencing TNF blockade for arthritis in clinical practice over 7 years; to address utility changes during treatment; to investigate the influence of previous treatment courses; to study the feasibility of health utility measures, and to compare them across diagnostic entities.

Methods. EuroQoL 5 Dimensions (EQ-5D) utility data were collected from a structured clinical follow-up program of anti-TNF treated patients with RA (N=2554), PsA (N=574) or SpA (N=586). Time trends were calculated. Completer analysis was used.

Results. There were weak or non-significant secular trends for increasing baseline utilities over time for RA, PsA and SpA. Maximum gain in utilities occurred already after 2 weeks for all diagnoses and remained stable for patients remaining on therapy. First and second anti-TNF courses performed similarly.

Conclusions. Utilities at inclusion remained largely unchanged for RA, PsA and SpA over 7 years. Improvement occurred early during treatment and not beyond 6 weeks at the group level. Improvement during the first course was not consistently greater than the second. There were no major differences between RA, PsA and SpA. EQ-5D proved feasible and applicable across these diagnoses. These “real world” data may be useful for health economic modelling.

Word count: 245

Key words: Anti-TNF treatment; EuroQoL-5-dimensions; health economics; health utilities; observational study; psoriatic arthritis; quality of life; rheumatoid arthritis;; spondarthritis; time trends.

Abbreviations: CRP, C-reactive protein; DMARD, disease modifying antirheumatic drug; EQ-5D, EuroQoL 5 dimensions; HAQ, Health Assessment Questionnaire; IL-1, interleukin 1; PsA, psoriatic arthritis; QoL, quality of life; RA, rheumatoid arthritis; RCT, randomized controlled trial; SD, standard deviation; SSATG, South Swedish Arthritis Treatment Group; SpA, spondarthritis; TNF, tumour necrosis factor.

Introduction

Societal costs of rheumatoid arthritis (RA), psoriatic arthritis (PsA), and other spondylarthritides (SpA) are substantial [1], and indirect costs predominate. Effective treatment for these diseases, preventing disability, should therefore be beneficial for society. On the other hand, the new effective biologic therapies (blockers of TNF, IL-1, T-cell costimulation and B-cell depletors) are costly. Therefore, the cost effectiveness of these drugs has been subject to health economic studies[2 3]. However, many studies on cost effectiveness rely upon clinical trial data [4-6] with their limited generalizability, and not on observational data from daily clinical practice [7 8]. Furthermore, several diagnoses from the same setting are rarely reported, and health utilities are derived from measures such as the health assessment questionnaire (HAQ) [9 10] in RA [11 12].

Changes in the indications for treatment with biologics can be anticipated when used in clinical practice, as physicians become more familiar with them. This could result in secular changes in baseline utilities as well as change in their improvement during treatment. Indeed, we and others have reported changes in baseline characteristics towards lower disease activity and disability at start of first treatment during the first three years after introducing anti-TNF therapy[13 14].

We have reported the costs and health economic benefits associated with early anti-TNF therapy for RA in clinical practice [7]. However, we had to use sensitivity analyses for cost effectiveness estimations, since we did not have multiple measurements during the first treatment year, and we also lacked utility values beyond this time. Another aspect not scrutinized in the study was that patients switched between different expensive biologic drugs (up to 35% in our setting)[14].

We undertook the present study on patients with RA, PsA, and other SpA treated in clinical practice in southern Sweden, with four specific goals:

- To determine if health utilities at initiation of anti-TNF treatment changed over the 7 year period between May 2002 and December 2008;
- To address changes in this measure during anti-TNF treatment both in the short and long perspective, including reasons for drug withdrawal;
- To study if previous biological therapy influenced this measure;
- To study the feasibility of the preference based health utility instrument EuroQoL-5-dimensions (EQ-5D) and apply it across different diagnostic entities.

Materials & Methods

Anti-TNF treatment courses for patients with RA, PsA and SpA according to the treating physician were retrieved from the South Swedish Arthritis Treatment Group Registry[15-17]. In 2002, collecting health utility data was introduced in routine clinical follow up. Data were collected using the 5 descriptive questions of the EuroQol 5 Dimension (EQ-5D)[18]. The visual analogue scale of the EQ-5D was not used. From this generic preference based instrument, utility values can be derived with a range from death (0) to full health (1), with values below 0 (-0.56) being possible[19 20]. The dimensions covered by the EQ-5D include mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Patients eligible for this study had a diagnosis of RA, PsA, or SpA according to the opinion of the treating physician. Patients with PsA and SpA were further classified as having peripheral

joint disease (arthritis distal of shoulder and hips ever) and/or clinical signs of spondylitis by the treating physician[21]. The different diagnoses and classifications have been validated in large groups of patients and found to be accurate in between 90-98 %[16 21] according to established criteria[22-25]. The patients were identified in the SSATG registry during the period May 2002 through December 2008 as starting a treatment course of infliximab, etanercept, or adalimumab. Treatment courses were classified as either first, second, or third or more anti-TNF. All EQ-5D utility values at treatment follow up time points 0, 0.5, 1.5, 3, 6, 12, 24, 30, 36, 48, and 60 months were retrieved from the database. Treatment courses lacking baseline EQ-5D were excluded. Anti-TNF treatments were grouped according to year of initiation for analyses of time trends at treatment onset. Reason for drug withdrawal was documented in the SSATG protocol as failure, adverse event, or other, but only one stop reason could be given. Distinction between primary failure (never having a response) and secondary failure (having an initial response, with deterioration later), was not always possible, and they were therefore grouped together. Other stop reasons include among others pregnancy, switching for convenience, or remission. Missing follow up data were requested from treating physicians 1-2 times per year, including possible withdrawal reason.

To assess feasibility of EQ-5D in the current observational setting, the number of follow up visits with full EQ-5D information was compared to those with data on HAQ.

Statistics: Values are given with mean and 95 % confidence interval (CI). Follow up times are given with median (range), and mean (SD) values. Generally, only observations with at least 20 valid N are presented. Patients remaining on therapy at given follow up time points were estimated from Kaplan-Meier plots. Patients with full data sets at time 0, 3, 6, 12, and 24

months were compared with all patients to see if there were relevant differences between those with complete and incomplete data.

Results

Baseline patient characteristics according to anti-TNF treatment and diagnosis are shown in table 1. Most patients receiving their second, third or more course of TNF-blocker were included in the first course group, thus making direct statistical comparisons of the patient groups hazardous. There were several differences between the diagnostic groups. RA patients were older, had tried more DMARDs, were more often treated with concomitant DMARDs, and were more often female. Overall, patients subject to more than one anti-TNF drug tended to be older, have longer disease duration and they were less often treated with concomitant methotrexate. As expected, clinical signs of spondylitis were more prevalent in the SpA group (77%); many patients belonged to the undifferentiated SpA entity. Clinical spondylitis was also present in almost 30 % of PsA patients.

The secular trends for baseline EQ-5D utility values at first anti-TNF treatment and the different diagnoses are illustrated by figure 1. There were weak, non significant trends for increasing baseline utility values for RA patients (Spearman's ρ=0.03, P=0.23), PsA (ρ=0.04, P=0.37), and SpA (ρ=0.05, P=0.29) over time.

The development of EQ-5D utilities at first, second, and third or more anti-TNF treatment course for RA, PsA and SpA patients is illustrated in figure 2A-C. For RA patients, utility improvement during the first and second anti-TNF treatments performed in a similar way. The third or more anti-TNF treatments started from a lower utility level and groups were smaller

with wider CIs, but nevertheless they performed with about the same numerical improvement as for first and second anti-TNF treatments.

Most gain in EQ-5D utilities was achieved already after 2 weeks for both first and second anti-TNF treatments for RA and PsA at the group level, while the SpA patients had a somewhat slower initial improvement.

RA patients stopping therapy demonstrated lower utility gain regardless of reason for withdrawing treatment (figure 3). Utility improvement in cases with stop reasons other than adverse event or failure seemed to perform like those remaining on treatment, but numbers were limited.

To assess the feasibility of EQ-5D in clinical practice, we compared the frequency of complete EQ-5D and HAQ questionnaires. Total number of follow up visits were 12585, 2553, and 2630 with presence of HAQ values in 98%, 97%, 97%, and presence of EQ-5D values in 93%, 94%, and 94% for RA, PsA and SpA, respectively.

To investigate the possibility of bias in patients with missing values, we compared the total amount of information for RA patients at time points 0, 3, 6, 12, and 24 months with RA patients with complete data sets at all these time points, grouped according to treatment order (figure 4). The pattern of improvement is similar regardless of data set completeness, but the magnitude of improvement is somewhat higher at some time points in first anti-TNF courses with complete data sets.

To facilitate health economic modelling, we calculated median/mean follow up time and life-table estimates of drug survival, in relation to diagnoses, anti-TNF treatment sequences, and

stop reasons (On-line supplemental Table 1, Figure 2A-C). Expectedly, patients with ongoing treatment had longer follow up, while those stopping because of adverse event had the shortest. Treatment courses terminated due to low response and failure had follow up times close to those due to adverse event. Other stop reasons were less common but resulted in longer follow up times. Overall follow up time decreased with increasing anti-TNF number, and follow up times were skewed towards early withdrawal as indicated by lower median compared to mean values.

Discussion

A major finding in this study was the rapid improvement in health utilities already after 2 weeks in RA patients treated with their first anti-TNF drug. The improvement was maintained for at least 5 years for patients remaining on therapy. Baseline utilities remained relatively stable during the period 2002-2008 for the first anti-TNF drug. This was somewhat unexpected, given our previously reported steady improvement of both disability (HAQ) and disease activity (DAS28) levels during 1999-2006[14]. Interestingly, there were no major differences between different chronic arthritis diagnoses, whereas there was a trend for lower baseline utilities with increasing number of anti-TNF drugs. However, limited number for third course anti-TNF in PsA and SpA patients precludes firm conclusions at present.

EQ-5D was chosen due to its simplicity, patient acceptability, and well established utilities. It is well suited for measuring diseases mainly involving locomotor organs, including dimensions such as pain, mobility, self-care, and usual activities, all of which are important in inflammatory joint diseases. We have found the visual analogue scale of the EQ-5D less suitable with low patient acceptability in clinical practice, and the core set already included

two VAS scales, one of pain and one of global disease activity. Our findings of only 6-7 percent missing health utilities compared to 2-3% for HAQ scores confirms the feasibility of the EQ-5D instrument in our observational setting.

EQ-5D is a generic measure thus intended for comparing various diseases. Our findings support this. This type of comparison had not been possible using disease specific measures such as the HAQ, RA-QoL, and PsAQoL[9 27-29]. Although VAS scales have been used as surrogates in health economic models[29], it should be better to use instruments with established health utilities. However, EQ-5D entails several subjective judgements made by the patients, and therefore it has to be complemented with more objective measures before making decisions regarding start or change of biological treatment.

Observational data like ours are more generally applicable as a reference for health economic modelling than RCT data, which are derived from highly selected patients[5 30 31]. Furthermore, in Sweden there are no formal requirements for inclusion or response, few economic restrictions, and drug costs are almost entirely funded by society. This may result in more missing data, but data may be less biased towards worse utility and disease activity.

Major strengths of the present study is that the variables have been prospectively collected and the setting can be regarded as truly population based[17]. It is also, to our knowledge, the first report giving comprehensive data on the development of EQ-5D utility over 7 years for patients with RA, PsA and SpA in a clinical setting. Our findings are in line with utility gain in RCTs of TNF blockers in RA[32 33] and AS[34] and an observational study of PsA[35].

Our investigation also has limitations. Firstly, it is difficult to obtain complete sets of data in the observational setting. Using all available data increases generalizability. This, however, will yield lower improvement estimates as compared to including only subjects with complete follow up information from all visits (Figure 4). Thus, there may be a possible bias if complete data sets are required. Incompleteness could be due to either withdrawal from therapy or missing reports for other reasons. Withdrawal may be the main reason why gain in health utility is less when using all available data as compared to only subjects with complete follow-up information. Those stopping therapy, irrespective of cause (lack of effect or adverse event), had less improvement in health utility prior to the stop (Figure 3). More emphasis should be put on overall withdrawal rate than on stop reason, since insufficient effect may lower the threshold for stopping treatment due to a mild adverse event.[21 36]. Secondly, regular follow up is a prerequisite for good data provision. This can be a problem in a voluntary multi-centre observational setting such as ours, where health care is provided in organisations changing over time for economical, political, or other reasons. Even so, the professional SSATG network has remained stable over the last 10 years, and we have not been able to identify any major bias in the missing follow up data which would seriously impair our conclusions.

Previously, when we only had baseline and 1 year measures, we had to make sensitivity analyses as to when the actual improvement occurred[7]. This can now be simplified. In the present dataset, the gain can be regarded as almost instantaneous and steady over the years after anti-TNF institution (figure 2A-C), thereby facilitating the calculation of gain in quality adjusted life years (QALYs). However, it must be kept in mind that these calculations are derived from patients remaining on therapy, and therefore selected as good responders. Drug continuation can vary substantially between different treatment remedies in our setting [37], and

this must be accounted for in health economic modelling. We consider the data in Figure 2A-C and on-line supplemental Table 2 fairly robust due to the active and regular search for treatment withdrawal reason when follow-up data are missing[16 37].

Our data illustrate, that irrespective of guidelines, there are trends regarding the baseline characteristics of patients that are started on biologics[14]. These trends seem less obvious for health utility measures, but long term follow up, as in the present study, is needed in addition to analyses of RCTs and shorter observational studies to establish true utility gain in the clinical setting.

In conclusion, this study demonstrates a rapid gain in EQ-5D utility after initiation of anti-TNF-treatment in chronic arthritis, irrespective of diagnosis, and that this changes little in the subsequent five years for patients remaining on therapy. The EQ-5D utility used to describe improvement is feasible in this observational population, and the similar results obtained for various diagnoses support its generic character.

Word count: 2382

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Legends

Table 1.
Patients characteristic at treatment initiation.

On-line supplemental Table 1.
Follow up time in months. Values are given as **median ; mean** (standard deviation), range; number.

Figure 1.
EQ-5D at first treatment initiation 2002-2008 for RA, PsA and SpA patients.

Figure 2A.
EQ-5D during follow up for RA patients, starting anti-TNF 2002-2008 and with baseline EQ-5D values.

Figure 2B.
EQ-5D during follow up for PsA patients, starting anti-TNF 2002-2008 and with baseline EQ-5D values.

Figure 2C.
EQ-5D during follow up for SpA patients, starting anti-TNF 2002-2008 and with baseline EQ-5D values.

Figure 3.
EQ-5D during follow up – stop reason. RA patients starting first anti-TNF 2002-2008 and with baseline EQ-5D values.

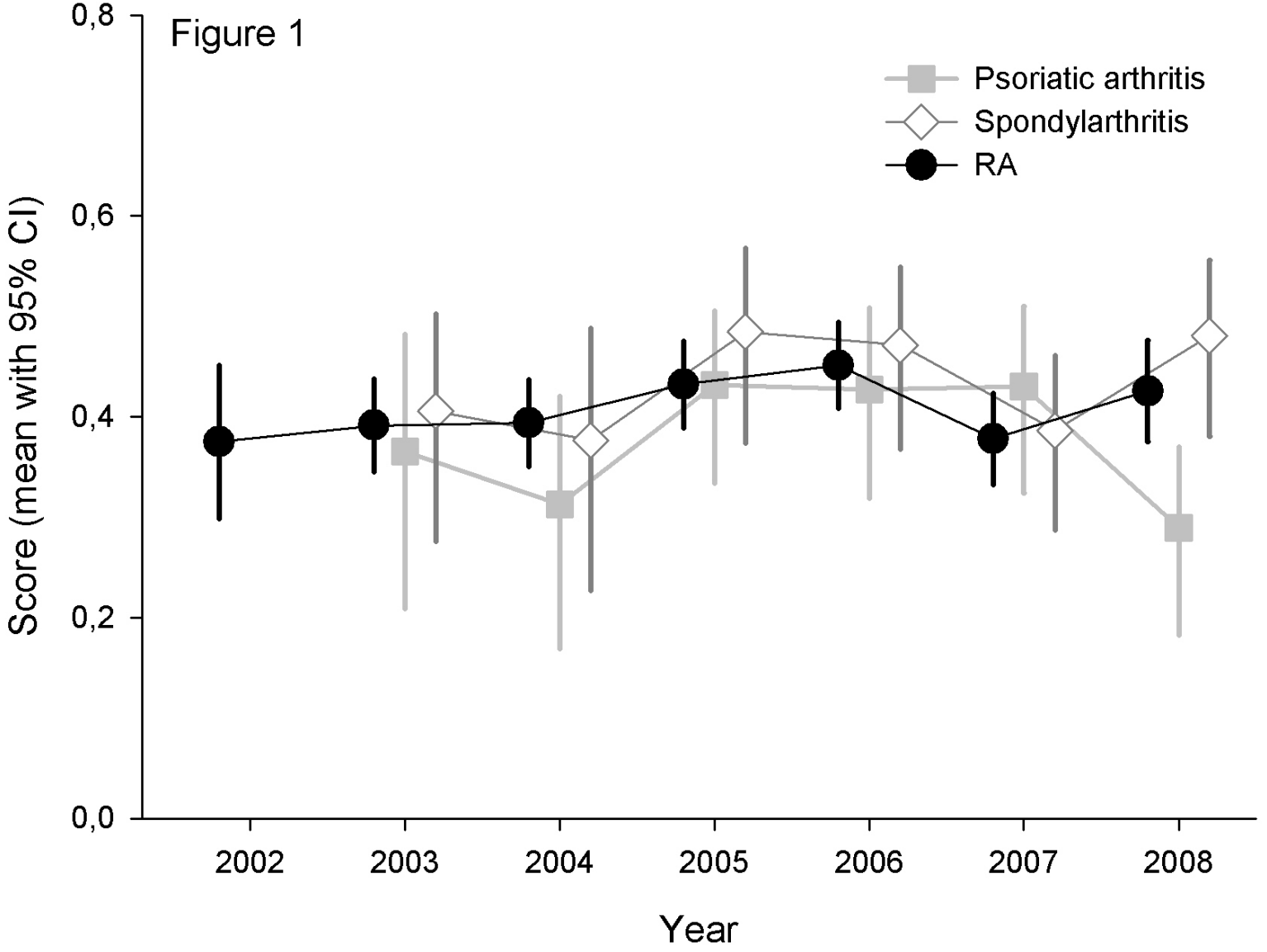
Figure 4.
EQ-5D during follow up for RA patients. All patients and patients with complete data.

Table 1
Baseline characteristics in the different diagnostic and treatment groups

	RA			Psoriatic arthritis			Spondylarthritis		
	1st anti-TNF	2nd anti-TNF	>2 anti-TNF	1st anti-TNF	2nd anti-TNF	>2 anti-TNF	1st anti-TNF	2nd anti-TNF	>2 anti-TNF
Valid N	1584	742	228	401	135	38	430	117	39
Male/Female (%)	23/77	19/81	17/83	51/49	41/59	34/66	60/40	54/46	58/42
Age years (Mean 95% CI)	55.0 (54.2-55.8)	55.1 (53.8-56.4)	57.0 (54.6-59.4)	46.8 (45.6-48.0)	48.4 (46.1-50.7)	52.0 (48.1-56.0)	43.2 (42.0-44.3)	43.9 (41.7-46.2)	47.0 (43.1-50.8)
Disease duration (Mean 95% CI)	9.8 (9.2-10.4)	12.1 (11.0-13.1)	14.2 (12.2-16.3)	10.1 (9.3-11.0)	12.0 (10.5-13.4)	16.0 (12.6-19.4)	13.1 (12.0-14.2)	16.1 (13.9-18.2)	16.3 (12.6-20.0)
Previous DMARD number# (Mean 95% CI)	2.3 (2.2-2.3)	4.0 (3.8-4.2)	5.7 (5.3-6.0)	1.7 (1.6-1.8)	3.0 (2.8-3.1)	4.6 (4.0-5.2)	1.4 (1.3-1.5)	2.9 (2.7-3.1)	4.5 (4.0-4.9)
Ongoing DMARD number (Mean 95% CI)	1.1 (1.1-1.1)	1.0 (1.0-1.1)	1.0 (1.0-1.1)	0.7 (0.7-0.8)	0.6 (0.5-0.7)	0.5 (0.3-0.7)	0.6 (0.5-0.7)	0.5 (0.4-0.6)	0.5 (0.4-0.7)
Ongoing Methotrexate (%)	68.1	52.5	51.3	62.8	54.1	39.5	42.6	41.9	43.6
Etanercept (%)	46.8	51.8	35.1	48.4	57.8	31.6	40.7	43.6	17.9
Adalimumab (%)	26.6	40.7	49.6	23.2	37.0	52.6	20.5	45.3	61.5
Infliximab (%)	26.6	7.5	15.4	28.4	5.2	15.8	38.8	11.1	20.5
Clinical spondylitis ever (%)				29.4	29.6	47.4	64.2	69.2	69.2
Peripheral arthritis ever (%)				66.3	77.0	88.8	44.0	48.7	64.1
Definite ankylosing spondylitis (%)				2.7	1.5	0	46.3	51.3	48.7

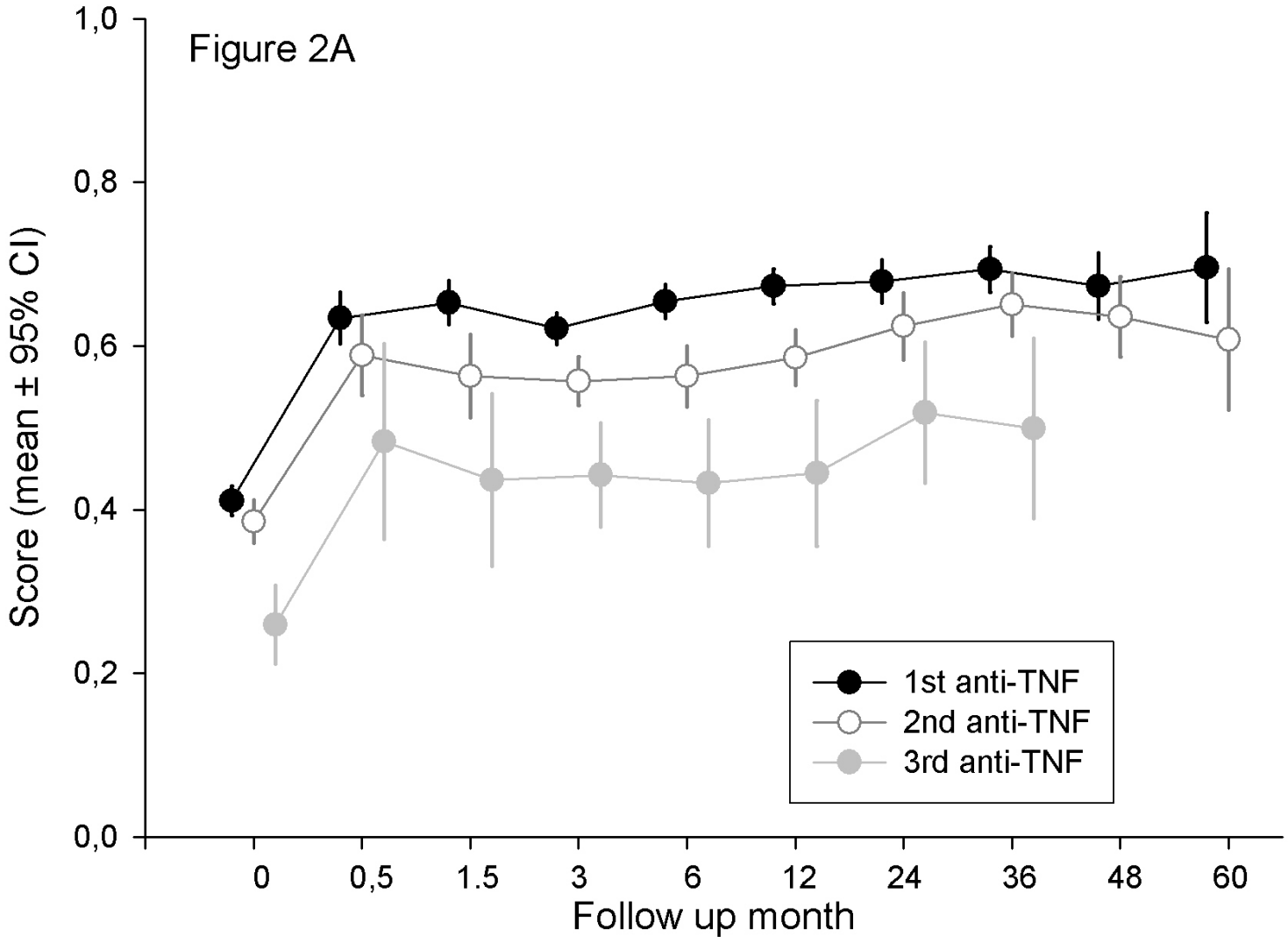
#Includes previous biologics

Figure 1



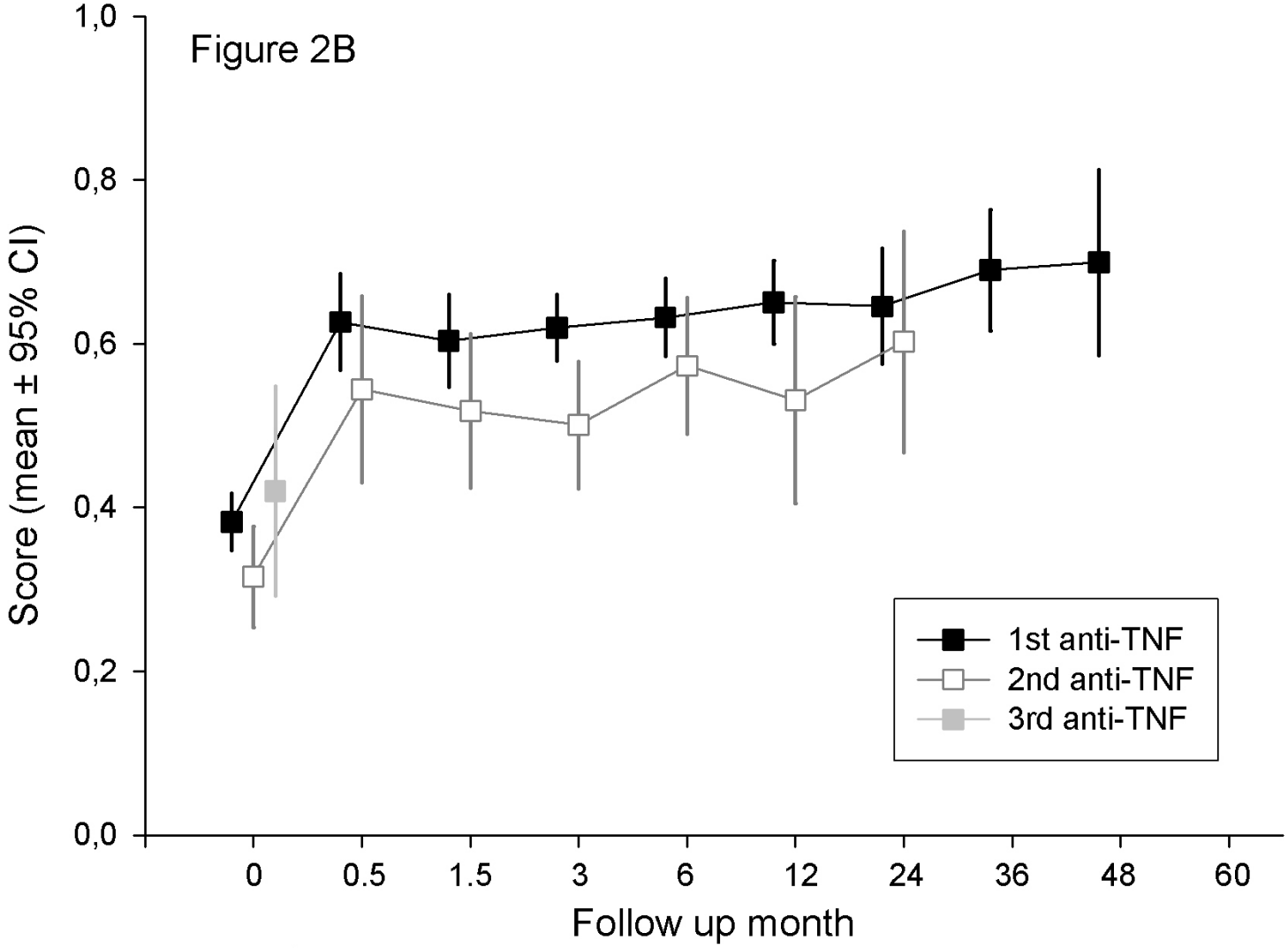
Number Initiated/Number with baseline EQ-5D values

RA	119/68	232/204	254/222	260/209	254/224	268/218	201/171
Spondylarthritis	24/10	45/35	47/42	59/54	79/73	89/77	93/79
Psoriatic arthritis	18/14	28/25	47/41	87/76	70/61	80/66	71/63



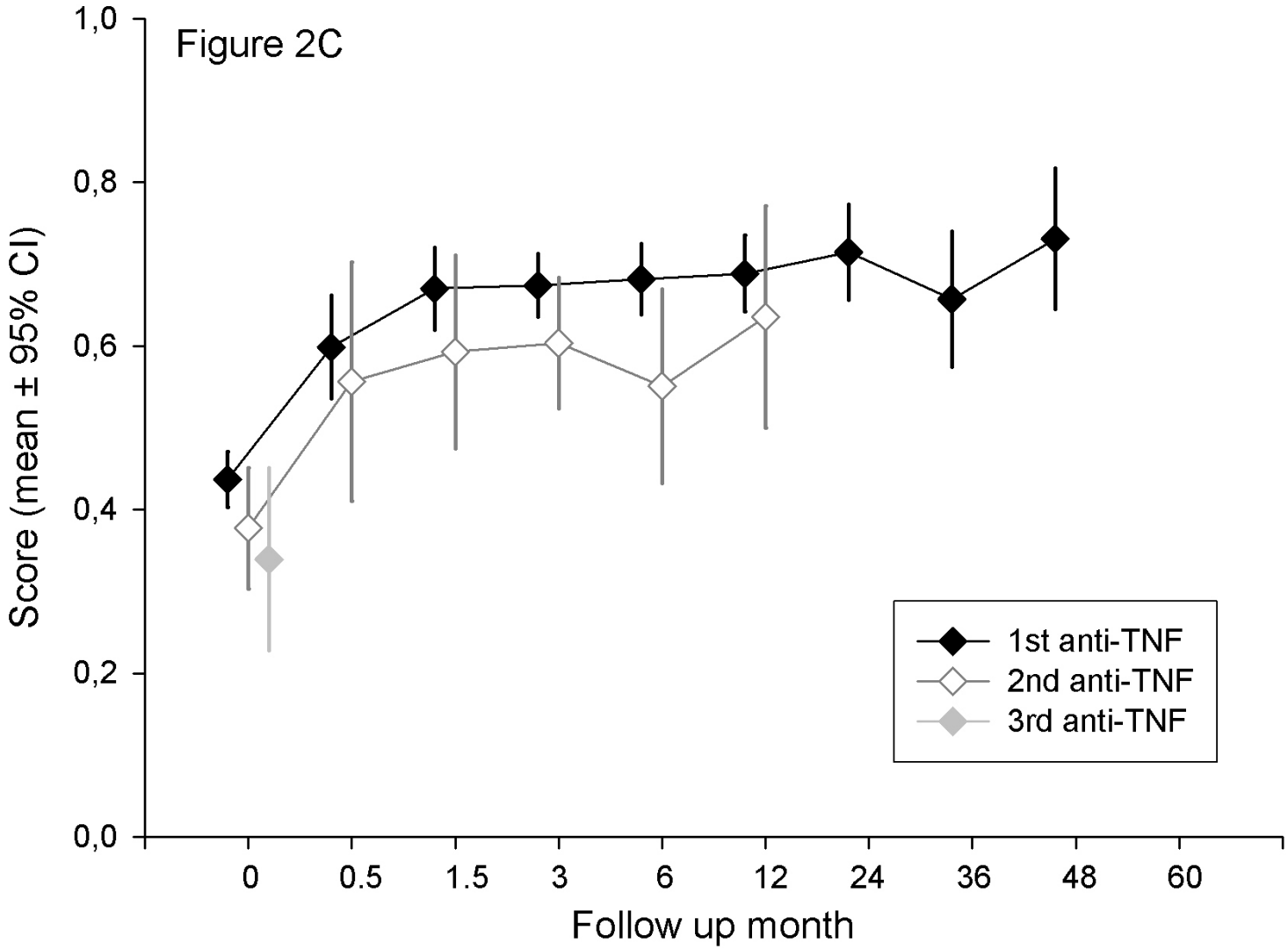
Valid N (number of EQ-5D values)										
1st antiTNF	1321	237	335	859	607	532	346	264	150	59
2nd anti TNF	631	111	152	377	274	249	167	153	97	29
3rd anti-TNF	193	32	45	110	75	63	43	31	17	4

Theoretical proportion remaining on therapy (%) (Kaplan-Meyer estimates)										
1st antiTNF	100	98.3	95.9	88.9	79.4	68.4	56.5	50.5	45.8	43.4
2nd anti TNF	100	93.9	90.3	85.0	78.7	68.3	59.5	54.6	50.4	47.7
3rd anti-TNF	100	92.3	88.7	80.3	67.6	57.7	48.6	45.4	41.6	



Valid N (number of EQ-5D values)										
1st antiTNF	344	72	99	216	144	136	80	58	22	6
2nd anti TNF	118	27	38	68	40	31	21	14	7	2
3rd anti-TNF	30	11	9	14	9	7	1	2	1	0

Theoretical proportion remaining on therapy (%) (Kaplan-Meyer estimates)										
1st antiTNF	100	99.2	94.9	90.2	81.3	69.9	59.8	54.7	52.6	50.1
2nd anti TNF	100	95.1	91.4	84.0	72.8	63.0	46.9	54.6		
3rd anti-TNF	100	94.7	73.7	63.2						



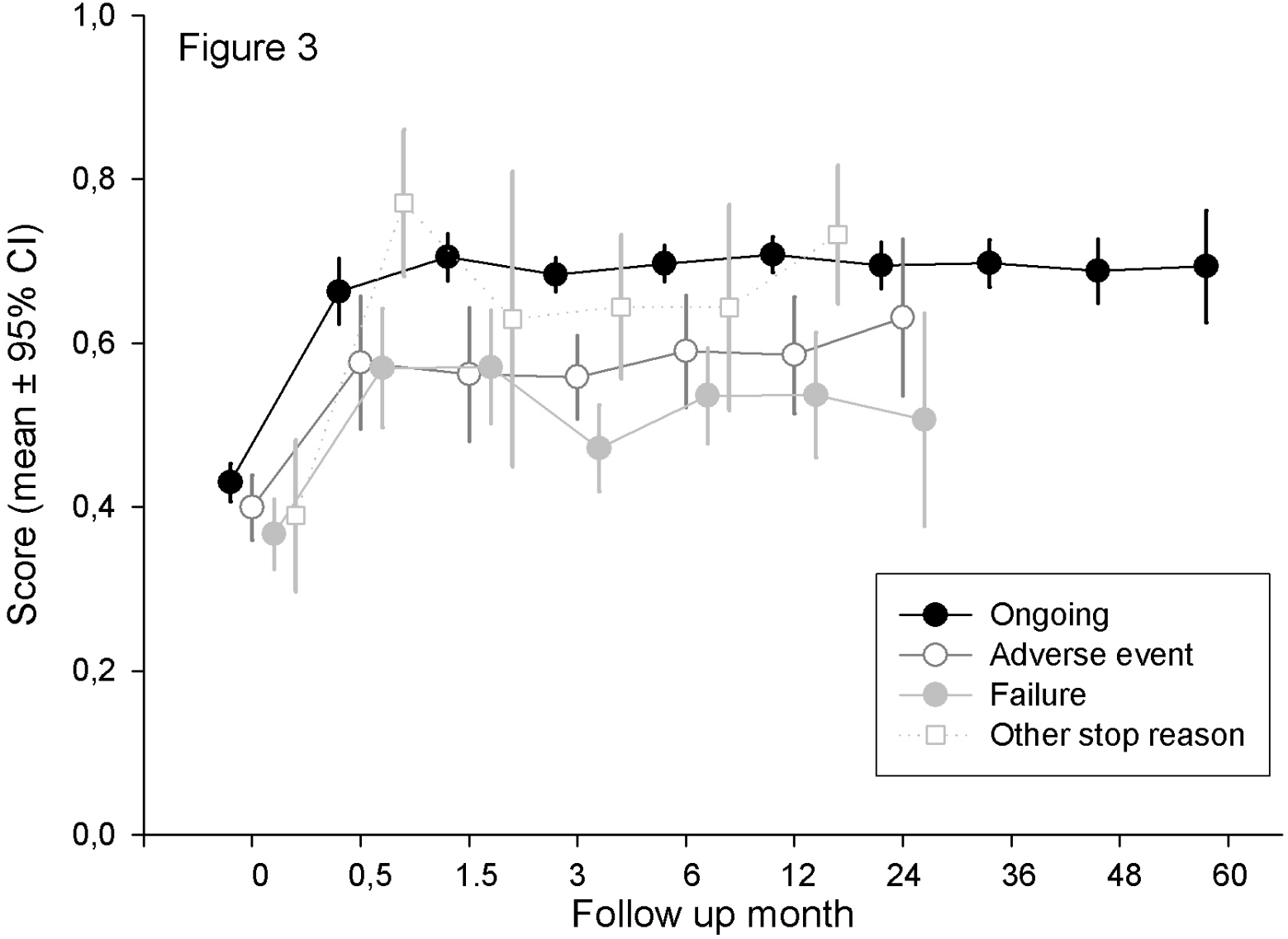
Valid N (number of EQ-5D values)

1st antiTNF	372	87	113	230	150	139	80	53	21	8
2nd anti TNF	99	22	33	58	34	25	15	15	5	2
3rd anti-TNF	37	7	12	18	8	9	5	4	1	0

Theoretical proportion remaining on therapy (%) (Kaplan-Meyer estimates)

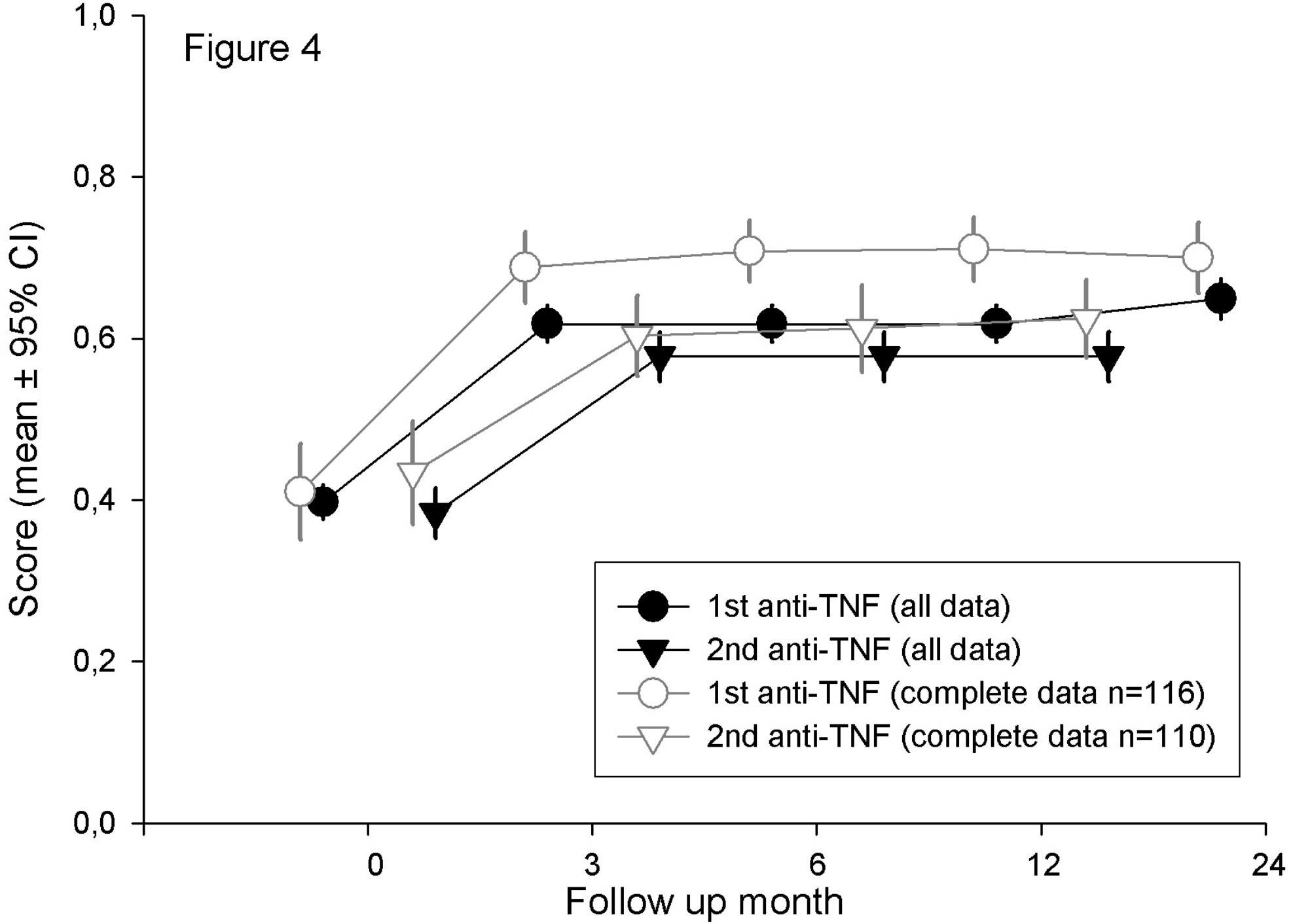
1st antiTNF	100	98.1	93.6	91.9	88.4	76.8	68.3	61.4	59.1	59.1
2nd anti TNF	100	98.5	89.4	83.3	71.2	62.1	51.5			
3rd anti-TNF	100	95.2	90.5	85.7	85.7	52.4				

Figure 3



Valid N (number of EQ-5D values)										
Ongoing	772	138	204	515	401	382	288	234	140	57
Adverse event	255	41	55	148	79	66	24	13	3	1
Failure	231	47	64	157	97	64	23	10	2	0
Other	63	11	12	39	30	20	11	7	5	1

Figure 4


1,0
0,8
0,6
0,4
0,2
0,0
Score (mean ± 95% CI)
0
3
6
12
24
Follow up month
1st anti-TNF (all data)
2nd anti-TNF (all data)
1st anti-TNF (complete data n=116)
2nd anti-TNF (complete data n=110)