Rheumatologists use different cut offs for disease activity in real life – the experience with Golimumab in ankylosing spondylitis – Subanalysis from the Non-Interventional German GO-NICE study

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Abstract

Objectives: International recommendations for the management of axial spondylo-arthritis including ankylosing spondylitis (AS) recommend a BASDAI level of disease activity of ≥4 to initiate treatment with biologics. We aimed to evaluate the level of disease activity used to initiate tumor necrosis factor inhibitor (TNFi) treatment and the level of responses to treatment based on different BASDAI cut-offs.

Methods: This is a posthoc analysis of the non-interventional, prospective, GO-NICE study in the subgroup of biologic-naïve AS treated with golimumab 50mg subcutaneously once monthly.

Results: Of the 244 biologic-naïve AS patients at baseline, 70.5% had a BASDAI ≥4 (Group 1), 14.3% 2.8 to <4 (Group 2), and 15.1% even <2.8 (Group 3). A total of 134 patients (54.9%) completed the 24-month observational period. The mean BASDAI in Groups 1, 2 and 3 was initially 5.9±1.3, 3.4±0.4 and 2.0±0.8, decreased to 2.2± 2.0, 1.9± 1.2 and 1.0 ± 1.2 within 3 months (all p<0.0001 vs. baseline), and decreased significantly to 2.2±1.7, 1.9±1.7 and 1.4±1.0 at month 24 (all p<0.005), respectively. BASDAI 50% improvement was noted in 68.8%, 44.8%, and 45.2% of patients at month 3, and in 84.9%, 61.9%, and 55.0% at month 24, respectively.

Conclusions: TNFi treatment was initiated in almost a third of AS patients with a lower disease activity states as assessed by BASDAI cut-off of ≥4. Patients with a BASDAI between 2.8 and <4 appeared to benefit significantly from golimumab treatment, while patients with BASDAI <2.8 did not. This finding should lead to a reevaluation of the established BASDAI cut-off of ≥ 4.

Key indexing terms

Ankylosing spondylitis, biological therapy, clinical trial

Background

Ankylosing spondylitis (AS), the 'radiographic' part of the spectrum of axial spondyloarthritides, is a chronic inflammatory rheumatic disease with predominant involvement of the axial skeleton by both, inflammation and new bone formation.(1) As shown in a recent systematic review and a Bayesian network metaanalysis comprising 20 trials of 6 tumour necrosis factor-α inhibitors (TNFi) and 3.220 participants, treatment with TNFi is effective.(2)

Ever since the first publication on the success of therapy with TNFi in patients with active AS,(3) the Bath Ankylosing Spondylitis Disease Index (BASDAI)(4) cut-off of 4 and above has been used,(5) and published evidence from various sources support this approach.(6-8) Correspondingly, this cut-off value ≥ 4 has been recommended for use in all major international guidelines.(9-11) The current ASAS/EULAR recommendations for patients with axial SpA define active disease by ASDAS ≥ 2.1 or BASDAI ≥4. Historically, active disease has been defined by a BASDAI level of at least 4, while ASDAS is the preferred measure today. (11)

However, the BASDAI threshold value has once been arbitrarily set,(3) and has never been thoroughly evaluated. This is in contrast to the Ankylosing Spondylitis Disease Activity Score (ASDAS), which has been developed on a data driven basis.(12, 13) Accordingly, it has remained unclear whether patients with a lower BASDAI may also benefit from therapy with biologic agents. In our personal experience, this is an issue because, especially young male patients, tend to dissimulate and report low BASDAI scores – even though they may have high CRP levels or strong evidence of axial inflammation by MRI.(14)

The assessment of disease activity in AS is based on clinical parameters such as inflammatory spinal pain, laboratory parameters such as C-reactive protein (CRP)(15) and magnetic resonance imaging (MRI). Conversely, the predictive value of baseline CRP levels on clinical and radiographic outcomes in patients with AS has been documented in many studies.(16-18)

In the GO-RAISE study with golimumab 50mg once monthly,(19-21) the drug has been shown to be safe and effective in adult patients with AS. In that study, in AS patients

treated with golimumab, elevated CRP at baseline or week 14/week 24 weakly predicted subsequent radiographic progression and modestly predicted residual spinal inflammation.(22)

We were interested to learn about the level of disease activity used in daily routine to start TNFi therapy, taking advantage of data obtained in the observational phase IV study GO-NICE performed in Germany in which unselected AS patients were treated with golimumab 50mg once monthly and observed up to 24 months.(23, 24) In GO-NICE, clinical effectiveness was assessed in 501 patients with AS according to the German standard of care using the 10-point BASDAI to quantify disease activity. (4, 25)

We performed a subgroup analysis of AS patients who were categorised into three BASDAI groups and described with respect to characteristics, treatment and outcomes. In addition, we studied the influence of baseline CRP values on clinical outcome parameters in a real world setting.

Methods

This is a posthoc analysis of the non-interventional, multicentre, prospective, study GO-NICE (Non-Interventional Clinical Evaluation with GOlimumab) that was performed between 2010-2015 in a real-life setting by rheumatologists in 158 sites in all parts of Germany.(23, 24) Patients were observed from baseline (BL) up to 24 months through 8 visits performed every three months. Safety data were also collected, and have been reported previously.(23) Golimumab was prescribed by the treating physicians based on patients' need for the therapy and in accordance with the recommendations of the Summary of Product Characteristics (SmPC). (26) The treatment decision had to be made independently of data documentation and prior to the inclusion of the patients in this study.

We limited the analysis of the GO-NICE data to those with the diagnosis of established AS and who were biologic-naïve and captured the initial BASDAI values before the start of therapy with golimumab 50mg subcutaneously once monthly. Patients were categorised into 3 groups: patients with BASDAI ≥4 (Group 1); the third of patients with a BASDAI <4 was divided into two equal groups, BASDAI between 2.8 and <4 (Group 2), and BASDAI < 2.8 (Group 3). Within each group, patients were split into patients with elevated CRP value (above upper limit of normal defined as >5mg/l) versus non-elevated CRP. No radiographic data were collected in this observational study.

Results

Patient disposition and flow is shown in Figure 1. Out of 543 AS patients, 244 had not received any biologic medications for pre-treatment and at least one documented follow-up visit after baseline (BL) assessment and were thus eligible for analysis. Of these, 134 patients (54.9%) completed the 24 month observational period (BL until visit at month 24).

Male patients accounted for more than two thirds in the sample (70.9%). Mean time since diagnosis was 9.0± 9.5 years. Mean CRP values were substantially elevated (19.7 52.7 mg/l), with substantial variety across patients.

At treatment initiation, the majority of patients (70.5%) had BASDAI ≥4 (Group 1), 14.3% had BASDAI of 2.8 to <4 (Group 2) and 15.2% had a BASDAI < 2.8 (Group 3).

Patient demographics did not differ much between groups; just the proportion of males was numerically lower in Group 1. Of note, the proportion of patients with an elevated CRP at BL was highest in Group 2 (Table 1).

Course of BASDAI over time. The mean BASDAI in Group 1 and 2 was initially 5.9 ±1.3 and 3.4 ±0.4, respectively. By month 3, the values decreased significantly to 2.9 ±2.0 and 1.9 ±1.2 (p <0.0001 vs. BL). By month 24, in Group 1 the value decreased significantly (p <0.0001 vs. BL) to 2.2 ±1.7 or and in Group 2, remained stable on this low level with 1.9 ± 1.7 (Group 2) (Figure 2).

In patients with a BASDAI < 2.8 at BL (Group 3) the mean score was initially 2.0 ±0.8 and further scores ranged from 0.7 to 1.9, although some of the changes were not significant versus BL.

BASDAI 50% improvement was noted in 68.8%, 44.8%, and 45.2% of patients at month 3, and in 84.9%, 61.9%, and 55.0% at month 24, respectively.

Influence of CRP levels. CRP levels did not have an influence on BASDAI levels (Figures 3a and 3b).

Discussion

In this real world study with unselected AS patients who were biologic naïve and started for their first time TNFi golimumab therapy, almost a third of patients had BASDAI levels at baseline which were below the recommended threshold of ≥4. Thus, based on the current ASAS/EULAR recommendations, those patients would formally not have been eligible for such therapy. If correctly documented, this result suggests that rheumatologists seem to feel that there are patients who, based on the level of inflammation present as evidenced by CRP levels or MRI findings, are in need for TNFi therapy but who judge themselves lower when ticking BASDAI boxes. This well established questionnaire is an outcome parameter that is solely based on subjective clinical symptoms. This is in contrast to the ASDAS in which subjective parameters are combined with CRP as an objective parameter. (12, 13) However, patient global and ASDAS, respectively, were not assessed in this study because it was performed under clinical practice condition, starting in year 2010.

The fact that the CRP levels in this study were higher in the groups with a low BASDAI (groups 2 and 3) do suggest that rheumatologists weighted the presence of objective signs of inflammation sometimes higher than the subjective grading of clinical symptoms. This view is actually well consistent with the treat-to-target concept (27, 28) and also with the results of recent cohort studies. Thus, this data may lead to a critical re-evaluation of the current BASDAI cut-off of ≥4 which would base on the thought that the burden of inflammation may, at least in some cases, be more important than the degree of clinical symptoms. This could be especially important for patients with high CRP and low BASDAI levels.

The other important observation of this study was that patients with relatively low BASDAI levels between 2.8 - 4 still had a clear treatment response to TNFi. The fact that absolute and relative treatment effects in patients with higher compared to lower initial BASDAI values were substantially stronger may be a real effect but could also represent an effect of regression to the mean.(29)

Since male sex (30) and CRP (16, 17) may be associated with a better response to TNFi therapy it seems possible that the high proportion of male patients and high CRP levels in the BASDAI 2.8 -4 group has contributed to the significant treatment response in this group.

Our results are in line with a cross-sectional study performed between 2001 and 2003 in an experienced centre in the UK. In his study, also about one third of patients (36%) did not meet the criteria for TNFi therapy according to recommendations at that time.(6) In a representative cohort of 1023 Belgian AS patients evaluated by 89 rheumatologists in 2004/2005, about 60% did not commence TNFi therapy. (31) Although the AS recommendations made an earlier start of TNFi treatment in the disease course possible, the BASDAI criterion (≥ 4) for treatment has remained unchanged for almost two decades. The high proportion of patients with low disease activity receiving TNFi in this posthoc analysis of the GO-NICE study suggests that German rheumatologists are currently initiating biologic therapy differently.

Why rheumatologists decided to treat patients with lower BASDAI scores cannot be completely clarified. It seems possible that some patients who used to have higher scores in recent history had lower scores at baseline assessment. Furthermore, recent interventions prior to the baseline assessment may have lowered BASDAI scores – for example an intensive physiotherapy course.(32) Natural variation of symptoms and patient-reported outcome measures has been reported for AS patients.(33)

Observed daily changes of BASDAI need to be interpreted with caution though.(34) Patients with BASDAI < 2.8 were not considered in detail in our analysis, since the BASDAI value shows considerable intrapatient week-to-week variability; thus, repeat evaluations may be needed before starting or stopping TNFi. (35, 36)

Of course, our findings cannot be readily generalized, especially if a group has small patient numbers, and the fact that the patients in this real world study were treated with only one TNFi does not exclude that they may have responded differently to other TNFi.

Differentiation within the BASDAI categories into normal versus high CRP did not change our overall findings. Patients with elevated vs not elevated CRP at baseline in a cohort of 289 AS patients had better responses to TNFi therapy according to all response measures, but patients without elevated CRP also responded.(37) This is consistent with the current approval situation for TNFi in patients with active AS.

Our study has some limitations, since it was non-interventional and, thus, was not randomised and had no control arm. The treating physicians may have selected patients to receive golimumab as compared to other treatment options, what may potentially lead to channelling bias and confounding by indication. The relatively high lost-to-follow up rate, although well comparable with other studies, may also imply some statistical uncertainty. As described above, Patient Global Assessment of the disease activity was not performed and thus, ASDAS could not be calculated.

However, even though we cannot be sure for what reason these patients received TNFi therapy, we think that these data are hypothesis generating in the way that different cut offs should to be evaluated in prospective studies.

Starting TNFi therapy is always a combination of individualised risk, benefit, current signs and symptoms of the disease, the patient characteristics, and costs that determines if a treatment is indicated.

Conclusion

The most interesting observation of this posthoc analysis of a real world study is that almost one third of the patients included in this study were not documented as having reached the internationally recommended BASDAI cut-off of ≥4. Furthermore, the data show that the patients with a BASDAI 2.8 to <4 seem to have significant benefit of TNFi therapy, while this was not the case with in patients with a BASDAI <2.8. This finding may lead to a re-evaluation of the established BASDAI cut-off of ≥ 4. Finally, CRP levels seem to have had no major influence on response rates.

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Disclosure of Interest:

J. Braun: AbbVie, Amgen, Biogen, Boehringer Ingelheim, BMS, Celgene, Celltrion, Centocor, Chugai, EBEWE Pharma, Epirus, Hospira, Janssen, Medac, MSD, Mundipharma, Novartis, Pfizer, Roche, Sanofi-Aventis, and UCB.

X. Baraliakos: AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Novartis, Pfizer, Roche, MSD, and UCB.

U. Kiltz: AbbVie, Chugai, Gruenenthal, Janssen, MSD, Novartis, Pfizer, Roche, and UCB.

G. R. Burmester: AbbVie, Bristol-Myers Squibb, MSD, Pfizer, Roche, and UCB.

K. Krüger: AbbVie, BMS, Celgene, Janssen Biologics, MSD, Pfizer, Roche, and Sanofi-Aventis.

S. Wassenberg: AbbVie, Chugai, Janssen Biologics, MSD, Novartis, Pfizer, and Roche.

M. H. Thomas: Employee of MSD Sharp & Dohme GmbH, Germany.

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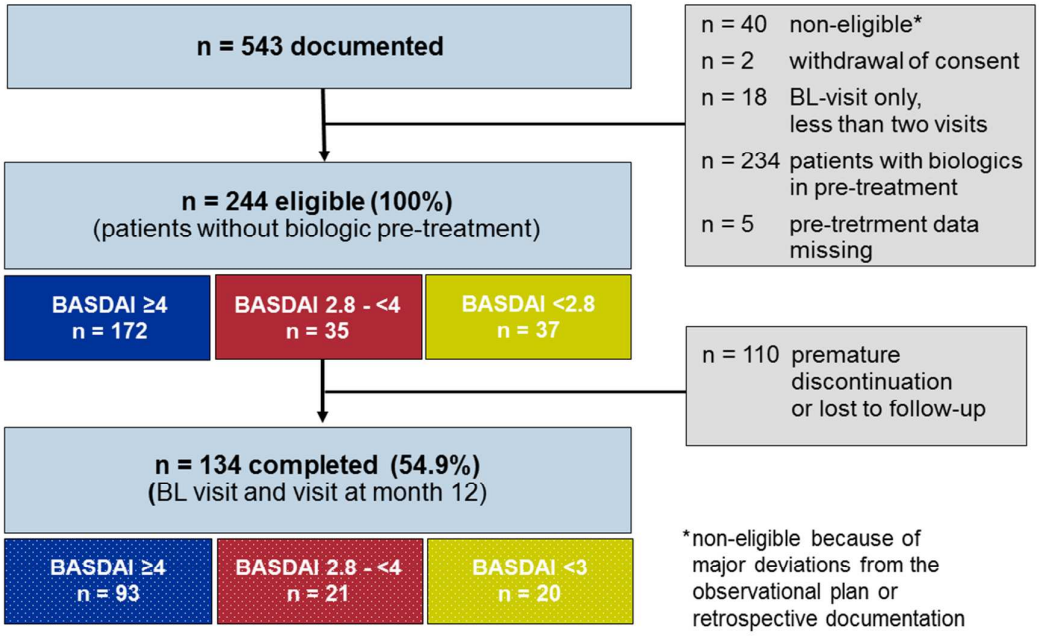
Legends

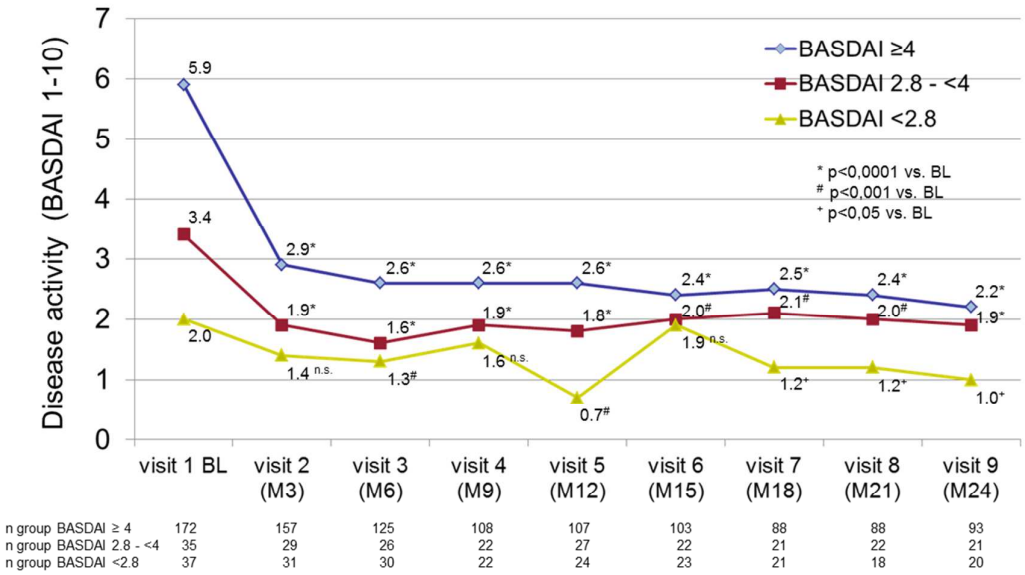
Figure 1. Patient disposition and flow

Figure 2. BASDAI course by subgroups and C-reactive protein

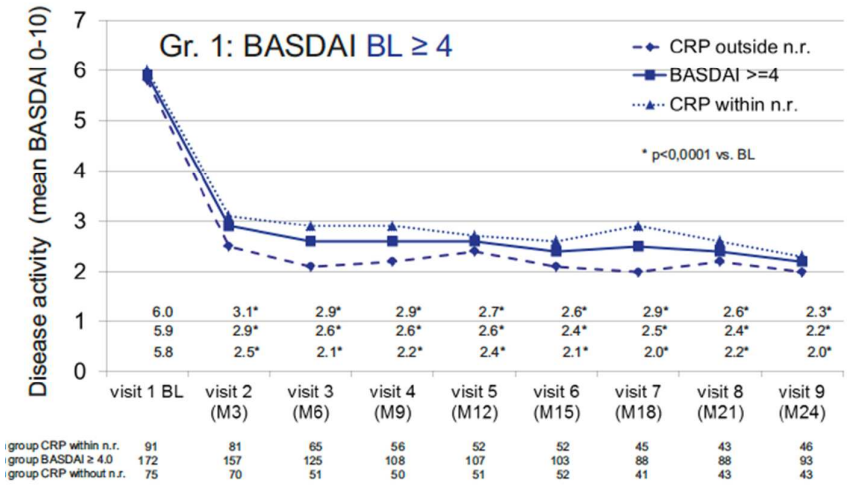
Figure 3. BASDAI course by subgroup over time

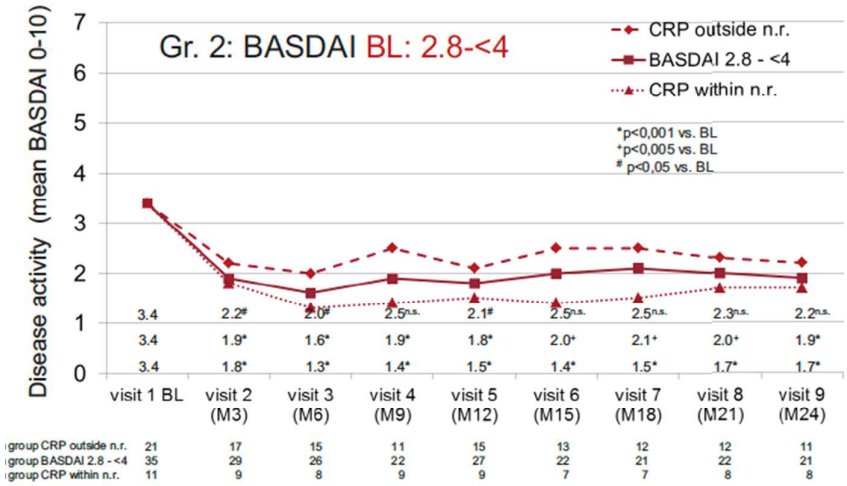
Table 1. Baseline characteristics of patients eligible for post-hoc analysis





n group BASDAI ≥ 4	172	157	125	108	107	103	88	88	93
n group BASDAI 2.8 - <4	35	29	26	22	27	22	21	22	21
n group BASDAI <2.8	37	31	30	22	24	23	21	18	20





Tab. 1. Baseline characteristics of patients eligible for post-hoc analysis

Demographics and baseline characteristics	**BASDAI ≥4 n=172**	**BASDAI 2.8 - <4 n=35**	**BASDAI <2.8 n=37**	**total AS patients (n = 244)**
Mean age [years] ± SD (range)	41.9±12.5 (18-72)	44.7±11.6 (20-69)	39.1±12.5 (23-69)	41.9±12.4 (18-72)
Proportion males n (%)	117 (68.0%)	29 (82.9%)	27 (73.0%)	173 (70.9%)
Mean time since first diagnosis [years] ± SD (range)	8.8±9.5 (0-49.2)	10.1±10.2 (0.1-37.9)	8.7±9.0 (0.2-36.5)	9.0±9.5 (0.0-49.2)
Mean C-reactive protein (CRP) [mg/l] ± SD (range)	18.4±52.8 (0.3-660.0)	27.7±74.1 (0.3-426.0)	18.3±17.8 (1.0-60.6)	19.7±52.7 (0.3-660.0)
Median C-reactive protein (CRP) [mg/l]	10.0	14.0	13.0	10.2
CRP ≥ 5mg/l yes, no, missing, n (%)	 75 (45.2%) 91 (54.8%) 6	 21 (65.6%) 11 (34.4%) 3	 18 (51.4%) 17 (48.6%) 2	 114 (48.9%) 119 (51.1%) 11

BASDAI= Bath Ankylosing Spondylitis Disease Index
AS= ankylosing spondylitis
CRP= C-reactive protein
n= number of patients
SD= standard deviation