The European Ankylosing Spondylitis Infliximab Cohort (EASIC): a European multicentre study of long-term outcomes in patients with ankylosing spondylitis treated with infliximab

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Abstract

Objectives

To study the long-term efficacy and safety of treatment with infliximab in patients with ankylosing spondylitis (AS) in a real life setting.

Methods

AS patients from 6 European countries who had finished the 2-year trial ASSERT were invited to participate in the open-label investigator-driven study EASIC. At baseline, 2 groups were formed: patients of group 1 had not been treated with infliximab after ASSERT, while those of group 2 had continuously received it. Patients of group 1 were further subdivided in group 1a: patients with a relapse and 1b: in remission. All patients of group 1a and 2 continuously received infliximab for 96 weeks, mean dose 5 mg/kg, intervals 6–8 weeks. Patients of group 1b were also treated in case of relapse.

Results

A total of 103/149 patients (69%) were included in EASIC, 1.3±0.9 years after the end of ASSERT: 9 in group 1a, 5 in group 1b and 89 in group 2. Most patients were male (83%), mean age 44 years. Most patients of group 2 completed the trial (86%) vs. only 5 of group 1 (33%) – mostly due to allergic reactions after readministration of infliximab. In total, there were 22 drop-outs due to 6 adverse events, 4 lack of efficacy, 3 planned pregnancy. All standard assessments indicated beneficial values over time, at week 96 significantly better than at baseline of ASSERT.

Conclusion

The majority of patients were continuously and successfully treated with infliximab for 5 years, whereas discontinuation and reintroduction of therapy was less satisfactory due to the frequent occurrence of hypersensitivity reactions. Anti-TNF therapy with infliximab proved to be effective and safe on a long-term basis.

Key words

ankylosing spondylitis, anti-TNF, infliximab

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Introduction

Ankylosing spondylitis (AS), the main subtype of the spondyloarthritides (SpA), is a chronic inflammatory rheumatic disease that affects about 0.5% of the adult Caucasian population (1) with an age of onset in early adulthood (2). AS is characterised by inflammatory back pain due to spinal inflammation which may result in new bone formation. AS patients may also have peripheral arthritis, enthesitis and uveitis (3).
NSAIDs are considered first line pharmacological therapy for AS, while other pharmacological treatments such as disease modifying anti-rheumatic drugs (DMARDs) and corticosteroids, much unlike rheumatoid arthritis, play only a limited role (4). There is consensus that TNF blockers should be given to patients with AS who have persistently high disease activity despite conventional treatment (4).
Several trials have shown that treatment with infliximab is efficacious in AS patients with active disease (5-9). This was also shown in the 2-year-trial ASSERT with 279 patients (10, 11). Magnetic resonance imaging (MRI) confirmed the decrease of spinal inflammation in this study (12). Whether TNF blockers decelerate structural damage in AS is still a matter of debate (13-15), but no inhibition of radiographic progression was seen in direct comparisons to the historical OASIS cohort (16-18). Long-term data on the clinical efficacy and safety of anti-TNF therapy in AS is still limited (19).
The collection of long-term data is also critical for better calculations of the economic burden of the disease with or without anti-TNF therapy (20, 21).
Therefore, the EASIC cohort was initiated by European rheumatologists – an open-label investigator-driven international multicentre trial with patients who had received infliximab for two years as part of ASSERT.

Material and methods

All European patients (n=149) who participated in ASSERT were invited to take part in the 2-year extension trial EASIC.
Since treatment strategies were different in the participating countries after the end of ASSERT, in EASIC, the patients had to be divided into 2 groups:

- The patients who had discontinued infliximab after ASSERT were allocated to EASIC group 1 which was subdivided into 2 subgroups:
- Group 1a: patients who had a relapse of AS before the start of EASIC. These patients received an MRI of the spine before reintroduction of infliximab and 4–8 weeks thereafter. Relapse was defined as Bath AS disease activity index (BASDAI) >4 and physician's global assessment >4 at screening and baseline. When the time between the end of ASSERT and the reintroduction of infliximab at the start of EASIC was more than 6 months, one additional infliximab infusion was given after 2 weeks.
- Group 1b: patients who had discontinued infliximab after ASSERT and were in a good clinical condition (not having met defined relapse criteria at one point in time). These patients did not receive infliximab infusions within EASIC, but had regular follow-up visits. When a relapse occurred in the first year of EASIC these patients switched to group 1a.
- Group 2: patients who had been continuously treated with infliximab after ASSERT were included in group 2. These patients were treated with infliximab infusions every 6-8 weeks in a dosage between 4 and 6 mg/kg bodyweight – similar to the treatment schedule and dosage they had received after the end of ASSERT.
- Patients were allowed to continue with different dosages and intervals as long as the dosages remained between 3–10 mg/kg body weight and the intervals between 4 and 12 weeks.

All European patients who had completed visit "week 96" of ASSERT, and who met the inclusion and exclusion criteria specified in the protocol, were eligible for EASIC. North American patients could not be included. The study design is summarised in Figure 1.
The study protocol was designed on the basis of current clinical practice. Analgesics, NSAIDs and prednisolone ≤10 mg daily were allowed as concomitant medication, but no increase

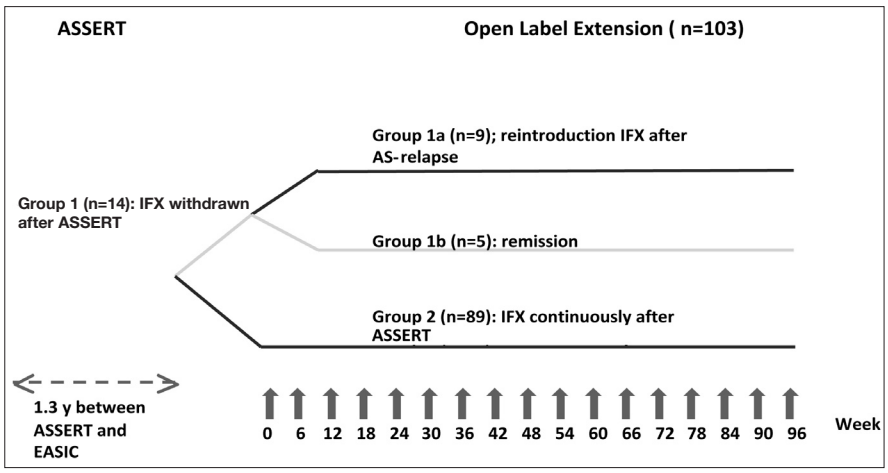

Fig. 1. Study design of EASIC.

of the dosage of these medications was possible. Intra-articular steroid injections were allowed, and concomitant DMARDs could be continued, but introduction of new DMARDs during the study was not possible. The use of cytotoxic drugs and TNF-blockers other than infliximab was not allowed. It seems likely, therefore, that efficacy assessments are rather exclusively attributable to infliximab therapy.

The study protocol was reviewed and approved by the respective institutional review board or independent ethics committees at each site and regulatory authorities in each country. All participating patients provided written informed consent prior to any trial associated procedure.

Efficacy analysis

The distribution of the patients into these 3 subgroups and the safety data were documented, and the patient status and response rates calculated.

This paper concentrates on the secondary endpoints of EASIC: the long-term clinical effectiveness after 4 years of therapy, as assessed by standard assessment tools such as: the ASAS response criteria (ASAS 20, 40, ASAS 5/6 and the ASAS partial remission rates), (22) Bath AS disease activity index (BASDAI), (23), Bath AS functional index (BASFI), (24), Bath AS metrology index (BASMI), (25), chest expansion, physician and patient global assessments on a visual analogue scale (VAS), enthesitis index, and the 44-swollen joint count. C-reactive protein levels were measured at baseline, week 24, 48, 72 and 96 in all patients. ASSERT data for comparison with EASIC were provided by Centocor Inc.

The predefined primary endpoint of EASIC was the change of radiographic progression after more than 4 years of infliximab treatment. Spinal inflammation as assessed by MRI was a secondary outcome. These analyses will be separately presented.

Safety analysis

The safety of infliximab was analysed on the basis of documented (serious) adverse events. The number of adverse events (AE), serious adverse events (SAE), infections, and infusion reactions was recorded. Information on the opinion of the investigator whether the AE was possibly related to the study medication was collected. The number of drop-outs possibly related to adverse events was documented.

The safety data were also compared to the ASSERT data.

Statistical analysis

All analyses performed were based on a modified intention to treat (mITT) population including all patients treated with infliximab. The same analyses were performed for the EASIC study completers.

For dichotomous endpoints, such as BASDAI 50 and ASAS 20, percentage improvements were calculated using ASSERT baseline data (before the first infusion) as reference. Response rates were calculated for each visit (end of ASSERT, baseline EASIC, week 12, 24, 36, 48, 72 and 96 of EASIC). Corresponding 95% confidence intervals were calculated (Wilson method). Response rates were compared by Fisher's exact test between groups 1 (1a and 1b combined) and 2.

For continuous endpoints, such as BASDAI and BASFI, descriptive statistics (n, mean, standard deviation, median, Q1 and Q3, minimum and maximum) were provided at each visit. Means were compared by one-way analysis of covariance with baseline values as the covariate. Two different baseline values were used: baseline and week 102 of ASSERT. All comparisons were 2-sided with a 5% significance level. Because of the small sample size in group 1a+1b and the imbalance between the groups, the Mann-Whitney Wilcoxon test was used for continuous endpoints. For sample sizes ≥30 a *t*-test was used, and for sample sizes <30 a signed rank test was used.

To handle missing data caused by missing visits or drop-outs, in addition to the analyses using the observed cases only, the same set of analyses was repeated using imputed data with the following rules: for monotonic missing values caused by early drop-outs, the last-observation-carried-forward (LOCF) method was used. For intermittent missing values caused by missing visits, the average of before and after values was taken for the missing visit.

Results

A total of 103/149 European patients (69%) who participated in ASSERT were included in EASIC (15 sites in 6 European countries: Germany (n=36), the Netherlands (n=26), Belgium (n=26), United Kingdom (n=9), France (n=4) and Finland (n=2).

Overall, 78.6% of patients completed visit week 96 of EASIC and therefore more than 5 years of infliximab treatment, which consists of 2 years of ASSERT, 2 years of EASIC and includes more than 1 year between the trials. There were 22 drop-outs (21.4% of patients), 6 of these were due to adverse events (4 due to infusion reactions), 4 due to inefficacy, 3 due to planned pregnancies, 9 due to other or unknown reasons.

The EASIC baseline characteristics of 97 patients with available efficacy data are presented in Table I. The demographics were comparable to ASSERT (n=279, 81% male, mean age 40 years). There were missing data on 6 patients in group 2.

EASIC started in December 2005. The mean time period between the end of ASSERT and the start of EASIC was 1.3±0.9 years. No patient could be directly switched from ASSERT to EASIC.

Out of the total of 103, 89 patients (86.4%) had continuously received infliximab after ASSERT (group 2), while 9 patients (8.7%) with active disease at the start of EASIC (group 1a) had not. In addition, 5 patients (4.9%) were in sustained remission without infliximab before EASIC (group 1b). One patient in group 1b, and 3 in group 1a had received infliximab but not continuously after ASSERT. The allocation of patients to the groups and the decision to interrupt treatment after ASSERT were not influenced by a potential lack of response to therapy or by the occurrence of adverse events during ASSERT. In contrast, all treatment decisions after the end of ASSERT were made by the local rheumatologists according to regional or national standards of care and individual requirements of the patients. Infliximab was given to all patients in the Netherlands, France and Finland, to 92% of patients in Belgium, to 83% in Germany and to 67% in the U.K. between ASSERT and EASIC. In Belgium all but 2 patients who were in clinical remission between the trials had been continuously treated with infliximab. In Germany 50% of patients who had not been continuously treated with infliximab were in remission, while the remainder was active. In the UK all patients not treated with infliximab had active disease. Concomitant treatment with corticosteroids and DMARDs was rare between ASSERT and EASIC. Only 4 patients (3.9%) received steroids and 2 (1.9%) were on DMARDs.

In EASIC, patients were given a mean infliximab dosage of 414.3±84.6 mg, which corresponds to 5.2 mg/kg. Overall, 66% of the patients of group 2 were treated at 6-week intervals and 34% at 8-week intervals. In contrast to ASSERT, there was some variety in the dosage of infliximab in EASIC. This is explained by the real life design of EASIC which allowed to continue treatment with the dosages and the dosing intervals that were started between ASSERT and EASIC.

For the statistical efficacy, analysis (LOCF) data of group 1 (n=14) and group 2 (n=83) with at least one post-treatment assessment were available. For the completer analysis there were 81 patients (5 of group 1 and 76 of group 2).

The efficacy analysis of the completers in group 2 are presented in Table II. All values significantly improved in comparison to ASSERT baseline ($p<0.05$).

The differences in ASAS response rates of completers and LOCF analysis between EASIC subgroups 1 and 2 are presented in Figures 2a and 2b, respectively. The difference between the subgroups at week 96 for ASAS 20 ($p=0.022$) and ASAS 5/6 ($p=0.020$) was statistically significant.

In Figures 3a-3c the mean values for BASDAI, BASFI and BASMI for patients of EASIC group 1 and group 2 (LOCF analysis) are shown for different time points during ASSERT and EASIC.

In the safety analysis a total of 545 AEs were reported, and 88 patients (85.4%) developed AEs, of whom 77 (87.5%) developed >1 AE (see Table IIIa). Almost half (47.2%) of these AEs were infections (Table IIIb). No opportunistic infections and mycobacterial infections were observed.

A total of 12 SAEs were documented of which 3 (25%) were considered

Table I. Baseline characteristics of EASIC patients (n=97)*.

	EASIC Group 1a+1b	EASIC Group 2
Number	14	83
Mean age (years)	38.2 ± 11.3	43.5 ± 10.2
Male gender (%)	71.4	84.3
Weight (kg)	79.6 ± 12.5	80.5 ± 12.6
BASDAI (mean)	5.1 ± 2.2	3.0 ± 1.9
BASFI (mean)	4.8 ± 2.2	3.3 ± 2.1
BASMI (mean)	2.9 ± 1.8	2.1 ± 1.6
Patient global assessment (mean)	5.5 ± 2.4	3.4 ± 2.3
Swollen joint count (mean)	0.5 ± 0.9	0.6 ± 1.8
Enthesitis index (mean)	1.2 ± 2.0	0.7 ± 1.7
CRP (mg/dl)	1.8 ± 1.6	0.8 ± 0.9

*only the 97 patients of which efficacy data were available are shown, no significant difference in demographic parameters between the groups.

Table II. Clinical efficacy data for the completers of group 2 (n=76).

Trial Time point	ASSERT Baseline	ASSERT 2 years	EASIC Week 0	EASIC Week 48	EASIC Week 96
Efficacy parameter					
BASDAI (mean)	6.4	2.4	2.9*	2.7*	2.5*
BASFI (mean)	5.9	2.9	3.2*	3.1*	3.1*
BASMI (mean)	4.0	2.7	2.1*	2.0*	2.2*
Patient global assessment (VAS)	7.0	2.7	3.3*	2.7*	2.8*
CRP (mg/dl)	2.9	0.6	0.7*	0.6*	0.5*
Enthesitis Index	9.0	3.7	0.6†	0.3†	0.4†
Swollen joint count (n)	1.6	0.6	0.6†	0.4†	0.6†
Arthritis free patients (%)	NA	81.6	74.3	78.9	78.4
BASDAI 50 response (%)	NA	68.4	59.5	60.5	67.1
ASAS 20 (%)	NA	82.9	78.9	84.2	82.9
ASAS 40 (%)	NA	67.1	57.7	67.1	61.8
ASAS 5/6 (%)	NA	69.7	68.9	73.3	77.6
ASAS partial remission (%)	NA	30.3	23.9	27.6	27.6

*$p<0.0001$ in comparison with ASSERT baseline; †significance level not calculated.

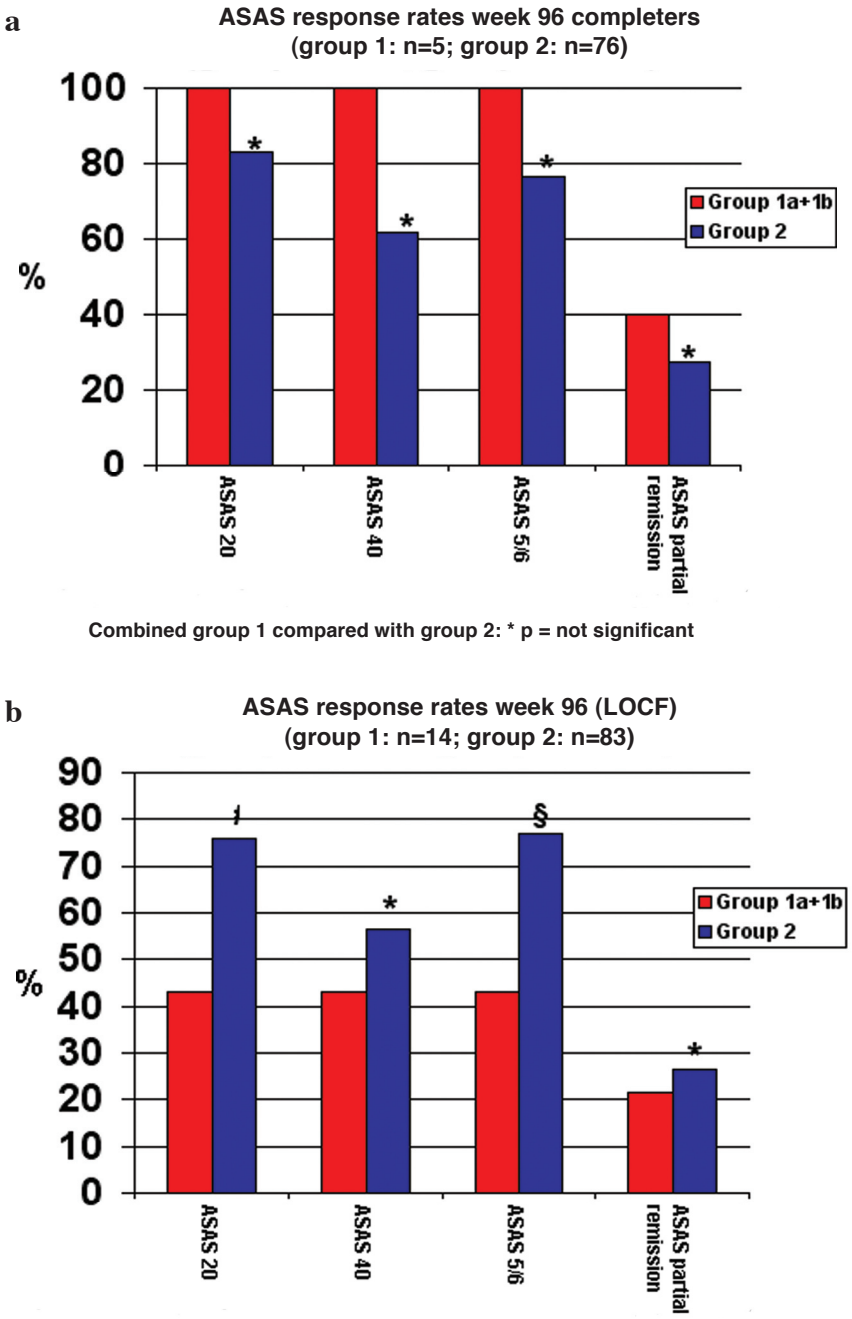

Fig. 2. ASAS response rates in EASIC.
a. ASAS response rates for EASIC completers at week 96.
b. ASAS response rates for EASIC week 96 (LOCF).

possibly related to infliximab: one pneumonia, one chronic sinusitis, and one diverticulitis with colon perforation that required colon resection and enterostomy, later on complicated by impaired wound healing. Two patients dropped out because of SAEs: the patient with diverticulitis and another one with an unrelated intraspinal calcified lesion.

Ten patients (9.7%) had a total of 20 allergic reactions during or after 15 infliximab administrations (3.7% of all AEs). There were 10 cases of flush, 3 cases of nausea, one syncope after infusion, one bradycardia during infusion, one case of fatigue, one pharyngeal edema, 2 cases of fever and one decrease of blood pressure during infusion. The majority of the observed infusion reactions (n=16; 80%) occurred in 7 patients of group 1. Four patients who had not been treated with infliximab after ASSERT dropped out due to allergic reactions which occurred after the reintroduction of infliximab (one patient dropped out after visit 1, one after visit 2 and 2 after visit 3.

There were 41 dermatologic AEs (skin infections excluded) including 2 cases of psoriasis and 3 of herpes zoster.

The incidence of anterior uveitis (AU) flares was 2.6/100 patient years. Eight cases were observed in 4 patients: 2 patients had one flare and the other 2 had 3 each. There was a history of AU in 3 patients. Thus, one case was a new onset.

Of the 9 patients in group 1a, 4 completed EASIC (44%), while 3 non-completers dropped out due to infusion reactions 97±22 days after screening, one due to lack of efficacy, and one was lost to follow-up. The mean BASDAI for group 1 decreased from 6.7±2.4 at EASIC baseline to 3.5±2.4 at the end, while the completers were at 1.6±1.3.

The 5 patients in group 1b had a mean BASDAI at baseline of 3±1.4 *vs*. 1.8±1.3 at week 96. Four patients relapsed after 61±50 days of which 3 were retreated with infliximab, one switched to adalimumab. The fifth patient remained in a good clinical condition at week 96 (BASDAI at baseline 2.4, at week 96 1.97). Two of the 3 retreated patients dropped out 89±29 days after retreatment, one due to an infusion reaction and the other due to lack of efficacy.

Infusion reactions occurred in 50% of patients in group 1 as compared to only 3.4% in group 2. Infusion reactions occurred in 0.3% in group 2 (4 infusions of 1147 infusions) and in 9.6% in group 1 (11 infusions of 114 infusions).

Discussion

EASIC is the first international investigator initiated open-label extension trial to study longterm outcomes of patients with AS treated with anti-TNF agents. As a follow-up study of ASSERT it also allows for comparisons between countries regarding post-trial care. The main result of this part of EASIC is that the majority of the patients had sustained clinical benefit and that

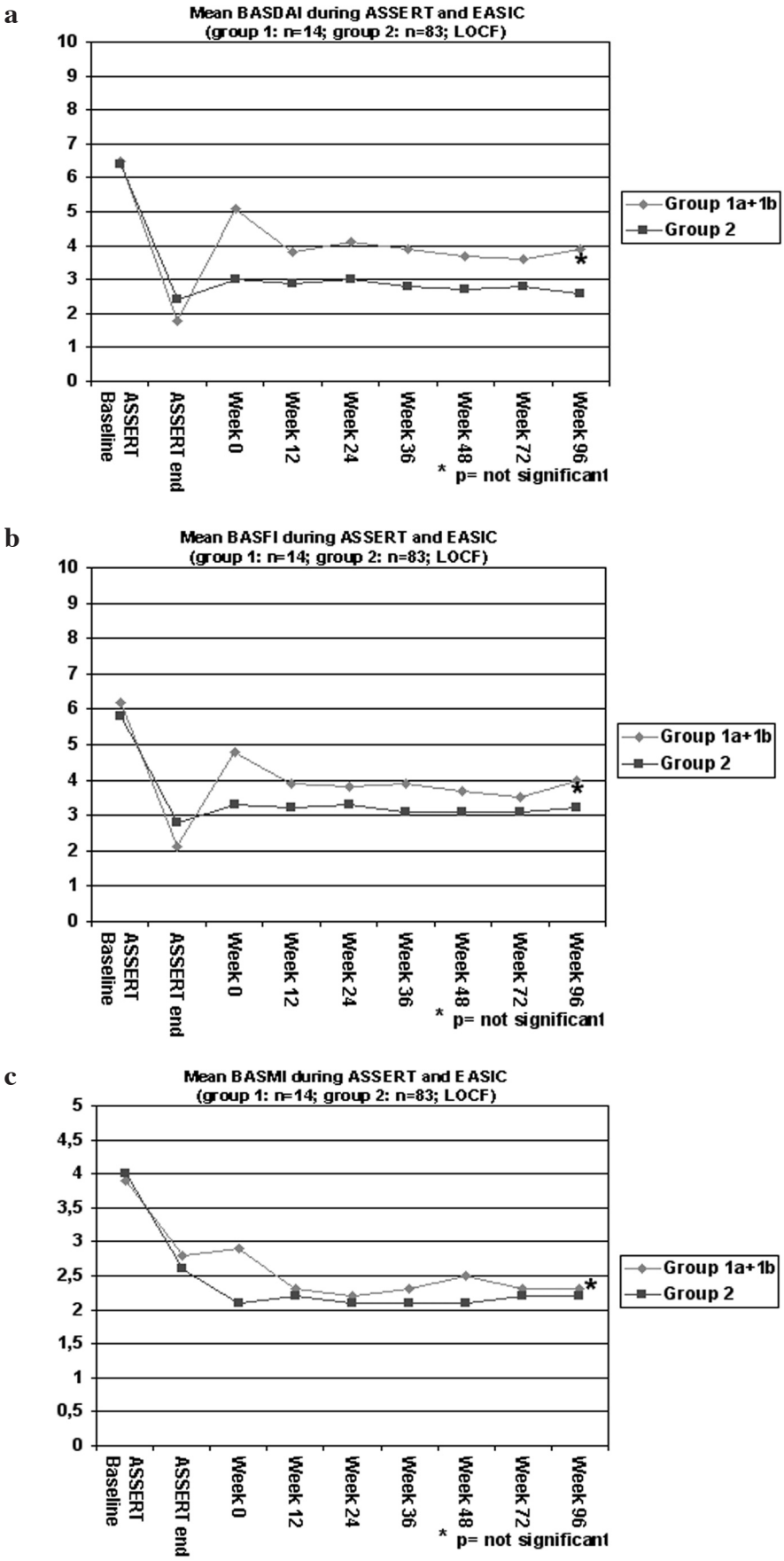

Fig. 3. Clinical assessment parameters in EASIC.

there were no new unexpected safety issues. Another important finding is that the discontinuation of therapy with infliximab very rarely leads to ongoing remission, and that reintroduction of infliximab therapy after a "drug holiday" is a frequent cause of allergic reactions and side effects.

Furthermore, it is noteworthy that the majority of the patients had been continuously treated with infliximab after the end of ASSERT.

The delay between the end of ASSERT and the start of EASIC was due to a variety of logistic reasons. In the interval between ASSERT and EASIC patients were treated by their rheumatologists, according to the local standard of care. Since most patients were continuously treated with infliximab the achieved percentage of 69% consenting for EASIC is a good result. EASIC was planned as a trial that reflects daily life in the treatment of AS patients. Therefore the patients who had already received infliximab could simply continue with the same dosage and dosing intervals. The mean dosage of 5mg/kg given every 6-8 weeks reflects the approval status of infliximab in AS and was comparable to ASSERT.

Because of the differences in national health care policies, the distribution between the EASIC subgroups was skewed to the group with 89 patients who had received infliximab continuously (group 2), while only 14 patients had interrupted therapy after ASSERT. This rather reflects that rheumatologists prefer continuous treatment – as recently suggested by data of a French trial (26).

The most important observation in the comparison between the groups was that the retention rates differed significantly: almost 92% of the patients in group 2 completed EASIC while this was only achieved by 42% of patients in group 1. The main explanation for this finding seems to be the increased frequency of infusion reactions in group 1 and the increased frequency of related drop-outs. These data are in some contrast to our earlier observations in a patient group that had discontinued therapy after 3 years (27, 28). Differences of the duration of drug holiday or

Table III. Adverse events in EASIC.

a: Overview of all adverse events (AE)	Number of AEs (% of all AEs)	
Total	545	
Infections	257	(47.2)
SAE	12	(2.2)
SAE: Infections	3	(0.6)
Opportunistic infections including Tb	0	
Infusion reactions /allergic reactions	20	(3.7)
Malignancies	0	
Elevation of liver enzymes	9	(1.6)
Worsening of AS	13	(2.4)
Other	246	(45.1)

Tb: tuberculosis

b: Overview of all infections	Number of infections (% of all infections)	
Total	257	
Upper respiratory infections (including ear infections)	178	(69.3)
Gastrointestinal infections	29	(11.3)
Urogenital infections	17	(6.6)
Skin infections	18	(7.0)
Other infections	15	(5.8)

the schedule of reintroduction (induction vs. single dose) may account for this difference.

Most patients completing EASIC had received infliximab for more than 5 years. The majority had a favourable disease related health and functional status and good response rates in line with earlier data on infliximab (13, 19) and other anti-TNF agents (29-31). Other clinical trials of shorter duration (5-9, 11, 26, 32) had comparable results, also for other anti-TNF agents (33-38). However, not only remission rates but also a state of low disease activity is important. In AS, there is no general consensus on such definition, a BASDAI value <3 has been proposed (39). This low disease activity threshold was reached in EASIC. Furthermore, low BASFI and BASMI values have been reported as important long-term outcome parameters (40). It is important to recognise that the function and spinal mobility of the AS patients in EASIC did not worsen over more than 5 years.

In general, the focus in long-term clinical studies is more on health status than on response rates, since it is of limited value to look at response in relation to baseline after 5 years. Nevertheless, major clinical responses in AS defined as BASDAI 50% or ASAS 40% improvement (41) were also favourable in EASIC. An important question related to the patients who do not fulfil ASAS 20 response criteria over time has been recently discussed in detail (19). The patients with type C responses seem to have benefit which is not easily measured by standard criteria.

TNF-blockers have been shown to work in patients with advanced spinal ankylosis (42-44). This subgroup analysis was not performed in EASIC.

In EASIC, long-term treatment with infliximab was safe for patients with AS. The most common adverse events during EASIC were infections, most of them in the upper respiratory tract including ear infections, but there were no opportunistic infections. As decribed, 3 SAEs were of infectious origin. The somewhat increased risk of infections in patients on anti-TNF therapy has been recently debated (45, 46).

There were no malignancies during EASIC including lymphomas. This is important because, in contrast to RA (47), patients with AS do not seem to have an increased risk of lymphoma (48). However, there has been no signal in any of the registries. Future long-term studies and registries with TNF-blockers are needed to shed more light on this important issue.

SpA are known to be associated with skin, gut and eye manifestations (3). The incidence of flares of inflammatory bowel disease or anterior uveitis was as low as previously reported (49-51).

Although TNF-blockers work very well in the treatment of psoriasis (52), there are some reports about the induction or exacerbation of skin psoriasis caused by anti-TNF treatment (53). Two cases of psoriasis occurred during 96 weeks of treatment but patients continued therapy.

The incidence of allergic infusion reactions is known to be at least in part related to the development of antibodies to the drug. This was associated with decreased efficacy of the drug (54). A higher incidence of allergic infusion reactions was seen in patients who discontinued infliximab in EASIC, this was different in another study with another design (27). Antibody titers to infliximab were not assessed in EASIC.

Taken together, EASIC provides meaningful long-term data on infliximab therapy in AS. The vast majority of patients is in a state of low disease activity or remission after 5 years of therapy and more than 60% have a major clinical response. Continuous therapy had better outcomes than discontinuation and re-administration. There were no new unexpected safety concerns over this period of time.

Key messages

- Anti-TNF therapy with infliximab provides long-term symptomatic benefit in patients with ankylosing spondylitis over more than 5 years.
- Long-term therapy with infliximab shows a favourable safety profile for patients with ankylosing spondylitis.
- Infusion reactions are less frequent in patients with continuous therapy than in patients with discontinued and reintroduced infliximab treatment.

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