ORIGINAL INVESTIGATIONS

Impact of the extraarticular manifestations on the efficacy and tolerability of seniprutug in radiographic axial spondyloarthritis: post hoc analysis of ELEFTA clinical trial

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Objective: *to assess the impact of extra-articular manifestations (EAM) on the achievement of clinical effect of seniprutug (SENI) in patients with active radiographic axial spondyloarthritis (r-axSpA) during 48 weeks of therapy.*

Material and methods. *A post hoc analysis of results from an international multicenter randomized placebo-controlled phase II clinical trial (CT) BCD-180-2/ELEFTA (ClinicalTrials.gov NCT05445076) involving HLA-B27 positive biologic-naive patients with active r-axSpA was conducted. The main results of the CT ELEFTA on the clinical efficacy and safety of SENI over 48 weeks of therapy have been previously published.*

A comparative post hoc analysis of SENI efficacy was conducted at week 48 in subgroups of patients with presence (n=48) and absence (n=212) of EAM, who received SENI at doses of 5 mg/kg or 7 mg/kg or Placebo/SENI 5 mg/kg. Efficacy parameters included dynamics in the ASDAS, BASFI, as well as total back pain intensity and night back pain scores on a numerical rating scale (NRS), and C-reactive protein (CRP) levels. Additionally, the frequency of achieving ASAS40, ASAS5/6 responses, ASDAS clinically important improvement (ASDAS-CII), and low disease activity or inactive disease according to ASDAS was analyzed.

The assessment of treatment tolerability included analysis of the frequency of worsening of existing EAM and the occurrence of cases of EAM de novo.

Results and discussion. *In both subgroups of patients with and without EAM of axSpA we observed decrease of CRP level with improvement of the disease activity according to the ASDAS index and improvement of functional impairments according to the BASFI index, as well as achievement of ASAS40 and ASAS5/6 responses and a reduction in of the total back pain and night back pain according to the NRS. Statistically significant superiority over placebo was demonstrated in the SENI subgroup without EAM at all efficacy parameters and at several assessment points in the SENI subgroup with EAM already in the first weeks of therapy and up to week 24. Further, the achieved clinical effect was maintained, up to week 48, in all SENI subgroups regardless of the presence of EAM, while in placebo subgroups, an increase in effect was observed due to switching to active drug therapy at week 24. In the SENI subgroup with EAM, a numerically more pronounced clinical effect was noted at the beginning of therapy without statistically significant differences compared to the SENI subgroup without EAM.*

In all studied subgroups, a favorable tolerability profile of SENI therapy was demonstrated. No EAM de novo was registered.

Conclusion. *SENI demonstrates significant stable clinical efficacy and good tolerability over 48 weeks of active r-axSpA treatment regardless of the presence or absence of EAM, with a trend to faster and more pronounced clinical effect in the first weeks of therapy in patients who had EAM.*

Key words: *seniprutug; radiographic axial spondyloarthritis; ankylosing spondylitis; extra-articular manifestations; TRBV9+ T-lymphocytes; anti-TRBV9-monoclonal antibody; biologic disease modifying anti-rheumatic drugs.*

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Axial spondyloarthritis (axSpA) is a chronic immunoinflammatory disease characterized by predominant involvement of the spine and sacroiliac joints, as well as the presence of genetic predisposition [1]. Among the genetic factors, the HLA-B27 antigen contributes most significantly to the development of the disease [2, 3]. In some patients with axSpA, in addition to axial skeleton involvement, peripheral arthritis, enthesitis, dactylitis are detected, as well as extraarticular manifestations of axSpA (EAMs), which include acute anterior uveitis, inflammatory bowel disease (IBD), and psoriasis [4]. Acute anterior uveitis is the most common EAM; its prevalence in axSpA is from 21% to 37% [5] and it is closely associated with HLA-B27 antigen carriage [4, 6]. At the same time, about 40% of patients diagnosed with acute anterior uveitis may have symptoms of axSpA, which is explained by similar immunopathogenic mechanisms of uveitis and axSpA development, in which the major histocompatibility complex class I (MHC-I) plays a significant role [7]. The presence of common genetic predisposition determines a higher frequency of acute anterior uveitis in HLA-B27-positive patients with axSpA [3]. At the same time, EAMs are observed more frequently in patients with axSpA against the background of active systemic inflammation, which reflects an unfavorable disease course [8]. In patients with radiographic axSpA (r-axSpA), the presence of EAMs, as well as comorbidities and smoking, determines an increase in overall mortality risk by more than 1.6 times (hazard ratio, HR 1.62; 95% confidence interval, CI 1.24–2.11) [3].

EAMs control is one of the most important components in achieving the treatment goals for axSpA along with inflammation suppression, improvement of function, and slowing structural damage [1]. Recurrent and refractory course of EAMs is an indication for revising the patient's management strategy and timely decision regarding the prescription of biologic disease-modifying antirheumatic drugs (bDMARDs). According to current clinical guidelines, tumor necrosis factor α inhibitors (iTNFα) are considered a priority therapeutic option for acute anterior uveitis and IBD associated with axSpA, whereas interleukin 17 inhibitors are recommended in the presence of psoriasis [1]. Expanding treatment approaches for r-axSpA, including patients with EAMs, remains an important ask.

Seniprutug (SENI) is an effector humanized monoclonal antibody to the TRBV9 segment of the T-cell receptor, which provides depletion of a limited pool of T-lymphocytes involved in the implementation of autoimmunity and triggering the immune-inflammatory process in r-axSpA. In a clinical trial including patients with r-axSpA or ankylosing spondylitis, SENI has demonstrated significant clinical efficacy and a favorable safety profile with a reduction in disease activity and functional impairments, regression of systemic inflammation, and improvement in dsmagnetic resonance imaging (MRI) parameters [9, 10], including in patients with r-axSpA and comorbidities [11]. In addition, according to data from an adjusted indirect comparison, SENI has showed statistically significant superiority over adalimumab in key efficacy endpoints by ASAS40 (Assessment of SpondyloArthritis International Society) and ASAS20 at week 24 in adult patients with r-axSpA [12].

The aim of this study was to assess the efficacy and tolerability of SENI depending on the presence or absence of EAMs in patients with active r-axSpA.

Materials and Methods. A post hoc analysis of the 48-week results of international, randomized, double-blind, placebo-controlled phase II ELEFTA study (ClinicalTrials.gov NCT05445076) was conducted, which included HLA-B27-positive patients with a confirmed diagnosis of active r-axSpA who had an inadequate response to nonsteroidal anti-inflammatory drug therapy and had not previously received bDMARDs or Janus kinase (JAK) inhibitors. The objective of the ELEFTA study was to evaluate clinical efficacy, safety, immunogenicity, pharmacokinetic and pharmacodynamic parameters of different doses of SENI. The inclusion criteria, study design, as well as the results of the placebo-controlled period and 48 weeks of SENI therapy were previously published [9, 11].

At the time of writing this article, the study is ongoing, the total duration of SENI therapy will be 156 weeks, and the patient observation period will be up to 160 weeks. In the presented work the assessment of efficacy and tolerability parameters was conducted at week 48.

For subgroup analysis, patients were divided into four subgroups: with and without EAMs, with further subdivision into those who received from the beginning of the study either SENI at doses of 5 mg/kg and 7 mg/kg or placebo, respectively.

EAMs were considered as pathological conditions developing in organs and tissues outside the musculoskeletal system but having common pathogenetic mechanisms with axSpA. Anterior uveitis, psoriasis and IBD (Crohn's disease or ulcerative colitis) were the key EAMs. Heart conduction system disorders, aortitis and IgA nephropathy could also be considered as EAMs provided that they were evaluated by a physician as a systemic manifestation of r-axSpA.

The following parameters were used for comparative analysis of the efficacy of SENI in patient subgroups: dynamics of the ASDAS (Ankylosing Spondylitis Disease Activity Score), BASFI (Bath Ankylosing Spondylitis Functional Index), overall back pain intensity (question #2 of the Bath Ankylosing Spondylitis Disease Activity Index – BASDAI), and night back pain intensity, assessed by the patients using a numerical rating scale (NRS), as well as C-reactive protein (CRP) concentration in blood (mg/l). In addition, in each subgroup, the relative number of patients who achieved ASDAS clinically important improvement (ASDAS-CII), 40% improvement according to ASAS criteria (ASAS40), improvement according to 5 out of 6 ASAS criteria (ASAS5/6), and low disease activity or inactive disease according to the ASDAS index (ASDAS <2.1) was determined. The presented parameters were assessed at weeks 1, 2, 4, 8, 12, 16, 24, 36 and 48.

Safety assessment results demonstrating a favorable profile of SENI therapy were presented earlier [9–11]. In the subgroup analysis, the tolerability of SENI therapy was evaluated based on

the exacerbation of existing EAMs or their de novo development during treatment.

Statistical analysis. The analysis of efficacy parameters was conducted in the FAS (full analysis set) population, which included 260 patients randomized into the ELEFTA study and receiving at least one dose of SENI or placebo. Subgroup distribution was performed according to the presence or absence of EAMs, regardless of the drug dose used: patients who received SENI at a dose of 5 mg/kg or 7 mg/kg were combined into one subpopulation.

For binary variables, the relative number of patients who achieved the specified endpoints was defined, and a generalized linear mixed effect model (GLMM) was used with the therapy group, visit, and the interaction factor of the group and visit as fixed effects, and subjects as a random effect. To model the variability between observations obtained for one subject, a common for all therapy groups covariance matrix (R-side matrix) with a first-order autoregressive structure (AR(1)) was used. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Odds ratios (OR) with 95% CI and p-values were defined for comparing the BCD-180 5 mg/kg or 7 mg/kg group and the Placebo/BCD-180 5 mg/kg group by subgroups with and without EAMs. For analysis of continuous variables, a mixed model repeated measures (MMRM) with similar fixed effects, covariance matrix structure, and method of estimating degrees of freedom was used. The results are presented as differences in adjusted means with 95% CI and p-values for comparing the BCD-180 5 mg/kg or 7 mg/kg group and the Placebo/BCD-180 5 mg/kg group by subgroups with and without EAMs.

Group differences were considered statistically significant at $p < 0.05$.

Missing values were not imputed; observations with missing outcome values were excluded from the analysis.

Results. A total of 260 patients with active r-axSpA were in-

Table 1. Baseline characteristics of patients

Parameter	Presence of EAMs (n=48)		No EAMs (n=212)		Differences between SENI subgroups with and without EAMs, p
	SENI (n=38)	Placebo (n=10)	SENI (n=172)	Placebo (n=40)	
Age, years	39,3±8,9	44,9±7,3	37,5±8,6	38,6±9,3	0,247
Male participants, n (%)	29 (76,3)	6 (60,0)	140 (81,4)	33 (82,5)	0,500
BMI, kg/m^2	24,9±3,8	28,8±6,3	25,4±4,9	26,3±4,4	0,470
Disease duration from the onset of symptoms, years	12,6±8,9	18,7±8,3	11,3±6,8	12,7±6,7	0,409
Disease duration from diagnosis, years	5,2±5,2	6,1±6,65	5,3±5,1	5,2±4,8	0,850
CRP, mg/L	21,4±17,6	18,8±14,0	23,9±22,4	23,2±17,8	0,452
ASDAS, score	4,0±0,7	3,9±0,9	4,0±0,8	4,0±1,0	0,707
Proportion of patients with very high activity according to ASDAS, n (%)	26 (68,4)	9 (90,0)	117 (68,0)	29 (72,5)	1,000
BASDAI, score	6,4±1,0	6,0±1,9	6,3±1,4	6,1±1,9	0,806
BASFI, score	4,1±1,7	5,2±2,0	5,0±2,2	5,1±2,5	0,007
Back pain according to the NRS	7,3±1,3	7,0±1,7	7,1±1,5	7,1±1,8	0,621
Nocturnal pain accordingto the NRS	6,1±2,4	5,6±1,9	6,3±2,0	6,5±2,1	0,584
Proportion of patients with swollen joints, n (%)	17 (44,7)	4 (40,0)	62 (36,0)	17 (42,5)	0,357
EAMs of axSpA, n (%):					
Uveitis	28 (73,7)	8 (80,0)	Нп	Нп	Нп
IBD	3 (7,9)	1 (10,0)	Нп	Нп	Нп
Psoriasis	6 (15,8)	1 (10,0)	Нп	Нп	Нп
Conduction disorders of the heart and aortitis	2 (5,3)	0	Нп	Нп	Нп

Note. Data are presented as M±SD unless otherwise specified. Categorical variables are presented as absolute and relative (percent) numbers of patients. NA, not applicable. BMI, body mass index.

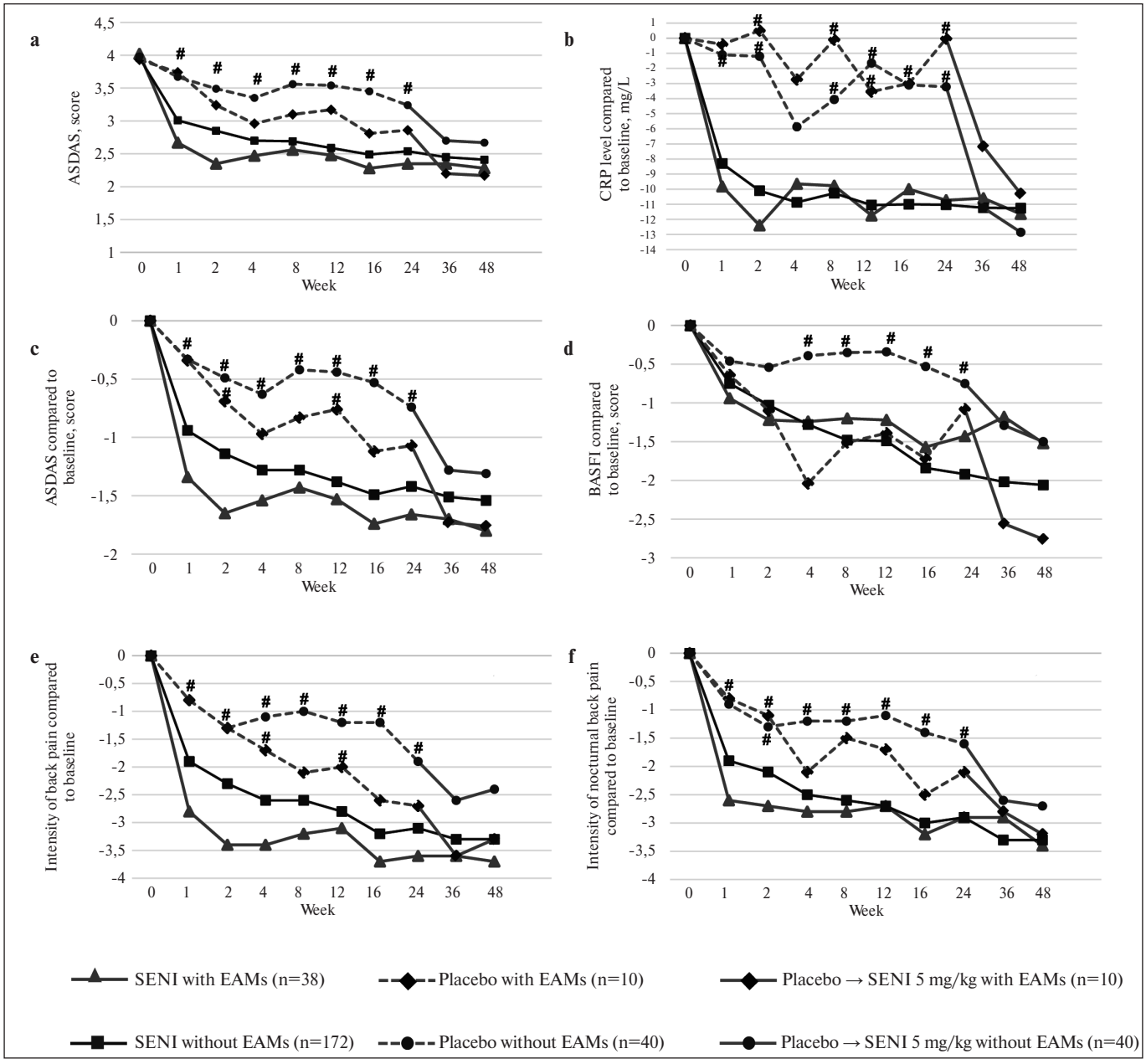

Fig. 1. *Dynamics of treatment efficacy outcomes in r-axSpA with SENI or placebo depending on the presence of EAM. # – statistically significant differences between the SENI subgroups and the placebo subgroups with and without EAM, respectively (p<0.05)*

cluded in the analysis and were divided into subgroups without EAMs (n=212) and with EAMs (n=48), of whom 172 and 38 patients, respectively, in each subgroup received SENI at a dose of 5 mg/kg or 7 mg/kg, or placebo with switching to SENI 5 mg/kg at week 24 - 40 and 10 patients, respectively. The baseline clinical-demographic characteristics of the subgroups are presented in Table 1. The mean age was about 40 years, with a predominance of men. The average duration of r-axSpA symptoms ranged from 11.3 to 18.7 years, the period from diagnosis to initiation of therapy averaged from 5.2 to 6.1 years. The disease activity was confirmed by high average levels of CRP and indices of ASDAS and BASDAI (averaging about 4 and 6 points, respectively). Approximately 70% of patients had very high disease activity according to ASDAS. Overall back pain and night back pain, assessed by patients on the NRS scale, indicated pronounced disease symptoms. About 40% of patients had peripheral joint involvement. Significant differences between subgroups were not found for the presented parameters, except for BASFI index, which had lower values in patients with EAMs receiving SENI therapy.

Among patients with EAMs, anterior uveitis was the most common manifestation, observed in 75% (36/48) of patients in the EAMs subgroup and in 13.8% (36/260) of all patients with r-axSpA. The least common were cardiac conduction disorders and aortitis, which were recorded in 2 (5.3%) patients with EAMs.

Efficacy assessment. The dynamics of efficacy parameters in patient subgroups are presented in Fig. 1 and 2. Positive dynamics

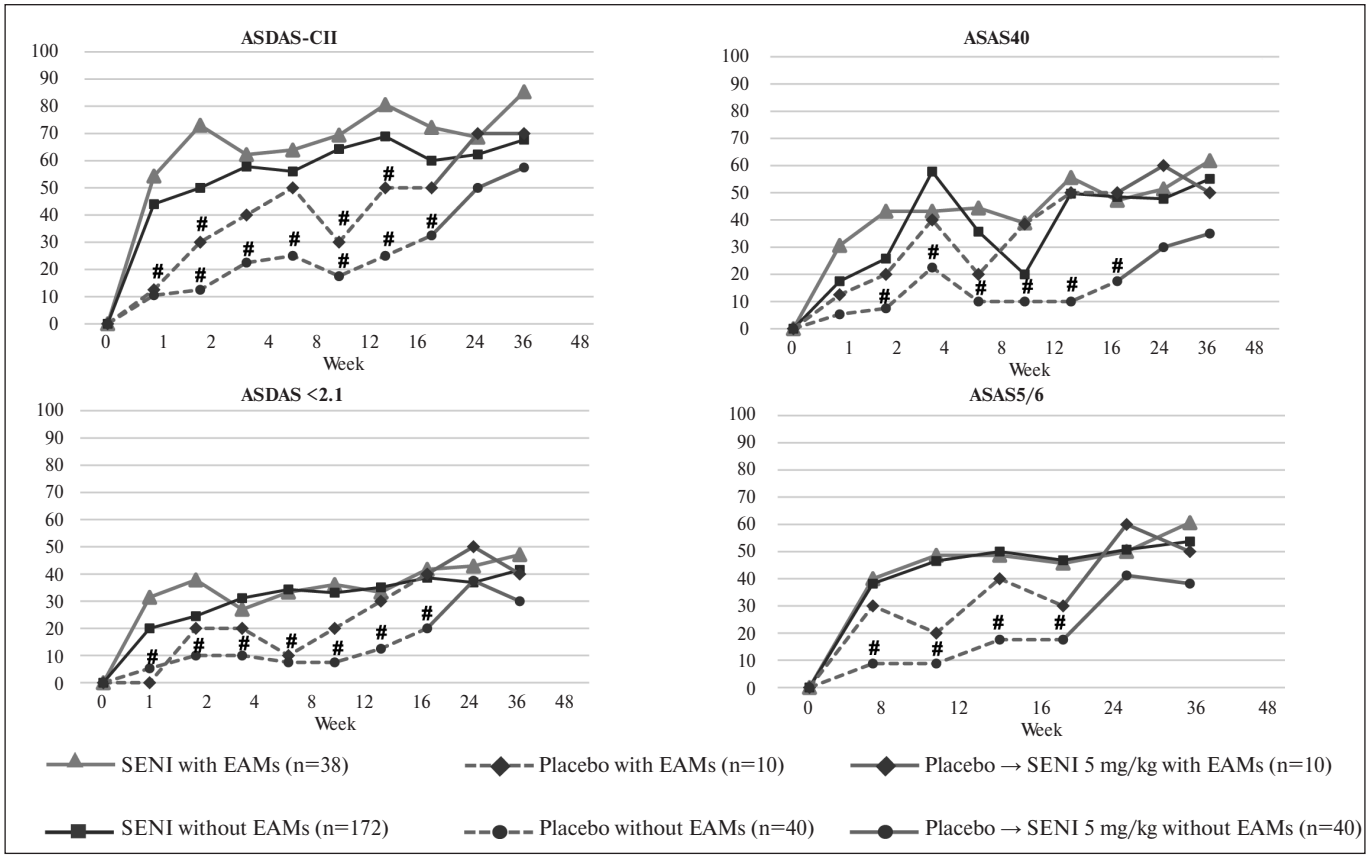

Fig. 2. *Dynamics of achieving efficacy parameters in subgroups according to the presence of EAM, % of patients. # – statistically significant differences between the SENI subgroups and the placebo subgroups with and without EAM, respectively (p<0.05)*

were noted in all evaluated efficacy parameters in both SENI subgroups, regardless of the presence of EAMs. In the subgroup of patients without EAMs receiving SENI therapy, statistically significant differences with the placebo subgroups were observed for most assessment points during the 24-week placebo-controlled period, while in the SENI subgroup with EAMs, differences were noted for some assessment points. After week 24 and up to week 48, positive changes in all efficacy parameters were observed in both placebo subgroups due to the switching of patients to therapy with SENI 5 mg/kg. More pronounced positive dynamics were identified in several efficacy parameters in the SENI subgroup with the presence of EAMs (see Figures 1 and 2).

The decrease in the ASDAS index (see Fig. 1. a) and its dynamics compared to the baseline level (see Fig. 1. c) show a similar pattern to the reduction in CRP concentration (see Fig. 1. b). Thus, the ASDAS index and CRP level in the SENI subgroups decreased as early as the first week of therapy, and positive dynamics were maintained throughout the observation period. At the same time, in the placebo subgroups, a significant decrease in CRP levels and the ASDAS index relative to baseline values occurred starting from week 24 and was due to switching the patients to treatment with SENI (see Fig. 1. a, b).

A positive trend in the BASFI index was observed in both the SENI subgroups and the placebo subgroup with EAMs (see Fig. 1. g). Throughout the placebo-controlled period, the change in the BASFI index in the SENI subgroup without EAMs was statistically more significant than in the placebo subgroup without EAMs, where a reduction in functional impairments occurred only after week 24 due to switching to therapy with SENI 5 mg/kg.

A reduction in back pain intensity, as well as night back pain, was noted in both SENI subgroups from the first week of therapy, and this positive trend persisted throughout the entire observation period (see Fig. 1. d, e). In the placebo subgroup without EAMs, the change in these parameters was statistically less significant compared to the SENI subgroup without EAMs during the period up to week 24, with subsequent marked positive dynamics after switching to SENI treatment and up to week 48.

When comparing the placebo subgroups at the beginning of the observation, it was found that patients with EAMs showed a numerically more pronounced change in ASDAS, BASFI indices, and CRP concentration, especially at weeks 4 and 16, which leveled off by the subsequent assessment points – weeks 8 and 24, respectively.

The achievement of ASDAS-CII, ASAS40, ASAS5/6, as well as low disease activity and inactive disease according to ASDAS was established in a significantly greater proportion of patients in the subgroups receiving SENI therapy compared to the placebo subgroups during the 24-week study (see Fig. 2). After week 24, the subgroups became comparable due to the switch of patients from the placebo subgroups to the active drug. The achieved efficacy parameters were maintained throughout the further observation period. At the same time, in the SENI subgroup with EAMs, more pronounced positive dynamics in achieving ASDAS-CII (see

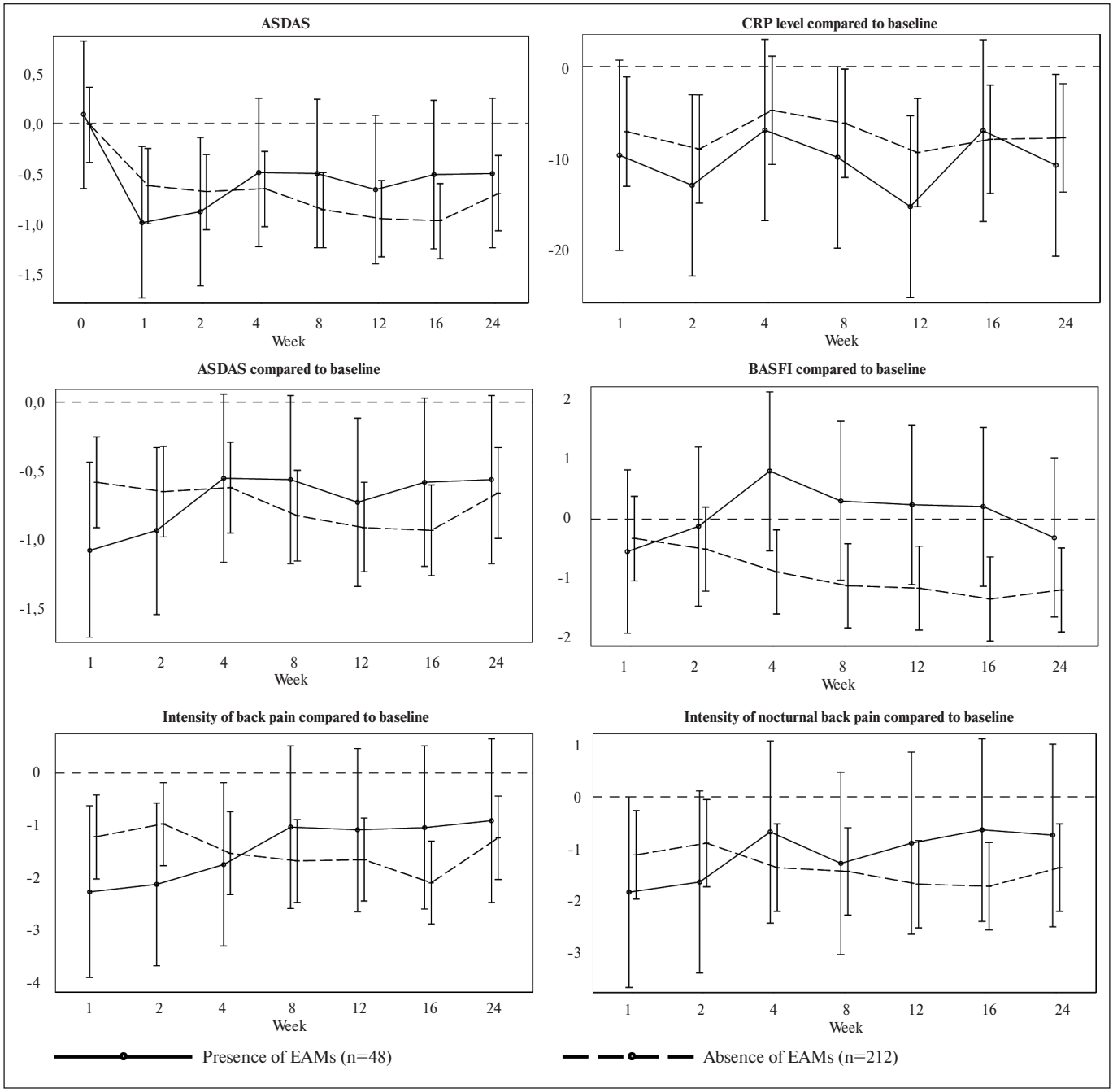

Fig. 3. *Comparison of the dynamics of efficacy parameters in the SENI and placebo groups (OR; 95% CI)*

Fig. 2. a), ASAS40 (see Fig. 2. b), as well as low disease activity and inactive disease according to ASDAS (see Fig. 2. c) were recorded in the first weeks of therapy compared to the SENI subgroup without EAMs. Subsequently, the results of achieving efficacy parameters in the SENI subgroups with and without EAMs were comparable.

The comparison of the dynamics of the efficacy parameters between subgroups does not allow for conclusions about the existence of differences in the effectiveness of the drug in patients with and without EAMs, considering the wide confidence intervals due to the limited size of the subgroup of patients with EAMs (Fig. 3. 4).

The favorable tolerability profile of SENI therapy was demonstrated in all studied subgroups. A single case of worsening of previously diagnosed moderate iridocyclitis was reported in a patient from the SENI 7 mg/kg group at week 35 of therapy, with symptoms regressing following a short course of topical GC and not requiring a change in the dosing regimen or discontinuation of SENI. According to the researchers' opinion, this adverse event was not related to therapy. During the observation period in the ELEFTA clinical trial, no cases of EAMs de novo were registered.

Discussion. The presence of EAMs in r-axSpA is a sign that allows for diagnosis and indicates higher disease activity and a poor

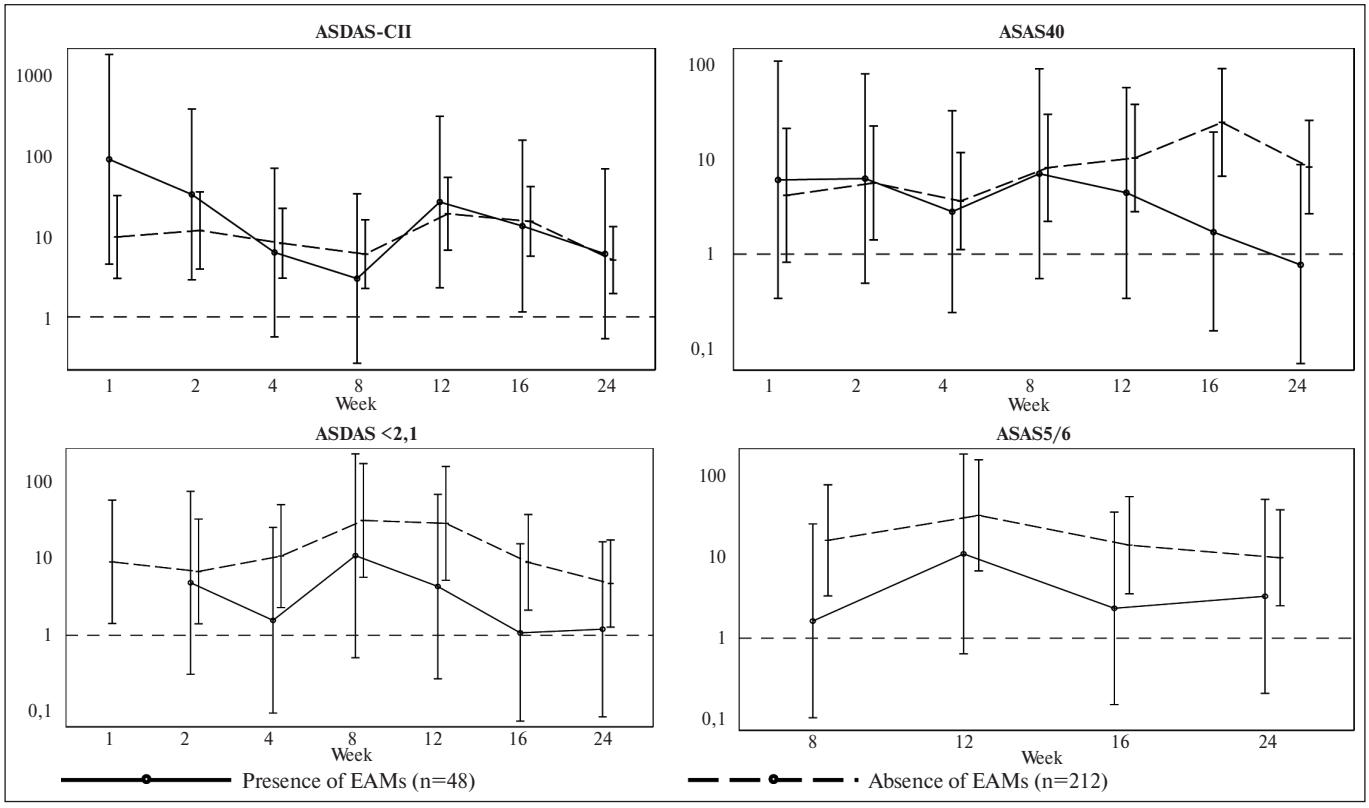

Fig. 4. *Comparison of the dynamics of achieving efficacy parameters in the SENI and placebo groups (OR; 95% CI)*

prognosis [13.14]. In the population of HLA-B27-positive patients with r-axSpA that we studied, uveitis was the most common EAM, occurring in 13.8% (36/260) of patients, which is consistent with literature data on its prevalence in axSpA patients [15] and is due to similar pathogenetic mechanisms associated with MHC-I, particularly the HLA-B27 antigen, and impaired recognition of self-peptides [16]. Cytotoxic TRBV9+ CD8+ T-lymphocytes play a significant role in the self-reactivity [17], and their targeted depletion using SENI demonstrates a pronounced clinical effect in patients with r-axSpA [9–12]. Accordingly, significant efficacy of anti-TRBV9 therapy with SENI can be expected in patients with EAMs, including those with anterior uveitis.

In our study, a pronounced clinical effect of SENI was demonstrated in subgroups of patients both with and without the presence of EAMs. Notably, there was a more pronounced effect of SENI therapy in the subgroup of patients with EAMs during the first weeks of therapy, especially at the 4-week assessment point. This fact can be explained by several aspects. Firstly, the presence of EAMs can be considered as a reflection of an active systemic process; in cases where therapy is correctly selected, such patients may exhibit more pronounced dynamics in efficacy parameters relative to baseline values. Secondly, the approach to SENI therapy includes premedication with glucocorticoids (GC), which themselves can influence the course of both axSpA and EAMs. This is confirmed by the positive dynamics of efficacy parameters in the subgroup of patients with EAMs who received placebo for 24 weeks. However, while in the placebo group the positive trend was followed by a deterioration in condition over approximately 4 weeks, corresponding to the cessation of prednisolone impact, in the SENI subgroup with EAMs, further improvement in efficacy parameters was observed throughout the entire observation period.

The identification of EAMs and their unfavorable course (pronounced, recurrent, and torpid nature of clinical manifestations) influence the choice of management tactics for patients with axSpA. According to current clinical guidelines [1], in the presence of such EAMs as uveitis and IBD, monoclonal antibodies to TNFα are considered as the preferred option for biologic therapy. It is known that approximately 30% of patients with r-axSpA experience a loss of effect after 2 years of treatment with TNFα inhibitors prescribed as the first-line therapy [18]. This means that development and study of drugs with alternative and innovative mechanisms of action are crucial. The present study provides data on the clinical efficacy of a fundamentally new approach involving the elimination of TRBV9+ T-cells that trigger mechanisms of self-reactivity and immune inflammation.

The presence of EAMs is associated with an increased overall mortality rate in patients with r-axSpA [3], which justifies an active management strategy, including the prescription of biologic therapy. At the same time, increased mortality is linked to infections, including serious infections observed in patients receiving TNFα inhibitors [3. 19]. Therefore, in addition to effective control of axSpA signs and EAMs, the choice of therapy that is safe regarding infectious complications is an important task. Anti-TRBV9 therapy with SENI has demonstrated a favorable safety profile with a low risk of infectious complications [9–11]. This fact is explained by the absence of significant immunosuppression due to the precise depletion of T-lymphocytes carrying the TRBV9 segment in their cell receptor, which constitute less than 5% of all T-cells. Considering the obtained results, SENI therapy

may be an optimal approach with a favorable balance of efficacy and safety for patients with r-axSpA and EAMs, especially those with acute anterior uveitis.

The conducted work is exploratory and has some limitations: a small subgroup size of patients with EAMs, which does not imply sufficient statistical power to identify intergroup differences depending on the presence or absence of EAMs. It seems necessary and promising to obtain additional data to compare the effect size of SENI between subgroups with and without EAMs in a larger number of patients and over a longer observation period.

Conclusion. SENI is characterized by significant stable clinical efficacy and good tolerability over 48 weeks of therapy for active r-axSpA, regardless of the presence or absence of EAMs, with a tendency for a faster and more pronounced development of clinical effect in the first weeks of therapy in the subgroup of patients with EAMs.

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