Efficacy and Safety of PEGylated Interferons for Relapsing-Remitting Multiple Sclerosis in Adult Patients: Results of Matching-Adjusted Indirect Comparison

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Abstract

Introduction. *Beta interferons are effective and safe agents for the treatment of relapsing-remitting multiple sclerosis (RRMS). PEGylated interferons have been developed in order to increase patient adherence. Direct comparisons of the efficacy and safety of PEGylated interferons have not yet been conducted.*

Our ***objective*** *was to evaluate the efficacy and safety of SamPEG-IFN-β1a versus PEG-IFN-β1a in adult patients with RRMS.*

Materials and methods. *We conducted a systematic search of randomized clinical trials (RCTs) using the PubMed, Embase and eLIBRARY.RU databases. Efficacy was assessed based on the proportion of patients with disease relapses and the annualized relapse rate (ARR) during the 1st and the 2nd years of treatment. Safety was assessed by the number of patients with adverse events (AEs), serious AEs (SAEs), and any AEs that led to the treatment discontinuation. We conducted pairwise matching-adjusted indirect comparison (MAIC) to assess comparative efficacy of PEGylated IFNs. To evaluate the efficacy, hypotheses of non-inferiority of SamPEG-IFN-β1a to PEG-IFN-β1a and superiority of SamPEG-IFN-β1a over PEG-IFN-β1a were tested.*

Results. *Based on results of the systematic review, four articles were selected wherein the results of phase 3 clinical trial of PEG-IFN-β1a and phase 2–3 clinical trial of SamPEG-IFN-β1a were described. In PEG-IFN-β1a group (n = 512) the agent was administered once every 2 weeks, in SamPEGIFN-β1a group (n = 114) the agent was administered at a dose of 240 μg. The analysis results confirmed the hypothesis of SamPEG-IFN-β1a non-inferiority to PEG-IFN-β1a in efficacy, while SamPEG-IFN-β1a superiority over PEG-IFN-β1a in efficacy was not confirmed. The hypothesis of SamPEG-IFN-β1a superiority over PEG-IFN-β1a in safety was also confirmed based on a significantly lower incidence of SAEs and any AEs that led to treatment discontinuation.*

Conclusions. *The proportion of patients with relapses and the ARR in 1 year and in 2 years of therapy indicates that SamPEG-IFN-β1a is non-inferior to PEG-IFN-β1a in efficacy. SamPEG-IFN-B1a demonstrated a more favourable safety profile than PEG-IFN-B1a as showing less odds of SAEs and AEs leading to treatment discontinuation.*

Keywords*: multiple sclerosis; immunomodulatory therapy; DMDs; PEGylated interferons; PEG-IFN-β1a; SamPEG-IFN-β1a; indirect comparison; efficacy; safety*

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Эффективность и безопасность пегилированных форм интерферона в лечении ремиттирующего рассеянного склероза у взрослых пациентов: результаты скорректированного непрямого сравнения

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Аннотация

Введение. *Препараты интерферона-β зарекомендовали себя как эффективные и безопасные препараты в лечении ремиттирующего рассеянного склероза (РРС). С целью повышения приверженности пациентов разработаны пегилированные формы интерферона. Прямого сравнения эффективности и безопасности пегилированных интерферонов между собой не проводилось.*

Цель: *оценка эффективности и безопасности применения сампэгинтерферона-β1а (СПИ) по сравнению с пэгинтерфероном-β1а (ПИ) у взрослых пациентов с РРС.*

Материал и методы. *Проведён систематический поиск рандомизированных клинических исследований в электронных базах данных PubMed, Embase и eLIBRARY.RU. Эффективность оценивали по доле пациентов с обострениями и среднегодовой частоте обострений на 1-м и 2-м годах терапии; безопасность – по числу пациентов с нежелательными явлениями (НЯ), серьёзными НЯ, любыми НЯ, приведшими к отмене терапии. Сравнительная оценка клинической эффективности пегилированных форм ИФН проводилась попарно методом скорректированного непрямого сравнения. Для оценки эффективности были выдвинуты гипотезы неменьшей эффективности и превосходства СПИ по сравнению с ПИ.*

Результаты. *По результатам систематического обзора были отобраны 4 статьи, описывающие результаты исследования III фазы для ПИ и исследования II–III фазы для СПИ. Общее количество участников в группе ПИ с режимом применения 1 раз в 2 нед – 512 человек, в группе СПИ в дозе 240 мкг – 114 человек. По результатам проведённого анализа подтверждена гипотеза неменьшей эффективности, но не гипотеза превосходства по эффективности препарата СПИ по сравнению с ПИ. Также подтверждена гипотеза превосходства СПИ над ПИ по безопасности, выражающаяся в значимо меньшей частоте серьёзных и любых НЯ, приведших к отмене терапии.*

Выводы. *По доле пациентов с обострениями и среднегодовой частоте обострений за 1 и 2 года терапии СПИ не менее эффективен, чем ПИ. Применение СПИ является более безопасным, чем ПИ, поскольку характеризуется существенно меньшими шансами развития серьёзных НЯ и любых НЯ, приводящих к отмене терапии.*

Ключевые слова*: рассеянный склероз; иммуномодулирующая терапия; препараты, изменяющие течение рассеянного склероза, пегилированные интерфероны; пэгинтерферон-бета 1а; сампэгинтерферон-бета 1а; непрямое сравнение; эффективность; безопасность*

Источник финансирования. Авторы заявляют об отсутствии внешних источников финансирования при проведении исследования.

Конфликт интересов. Сапожников К.В., Толкачева Д.Г., Соколова В.Д., Саблева Н.А., Мироненко О.Н., Химич Т.В. являлись сотрудниками АО «Биокад» на момент проведения исследования.

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Introduction

Beta interferons (IFN-β) are effective and safe agents for the treatment of relapsing-remitting multiple sclerosis (RRMS). However, the need of frequent dosing along with known adverse reactions (AR), including injection site reactions, make patients less adherent to the therapy, which results in higher risk of the disease relapse. To increase patient adherence, PEGylated IFNs were developed: peginterferon-β1a (PEG-IFN-β1a) and sampeginterferon-β1a (SamPEG-IFN-β1a). Both agents have the mechanism of action similar to that of IFN-β, belong to the class of disease-modifying drugs (DMDs) and may be prescribed as the first-line therapy for the RRMS patients aged ⩾ 18 [1–3].

IFN PEGylation significantly increases the hydrodynamic radius of the IFN molecule improving its pharmacokinetics, reducing fluctuations of IFN concentration in the blood due to lower levels of receptor- and antibody-mediated clearance and proteolysis, increasing the half-life of the molecule in the body and its general activity *in vivo* (along with decreased activity *in vitro*). PEGylated IFN-β are characterized by conjugation with a PEG molecule with a molecular weight increased to 30 kDa, so that IFN-β lasts longer in the body and can be used once in 14 days. SamPEG-IFN-β1a is characterized by the intramuscular route of administration [1, 2]. Moreover, IFN PEGylation might potentially decrease the antigenicity of the protein because PEG can inhibit recognition of antigenic epitopes in the IFN molecule by the immune system. Furthermore, PEGylation contributes to higher solubility and stability of the proteins, which is especially useful for the manufacturing and storage of the finished therapeutic proteins [1].

PEG-IFN-β1a is the first PEGylated IFN used for the treatment of RRMS patients. Its introduction into the clinical practice allowed not only to reduce the incidence of reported ARs, but also to increase patient compliance [3]. At the moment of systematic search and data synthesis, only subcutaneous dosage form of PEG-IFN-β1a was authorized in Russia (Plegridy, Biogen IDEC, Ltd.). Intramuscular dosage form was approved in 2023 and, according to its SmPC, is bioequivalent to the subcutaneous PEG-IFN-β1a[1].

SamPEG-IFN-β1a, the next in the line of PEGylated IFNs [1], was authorized in 2023 (Tenexia, JSC BIOCAD). This agent demonstrated superiority over low dose IFN-β [2]; however, there is no direct comparison with PEG-IFN-β1a, and this lack of evidence determines the relevance of our study.

The **objective** of the study was to evaluate clinical efficacy and safety of SamPEG-IFN-β1a vs PEG-IFN-β1a in adult patients with RRMS using matching-adjusted indirect comparison (MAIC).

Materials and methods

Systematic literature review

To gather the evidence on clinical efficacy and safety of SamPEG-IFN-β1a and PEG-IFN-β1a, three independent researchers conducted a systematic search of RCTs in PubMed, Embase and eLIBRARY.RU electronic databases. Date of the systematic search: February 4, 2022. The search strategy is presented in Appendix 1. Publications were selected by two independent researchers using EndNote X9.2 and MS Excel software.

The systematic review and further evidence synthesis were performed on publications describing the results of phases II and III clinical trials of SamPEG-IFN-β1a and PEG-IFN-β1a. The efficacy endpoints include the proportion of patients with the disease relapse and annualized relapse rate (ARR) for years 1 and 2 of the therapy. The safety outcomes are the proportion of patients with adverse events (AE), serious adverse events (SAE), and any AE led to treatment discontinuation over the first year of therapy. Additionally, data on the same parameters for 2 years of treatment were analyzed.

Target population consisted of the adult patients with the signs of active RRMS according to the clinical examination and diagnostic imaging data. The patients were either IFN (IFN-β1a, IFN-β1b)-naive or discontinued the IFN therapy at least 6 months prior to RCT.

In the selected publications, clinical and methodological heterogeneity was evaluated. Risk of bias was assessed by the Cochrane risk-of-bias tool (RoB2) [4].

If the total number of relapses in the comparator agent group was unavailable, it was calculated from the ARR confidence interval (CI) using the formula for its standard error.

Evidence synthesis

Due to the absence of the common comparator efficacy endpoints were compared between PEGylated IFNs by the pairwise unanchored MAIC. Hypotheses of non-inferiority of SamPEG-IFN-β1a to PEG-IFN-β1a and superiority of SamPEG-IFN-β1a over PEG-IFN-β1a at years 1 and 2 were tested. Confidence limits from ADVANCE clinical trial [5, 6] for the relative PEG-IFN-β1a efficacy versus placebo and versus delayed treatment were used as pre-specified margins for non-inferiority and superiority, respectively (Table 1). Superiority hypothesis without a margin was tested for each safety endpoint.

[1] Plegridy, 125 μg, solution for intramuscular injection. Summary of Product Characteristics (SmPC) ЛП-№ (003419)-(РГ-RU). URL: https://lk.regmed.ru/Register/EAEU_SmPC

Table 1. Margins for non-inferiority of SamPEG-IFN-β1a to PEG-IFN-β1a and for superiority of SamPEG-IFN-β1a over PEG-IFN-β1a at year 1 and year 2 of the treatment

Parameter	Assessment time point	Non-inferiority margin	Superiority margin
ARR ratio	1 year	≤ 2.0	≤ 0.5
	2 years	≤ 2.0	≤ 0.5
Relapse Odds Ratio	1 year	≤ 2.5	≤ 0.4
	2 years	≤ 2.5	≤ 0.4

For data analysis, R-Studio 2022.07.2 software was used (R version 4.2.1, maic package). Individual patient data on the efficacy and safety of SamPEG-IFN-β1a, as well as on therapy effect modifiers, were obtained in the clinical trial BCD-054-2 (RCT register No. 237 from April 28, 2017). Effect modifiers included all possible predictors of the ARR in RRMS patients, and their list was prespecified before the analysis. The SamPEG-IFN-β1a study population was weighted for the values of these effect modifiers derived from the selected trials for the comparator (PEG-IFN-β1a) using the Newton–Raphson method. Adjusted (weighted) and unadjusted odds ratios (OR) of relapse or AEs for years 1 and 2 of the treatment were estimated using logistic regression with robust CIs. The adequacy of the adjustment for the effect modifiers was assessed by comparing the effective sample size to the initial sample size of the SamPEG-IFN-β1a study population.

Results

Systematic search results

Systematic search yielded five articles (three in English and two in Russian) reporting the results of phase III ADVANCE clinical trial for PEG-IFN-β1a [5–7] and phase II–III clinical study for SamPEG-IFN-β1 (Clinical trial ID: NCT02744222) [1, 2]. The search strategy is available on the journal website in Appendix 1, article selection results are presented in the form of a PRISMA diagram in Appendix 2.

Overview of the selected trials and target population

In ADVANCE randomized, double-blind, controlled clinical trial of PEG-IFN-β1a vs placebo, the PEG-IFN-β1a

Table 2. Population parameters in SamPEG-IFN-β1a and PEG-IFN-β1a trials

Parameter	Patients receiving SamPEG-IFN-β1a	Patients receiving PEG-IFN-β1a
Number of participants	114	512
Age, years; *M* ± σ	33.8 ± 9.0	36.9 ± 9.8
Females, *n* (%)	75 (65.8%)	361 (70.5%)
Screening EDSS score; *M* ± σ	2.43 ± 1.00	2.47 ± 1.26
Confirmed MS diagnosis, years ago; *M* ± σ	1.5 ± 2.2	4.0 ± 5.1
MS symptom onset, years ago; *M* ± σ	5.5 ± 5.5	6.9 ± 6.6
DMD-experienced patients, *n* (%)	29 (24.6%)	95 (18.6%)
Relapse rate in the last year; *M* ± σ	1.3 ± 0.6	2.6 ± 1.0
T2-weighted MRI lesions; *M* ± σ	50.7 ± 41.5	48.1 ± 36.8
Contrast-enhancing lesions in T1-weighted MRI; *M* ± σ	1.3 ± 3.4	1.2 ± 3.4
Patients without GD^+ MRI lesions at screening, *n* (%)	73 (64.0%)	334 (65.2%)

Note. *M* — mean value, σ — standard deviation.

Table 3. Primary efficacy endpoints for PEGylated IFNs

Parameter	Assessment time point	Patients receiving SamPEG-IFN-β1a	Patients receiving PEG-IFN-β1a
ARR, relapses/year (95% CI)	1 year	0.13 (0.08–0.23)	0.26 (0.21–0.32)
	2 years	0.11 (0.07–0.17)	0.22 (0.18–0.27)
Proportion of patients with relapses, *n/N* (%)	1 year	13/114 (11.4%)	90/512 (17.6%)
	2 years	19/114 (16.7%)	124/512 (24.2%)
Proportion of patients with any AE, *n/N* (%)	1 year	108/114 (94.7%)	481/512 (93.9%)
	2 years	109/114 (95.6%)	699/740 (94.5%)
Proportion of patients with any SAE, *n/N* (%)	1 year	1/114 (0.9%)	55/512 (10.7%)
	2 years	4/114 (3.5%)	120/740 (16.2%)
Proportion of patients with AEs/SAEs led to treatment discontinuation, *n/N* (%)	1 year	2/114 (1.8%)	25/512 (4.9%)
	2 years	2/114 (1.8%)	41/740 (5.5%)

Note. *n* — number of patients with a registered event; *N* — total number of observations; % – proportion of patients with a registered event in the total number of patients.

group (n = 512) received study agent once every 2 weeks. NCT02744222 is a randomized, double-blind clinical trial aimed at comparison of two doses of SamPEG-IFN-β1 vs placebo and vs intramuscular IFN-β1a injection. 114 participants were assigned to SamPEG-IFN-β1 240 μg group.

Baseline clinical parameters of each trial participant are presented in Table 2.

Assessment of selected efficacy endpoints

Baseline efficacy and safety data for PEGylated IFNs are presented in Table 3. In the SamPEG-IFN-β1a group, ARR was calculated as the ratio of the total number of relapses during the period to the total number of patient years for patients who received at least 1 dose of the agent. In year 1 of the treatment there were 14 events per 104.26 patient years; in year 2 – 22 events per 194.49 patient years.

Risk of bias assessment

The risk of bias in both RCTs (NCT00906399[2] and NCT02744222[3]) was considered low [7, 8]. See Appendix 3 on the journal website.

[2] Efficacy and Safety Study of Peginterferon Beta-1a in Participants with Relapsing Multiple Sclerosis (ADVANCE). URL: https://clinicaltrials.gov/study/NCT00906399

[3] Comparative Clinical Trial to Evaluate Efficacy, Safety and Tolerance of BCD-054 and Avonex® for Treatment of Patients with Remitting-relapsing Multiple Sclerosis. https://clinicaltrials.gov/study/NCT02744222

Effect modifiers

To achieve comparability between populations, the following baseline characteristics were considered as effect modifiers: patient age, EDSS scores, and the relapse rate over the last year. The list of effect modifiers was prespecified based on the clinical guidelines for multiple sclerosis.

The choice of the first-line DMD therapy for each patient is determined by the clinical course of MS, patient's age, and EDSS score. The first-line DMDs are not recommended for the fulminate MS determined, inter alia, by the relapse rate in year 1 of follow-up. For this reason, relapse rate in the last year was classified as a balancing criterion. Descriptive statistics for all effect modifiers were presented in in the ADVANCE clinical trial, as well [5, 7].

Results of matching-adjusted indirect comparison

Target values for descriptive statistics for effect modifiers, as well as their values in the SamPEG-IFN-β1a group before and after adjustment are presented in Table 4. The effective sample size (n = 77) can be considered as slightly different from the SamPEG-IFN-β1a initial sample size (n = 114).

MAIC results for efficacy endpoints are presented in Figures 1 and 2.

Table 4. Target and mean values of effect modifiers in SamPEG-IFN-β1a group prior to and after adjustment

Effect modifier	Target value	Unadjusted value	Adjusted value
EDSS score	2.47	2.4	2.4699
Age, years	36.9	33.8	36.8997
Relapse rate in the last year	1.6	1.3	1.6000

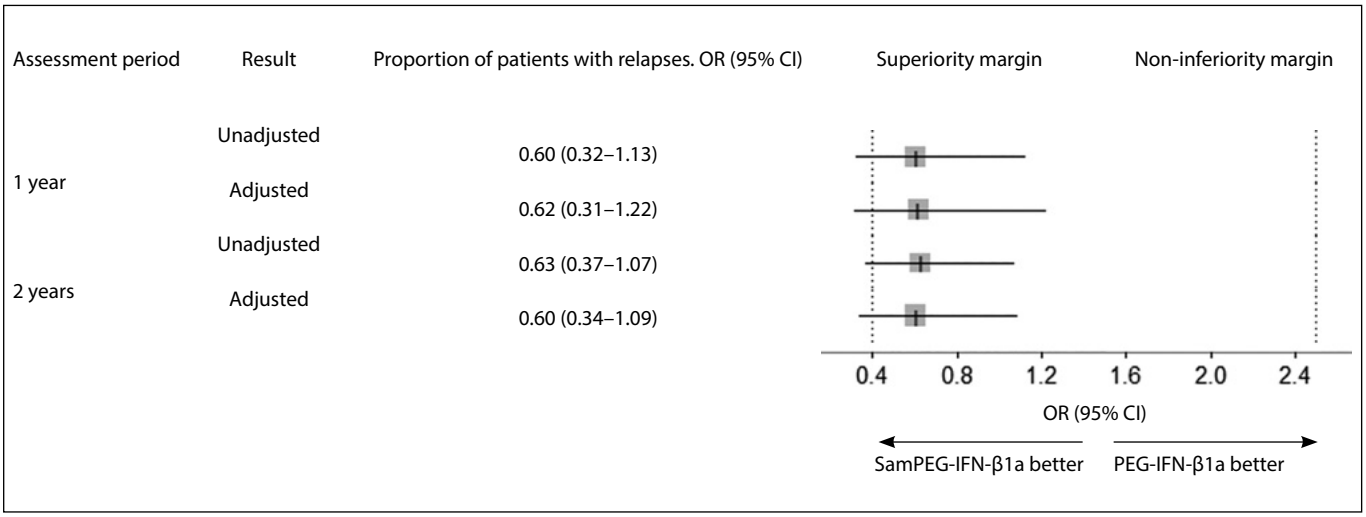

Fig. 1. SamPEG-IFN-β1a vs PEG-IFN-β1a: odds ratio for relapses of multiple sclerosis.
Note: CI – confidence interval; OR – odds ratio.

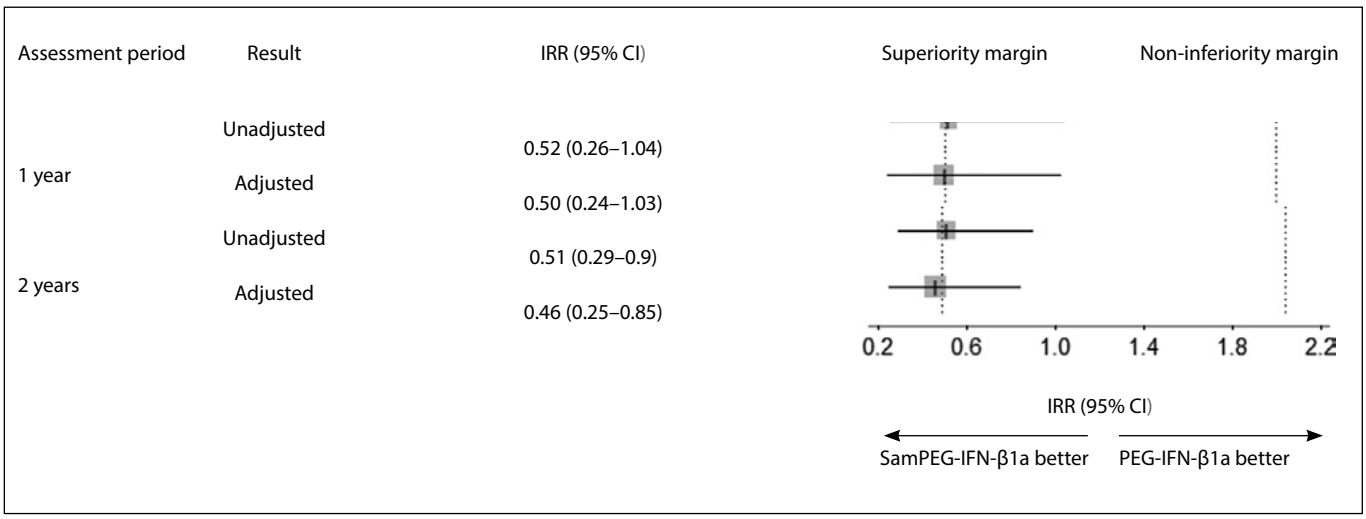

Fig. 2. SamPEG-IFN-β1a vs PEG-IFN-β1a: annualized relapse rate.
IRR – incidence rate ratio.

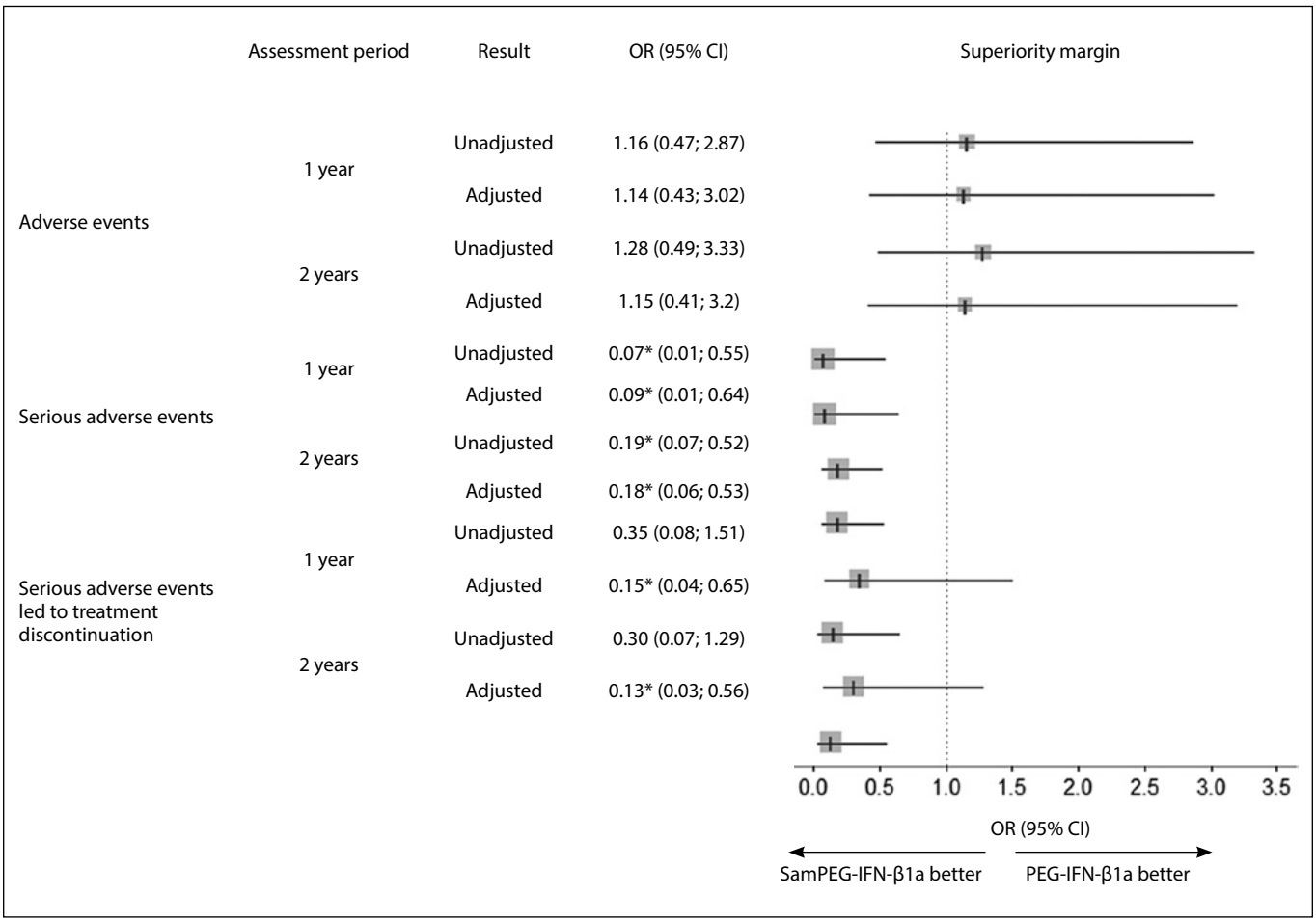

Fig. 3. SamPEG-IFN-β1a vs PEG-IFN-β1a: odds ratio for various categories of adverse events.
*Statistically significant difference.

MAIC results for safety endpoints are presented in Figure 3.

Based on the results of our study, the hypothesis of non-inferiority of SamPEG-IFN-β1a to PEG-IFN-β1a was confirmed, while the hypothesis of superiority of SamPEG-IFN-β1a over PEG-IFN-β1a in efficacy was not confirmed. We also confirmed the hypothesis of SamPEG-IFN-β1a superiority over PEG-IFN-β1a in safety, based on a significantly lower odds of SAE and any AE led to treatment discontinuation.

Discussion

Beta interferons are effective and safe agents playing an important role in the treatment of RRMS[4]. All IFN-β types share the same mechanism of action, but differ in dosing regimen and route of administration. IFN-β1b and IFN-β1a administered subcutaneously require frequent high-dose administration (high-dose IFN-β), while IFN-β1a administered intramuscularly can be used in a relatively small dose (low-dose IFN-β). PEG-IFN-β1a can be administered either subcutaneously or intramuscularly once every 2 weeks [3]. SamPEG-IFN-β1a is administered intramuscularly once every 2 weeks, which allows for longer intervals between injections increasing patient adherence due to a lower incidence of injection site AEs [1, 2].

MAIC was used to estimate clinical efficacy and safety of SamPEG-IFN-β1a vs PEG-IFN-β1a in adult patients with signs of RRMS activity as evidenced by clinical examination or diagnostic imaging results. Patients were either IFN-experienced (IFN-β1a, IFN-β1b) or had discontinued IFN therapy for at least 6 months prior to the enrollment in an RCT. The results of our analysis demonstrated non-inferiority of SamPEG-IFN-β1a to PEG-IFN-β1a in this patient population. Efficacy endpoints included the proportion of patients with relapses and ARR in 1 year and in 2 years of treatment. These estimands are used for DMD efficacy evaluation according to NEDA criteria (No Evidence of Disease Activity), according to which the optimal response to DMD therapy is determined by the

[4] Ministry of Health of the Russian Federation, Guidelines for Multiple Sclerosis, 2022, published on July 13, 2022.

absence of relapses, absence of progression of neurological deficit during the follow-up period, and absence of the MRI signs of disease activity. Safety endpoints included the number of patients with AEs, SAEs, and AE led to the treatment discontinuation. In the SamPEG-IFN-β1a trial, the severity of any registered AE or deviation in laboratory results was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) recommended by the National Cancer Institute of the United States and used in European RCTs [2].

There is no literature available on the direct comparison of PEGylated interferons-β for RRMS, which makes it relevant to continue the research to obtain results of direct comparison. Existing data from comparative meta-analyses on the use of non-PEGylated IFN-β demonstrates their comparable clinical efficacy. So, meta-analysis data presented by T.R. Einarson et al. showed that clinical profiles of Avonex (low-dose IFN-β1a), Rebif® (high-dose IFN-β1a), and Betaseron® (high-dose IFN-β1b) were similar [9]. At the same time, there is data indicating that the high-dose IFN-β therapy is more effective compared to low-dose IFN-β therapy. A systematic review of comparative trials conducted by B.J. Oliver et al. demonstrated that high-dose IFN-β treatment was superior to low-dose IFN-β treatment for relapse control and stability of MRI results [10]. The results of the direct comparative EVIDENCE study showed that treatment with subcutaneous high-dose IFN-β1a was associated with the significant decrease in clinical and imaging signs of disease activity over 1–2 years compared to intramuscular low-dose IFN-β1a treatment [11]. Recent data on SamPEG-IFN-β1a 240 μg confirmed its superiority over low-dose IFN-beta1a in efficacy, as evidenced by a longer period till the next relapse [2].

Non-PEGylated IFN-β are effective and safe agents playing an important role in the treatment of RRMS [3]. However, frequent dosing leads to the decrease in patient adherence. SamPEG-IFN-β1a and PEG-IFN-β1a allow to increase intervals between the injections and require less frequent dosing: once every 2 weeks [1, 2]. It is also known, that IFN-β agents (IFN-β1a and IFN-β1b) are immunogenic and their use is associated with an increased level of neutralizing antibodies (NAbs) to IFN-β. It has been proven that neutralizing antibodies can reduce the clinical effectiveness of IFN-β agents in patients with multiple sclerosis. The NAb development rate in patients receiving non-PEGylated IFN-β ranges from 5.6% to 44% [12]. PEGylated IFNs are known to cause less NAb development. According to the ADVANCE study, 4.63% of patients[5] treated with SamPEG-IFN-β1a and less than 1% patients treated with PEG-IFN-β1a develop NAbs [5].

The subcutaneous route of administration is associated with the lower incidence of injection site adverse reactions [1, 2, 13]. Direct comparative study on effects of subcutaneous vs intramuscular PEG-IFN-β1a showed that intramuscular administration was associated with a lower incidence of injection site events, which are a key factor of the non-adherence or therapy discontinuation among RRMS patients receiving DMD injections [13].

Limitations. Any indirect comparison is inevitably associated with limitations. Although using individual patient data was the only way to adjust for differences between studies in the conducted indirect comparison, the lack of a common comparator group is a significant limitation, as it makes validation of matching and assessment of relative effects impossible. At the same time, this method of analysis is widely recognized both in Russia[6] and worldwide.

Matching-adjusted indirect comparison allowed to take into account only observable and measurable effect modifiers, excluding any unobservable ones. Nevertheless, the effective sample size after weighting showed sufficient statistical power of the comparisons made.

We compared the data on efficacy and safety of intramuscular SamPEG-IFN-β1a vs subcutaneous PEG-IFN-β1a due to insufficient evidence database on intramuscular administration of a comparator agent: our systematic review only yielded phase I clinical trial on bioequivalence of two PEG-IFN-β1a dosage forms in healthy volunteers conducted by Y. Zhao et al. [13], which did not meet inclusion criteria of the review.

Compared to the number of patients included in the ADVANCE RCT, data for SamPEG-IFN-β1a from BCD-054-2 RCT was obtained for relatively smaller sample, which may limit the power of statistical inference. The analysis is to be updated after post-marketing studies of SamPEG-IFN-β1a. We will use hybrid individual patient data for MAIC, as it was done in the study of treatment options for patients with melanoma [14].

In clinical trials conducted in Russia and Eastern Europe, AEs are reported reluctantly [15], which may also affect the BCD-054-2 trial results. At the same time, registration of SAEs and AEs led to treatment discontinuation depends much on the medical personnel qualification, thus, including them into the analysis compensates this limitation.

The approach we used for setting up the margins for non-inferiority for ARR ratio and odds ratio of relapse (inverse value of the lower 95% CI limit for respective

[5] Summary of Product Characteristics TENEXIA®, ЛП-N=(002167)-(РГ-RU) from 13.04.2023. URL: https://tenexia.ru/v1_1.3.1%20Проект%20ОХЛП_SPC.054.1.EAEU-RU.01.07%20(1467910531)%20штамп%20М3.pdf

[6] Methodological guideline for indirect comparison of drug products. Approved by the Center for Healthcare Quality Assessment and Control of the Ministry of Health of the Russian Federation, order No.181-од. from December 29, 2017.

endpoints from clinical trial of PEG-IFN-β1a vs placebo or vs delayed treatment) cannot be considered conservative, as according to this approach any SamPEG-IFN-β1a superiority over placebo or delayed treatment would mean its non-inferiority to PEG-IFN-β1a. On the other hand, less conservative approach is acceptable if a study agent is superior in safety, which was expected for SamPEG-IFN-β1a, namely in the lower incidence of injection site AE due to intramuscular administration instead of PEG-IFN-β1a subcutaneous administration. Moreover, the results obtained in our study show that SamPEG-IFN-β1a non-inferiority could have also been confirmed with the more conservative margin for non-inferiority, as if we compared this parameter with a certain positive effect of PEG-IFN-β1a.

The studied therapy options were not compared by any secondary efficacy endpoints, namely, by the duration of period till the next relapse and by confirmed disability progression. This can be considered as another limitation of this study. Due to the limited number of patients, no comparison in subgroups was conducted (i.e., DMT-naive and DMT-experienced patients, etc.).

Despite the stated limitations, we expect the results of this indirect comparison to be reliable and justified due to the high quality of the data and due to the fact that all the assessments were adjusted for clinically significant effect modifiers.

Conclusion

This study presents the results of the unanchored matching-adjusted indirect comparison of SamPEG-IFN-β1a and PEG-IFN-β1a as the first-line therapy in adult patients with signs of RRMS activity based on data collected during a 2-year follow-up period.

The results of indirect comparison indicate that first-line SamPEG-IFN-β1a therapy is non-inferior to PEG-IFN-β1a first-line therapy. This conclusion is based on the proportion of patients with MS relapses and ARR over 1 year and 2 years of the treatment. In addition, the odds of SAEs and any AE led to discontinuation of the treatment is significantly smaller for SamPEG-IFN-β1a in comparison to PEG-IFN-β1a.

This study might help clinicians in choosing first-line therapy for adult patients with the signs of RRMS activity based on clinical examination or diagnostic imaging results.

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