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Title: Neurofilament light chain response during therapy with antisense oligonucleotide Tofersen in SOD1-related ALS – treatment experience in clinical practice.

Running title: Tofersen in SOD1-ALS

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We, the authors, confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Abstract

Introduction/Aims: In amyotrophic lateral sclerosis (ALS) caused by superoxide dismutase 1 (*SOD1*) gene mutations (SOD1-ALS), the antisense oligonucleotide tofersen had been investigated in a phase 3 study (VALOR) and subsequently introduced in an expanded access program. This study assesses neurofilament light chain (NfL) before and during tofersen treatment.

Methods: In six SOD1-ALS patients treated with tofersen at three specialized ALS centers in Germany, NfL in cerebrospinal fluid (CSF-NfL) and/or serum (sNfL), the ALS Functional Rating Scale–Revised (ALSFRS-R), and ALS progression rate (ALS-PR), defined by monthly decline of ALSFRS-R, were investigated.

Results: Three of six SOD1-ALS patients reported a negative family history. Three patients harbored a homozygous c.272A>C, p.(Asp91Ala) mutation. These and two other patients showed slower progressing ALS (defined by ALS-PR <0.9) whereas one patient demonstrated rapidly progressing ALS (ALS-PR=2.66). Mean treatment duration was 6.5 months (range 5-8). In all patients, NfL decreased (mean CSF-NfL -66%, range -52 to -86%, mean sNfL -62%, range -36 to -84%). sNfL at 5 months of tofersen was significantly reduced compared to the measurement closest before treatment (p=0.017). ALS-PR decreased in two patients whereas no changes in ALSFRS-R were observed in four participants who had very low ALS-PR or ALSFRS-R values before treatment.

Discussion: In this case series, the significant NfL decline following tofersen treatment confirmed its value as response biomarker in an expanded clinical spectrum of SOD1-ALS. Given the previously reported strong correlation between sNfL and ALS progression, the NfL treatment response contributes to the notion of disease-modifying activity of tofersen.

Keywords: amyotrophic lateral sclerosis (ALS), Tofersen, neurofilament light chain (NfL)

INTRODUCTION

In approximately 2% of people with amyotrophic lateral sclerosis (ALS), disease-causative, toxic gain-of-function mutations in the gene encoding superoxide dismutase 1 (*SOD1*) are found.[1,2] Tofersen is an intrathecally administered antisense oligonucleotide degrading the SOD1-messenger RNA and reducing SOD1 protein levels.[3,4] Recently, tofersen has been investigated in a phase 3 trial (VALOR study) that yielded a complex outcome, as the primary endpoint of Functional Rating Scale–Revised (ALSFRS-R) did not reveal statistical significance while trends favored tofersen across secondary endpoints, including neurofilament light chain (NfL).[5,6,7] These early reductions in NfL – as observed in VALOR – preceded the further slowing of ALSFRS-R decline during the open-label extension study.[5] The effect of tofersen on NfL was of particular relevance as NfL is an established prognostic biomarker of ALS for which a close correlation between NfL, ALS progression and survival has been demonstrated.[8-12] Based on the positive signals from the phase 3 trial, an expanded access program (EAP) was started in which tofersen is provided to ALS patients with *SOD1* gene mutations (SOD1-ALS) outside of clinical trials. In Germany, the EAP was authorized in February 2022. Prior to the tofersen EAP, a large-scale multicenter NfL study was initiated, in which longitudinal clinical and serum NfL (sNfL) data are collected. This combination of the EAP with the ongoing NfL study provided a window of opportunity to analyze the clinical and biomarker course before and during tofersen treatment.

METHODS

Study design

This study is a secondary use of existing data. The investigation was reported according to the STROBE criteria.[13]

Studied cohort

Data analysis was performed in patients fulfilling three selection main criteria: 1) diagnosis of ALS, 2) harboring an *SOD1* gene mutation, 3) treatment with tofersen for at least 5 months.

Setting

Access to existing data

Patients at 3 multidisciplinary ALS centers in Germany (Berlin, Bonn, and Hannover) were identified. Data on clinical characteristics and NfL were obtained from the "NfL-ALS" study. *SOD1* mutation status was assessed in the "ID-ALS" study. Data on demographics, ALSFRS-R, and medication data, including tofersen treatment, were derived from the "APST registry study".

Data collection

Demographic, clinical, and NfL data were captured up to 12 months before tofersen therapy and during the treatment. ALSFRS-R data were assessed by self-rating either on a printed form or using the "ALS-App".[14] Data were collected between October 2021 and November 2022.

NfL analysis

Serum NfL (sNfL) concentrations were analyzed in a core facility at the ALS center in Berlin. sNfL was measured by means of the single molecule analysis technology (SIMOA) using the commercially available NfL advantage kit (Quanterix Inc., USA). Cerebrospinal fluid (CSF) NfL concentrations (CSF-NfL) were measured at the Labor Berlin – Charité Vivantes GmbH using the NF-light ELISA (UmanDiagnostics, Sweden)

Protocol approvals and registrations

The study protocols were approved by the Medical Ethics Committee of Charité – Universitätsmedizin Berlin, Germany. Written informed consent was obtained from all participants.

Variables

Clinical characteristics

Demographic data, *SOD1* mutation details and clinical characteristics were collected.

Functional deficit as measured by the ALSFRS-R

The ALSFRS-R is a 12-item disease-specific instrument that measures bulbar, gross, and fine motor functions and respiratory symptoms.[15,16]

ALS progression rate (ALS-PR)

ALS-PR was calculated using the following formula: (48-ALSFRS-R divided by disease duration in months).[17] Two classifications of ALS-PR were applied. In ALS-PR classification 1, patients with slower (<0.5 ALSFRS-R/month), intermediate (≥0.5 and ≤1.0 ALSFRS-R/month) and faster (> 1.0 ALSFRS-R/month) progression were differentiated.[17] In ALS-PR classification 2, a distinction between faster progressing ALS (≥0.9 ALSFRS-R/month) and slower progressing ALS (<0.9 ALSFRS-R/month) was made.[5]

sNfL and CSF-NfL

sNfL and CSF-NfL concentrations were analyzed as described and referred to the time of sampling.

Tofersen treatment

Treatment with tofersen was assessed as the number of months receiving tofersen.

Statistical methods

Descriptive statistics were used (frequency in percent, mean, median, and ranges) and statistical analyses were performed by Statplus version 7.7.11 (Brandon, FL) and GraphPad Prism version 9.0.0 (Boston, MA). Mann-Whitney U test and repeated measures ANOVA with Greisser-Greenhouse correction were applied. Significant levels are defined as $p \leq 0.05$.

RESULTS

Patient cohort and clinical characteristics

Six SOD1-ALS patients with 3 unique *SOD1* mutations were investigated. Three of these six patients reported a negative family history. Clinical characteristics are summarized in Table 1 and Supplement 1. The mean tofersen treatment duration was 6.5 months (range 5-8 months).

ALSFRS-R before and during tofersen treatment

Five patients showed high functional status at the time of treatment initiation, while one patient showed profound loss of motor function. Results are summarized in Table 2.

ALS-PR before and during tofersen treatment

ALS-PR before tofersen treatment was slow in four patients (range 0.05-0.27), intermediate in one patient (0.8), and fast in another case (2.66)(Table 1). Other results are summarized in Table 2.

sNfL and CSF-NfL before and during tofersen treatment

In all patients, CSF-NfL (ΔCSF-NfL: -66% [range -52 to -86], p= 0.028) and sNfL (ΔsNfL: -62% [range -36 to -84]; p=0.049) significantly decreased during tofersen treatment compared to baseline. Repeated measures ANOVA also showed significant results (sNfL p=0.047). Results are summarized in Table 2 and Figure 1.

DISCUSSION

Here, we report an exploratory analysis of NfL in six SOD1-ALS patients treated with tofersen – as part of an EAP. In fact, all patients showed a significant NfL decrease in response to tofersen therapy. Thus, the principle finding of NfL responsiveness – as previously demonstrated in the VALOR and open label extension study – was reproduced.[5]

Furthermore, our study has expanded the treatment experience with tofersen as five of the six EAP patients showed clinical characteristics that were not included or less frequent in the VALOR study: One patient underwent invasive ventilation and had near-total loss of motor function (ALSFRS-R=1) – a functional deficit not reported in VALOR (minimum ALSFRS-R=15).[5] Three patients harbored a homozygous Asp91Ala mutation, which was rarely included in the VALOR study (n=2, 1.9%).[5] Two patients showed a very slow progression (ALS-PR before treatment of 0.05 and 0.06, respectively, Table 1) that was well below the mean ALSFRS-R slope of the VALOR slower progression subgroup (–0.30±0.20).[5] Despite the different clinical and genetic characteristics of the treated patients, the decrease in NfL was a common feature of tofersen therapy. Also, the extent of NfL reduction was comparable to the VALOR data.[5] This finding underscores the feasibility of NfL as a therapeutic biomarker in an expanded clinical spectrum of SOD1-ALS – including very slow progression or severe motor deficits.

Four of the six patients were treated for at least 7 months and thus correspond to the placebo-controlled phase of the VALOR trial (28 weeks).[5] Despite this, the findings of this study must be considered in the context of their limitations. With six patients and the short treatment time, the scope of this study was limited. In particular, in patients with slow ALS progression, a longer observation time is essential to establish the correlation between the clinical and biomarker treatment response. Given the pathophysiological role of NfL as an indicator of neuroaxonal damage and the strong correlation between NfL and ALS progression, the prognostic significance of NfL reduction can be assumed but requires confirmation by further research. More specifically, a continued investigation of our cohort as well as the inclusion of additional patients will clarify the latency and effect size in which NfL response converges with clinical outcome including ALSFRS-R.

The ALSFRS-R was the primary endpoint in the VALOR trial and was also of interest in this case series. Two patients (#3, #5) showed a reduction of ALS-PR. Although any individual

case data must be treated with caution, these EAP participants showed that a reduction in NfL was associated with a stabilization of the clinical course. Three of the six patients showed such a slow progression rate that – given the short duration of therapy – no change in ALSFRS-R could be expected. Furthermore, in one patient (#6), the ALSFRS-R (total score=1) became uninformative due to the floor effect of ALSFRS-R.[18] With a longer duration of treatment with tofersen, it will be of major interest whether patients with large deficits also show a stabilization of the disease or even a return of certain motor functions. In patients with severe deficits or slow progression, the assessment of patient-reported outcomes (PROs) will be of particular importance, which allows a systemic detection of apparently minor changes that are not reflected in the ALSFRS-R but may have a high functional meaning at the individual level. Thus, systematic analysis of PROs in patients with spinal muscular atrophy and nusinersen treatment has shown a response to therapy in addition to and beyond clinical functional scores.[19]

Overall, the NfL data correspond with the VALOR results and underscore the role of NfL as an early treatment response marker in ALS. Furthermore, the presented data support the disease-modifying activity of tofersen in SOD1-ALS. The expansion of the observation in terms of treated *SOD1* mutations, treatment duration, the number of included patients, and by that means of ALSFRS-R endpoint data, as well as the exploration of PROs, will provide additional information on the efficacy of tofersen in SOD1-ALS.

Competing interests

TM is on the advisory board of Biogen and has received consulting fees from Biogen. PK received consulting fees from Biogen. RG has received grants, personal fees, non-financial support and research support from Biogen and serving on the advisory board of Biogen, outside of the submitted work. SP has participated in advisory boards of Biogen and has received consulting fees from Biogen. TM and CM are founders and shareholders of the Ambulanzpartner Soziotechnologie APST GmbH, which makes the internet platform Ambulanzpartner and the mobile application “ALS-App”. APST received a research grant from Biogen.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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List of abbreviations

ALS, amyotrophic lateral sclerosis

ALSFRS-R, ALS Functional Rating Scale–Revised

ALS-PR, amyotrophic lateral sclerosis progression rate

CSF-NfL, CSF neurofilament light chain

EAP, expanded access program

NfL, neurofilament light chain

sNfL, serum neurofilament light chain

PEG, percutaneous endoscopic gastrostomy

PRO, patient-reported outcomes

SOD1, superoxide dismutase 1

SOD1-ALS, amyotrophic lateral sclerosis caused by superoxide dismutase 1 gene mutations

TIV, tracheostomy invasive ventilation

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Table 1. Clinical and genetic characteristics

ID	Age (years)	M/F	Duration (months)	Family history	TIV	PEG	ALSFRS-R	ALS-PR	ALS-PR classification 1	ALS-PR classification 2	SOD1 mutation	Allele genotype
#1	59	F	45	negative	no	no	45	0.18	slow	slower progressing	c.272A>C, p.(Asp91Ala)	homozygous
#2	59	M	33	negative	no	no	46	0.06	slow	slower progressing	c.272A>C, p.(Asp91Ala)	homozygous
#3	49	F	22	negative	no	no	42	0.27	slow	slower progressing	c.272A>C, p.(Asp91Ala)	homozygous
#4	54	M	105	positive	no	no	43	0.05	slow	slower progressing	c.346C>G/p.(Arg116Gly)	heterozygous
#5	60	F	16	positive	no	no	35	0.80	intermediate	slower progressing	c.346C>G, p.(Arg116Gly)	heterozygous
#6	39	F	18	positive	yes	yes	1	2.66	fast	faster progressing	c.396_399dup, p.(Glu134*)	heterozygous

M, male, F, female; duration, disease duration; ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS functional rating scale revised; ALS-PR, ALS progression rate before tofersen treatment; PEG, percutaneous endoscopic gastrostomy; TIV, tracheostomy invasive ventilation.

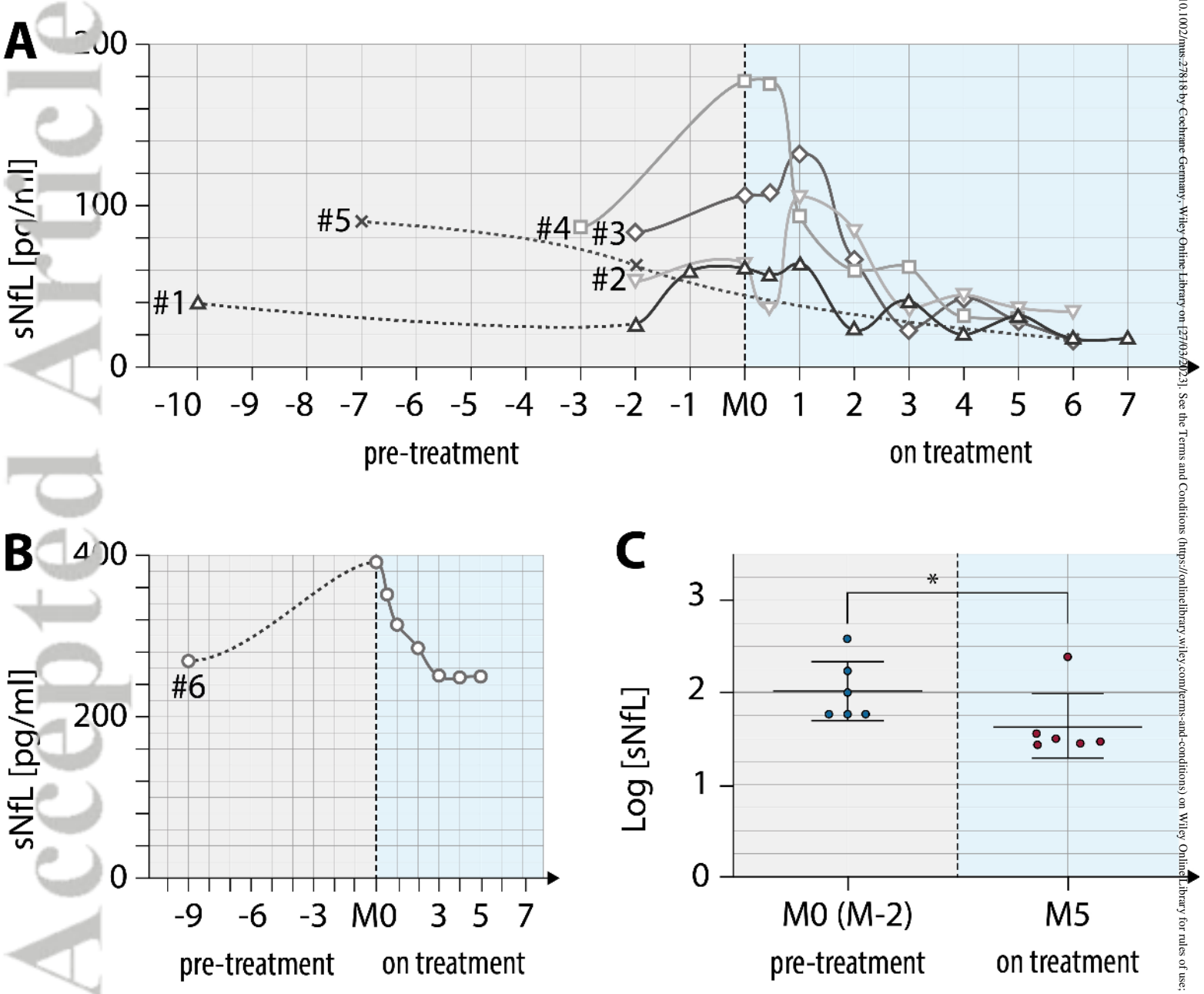
Table 2. Neurofilament light chain (NfL) and clinical course in SOD1-ALS patients before and during tofersen treatment

Para-meters	Patient-ID	#1					#2					#3				
	Duration (months)	42					32					22				
	Outcome	sNfL	NfL-CSF	ALS-FRS-R	ALS-PR	SVC	sNfL	NfL-CSF	ALS-FRS-R	ALS-PR	SVC	sNfL	NfL-CSF	ALS-FRS-R	ALS-PR	SVC
Disease course (months)	-10	39.47				142										
	-7					127										
	-2	28.53		45	0.07		53.90		44	0.13	104	83.77		42	0.30	97
	-1	59.68				157			46	0.06				43	0.24	
	0	61.59	2607	45	0.07	125	63.26	2965	46	0.06	85	107.01	2182	42	0.27	95
	0.5	58.80	2557			120	37.20	2968	45	0.09	89	108.07	2864	41	0.12	100
	1	63.26	3094	43	0.12	135	107.88	1596	45	0.09	113	132.48	1400	42	0.26	96
	2	23.32				117	83.70	1977	45	0.09	108	66.03	1415	42	0.25	89
	3	41.61	1484	42	0.13	109	37.31	2187	44	0.11	131	24.14	1282	43	0.20	102
	4	20.20	1748	43	0.11	132	45.55	1527	44	0.11	114	42.09	1349	43	0.19	100
	5	32.98	1121			112	36.25	1298	44	0.11	111	28.06	934	43	0.19	100
	6	18.15	776			112	33.54	1370	44	0.11	89	17.57	1041	43	0.18	97
	7	18.35	1235	42	0.12	122		958	44	0.10	107		577	43	0.17	103
	8			43	0.10											
Change		-70%	-53%	-2	0.05	-3	-47%	-68%	-2	0.04	22	-84%	-52%	1	-0.10	8

Para-meters	Patient-ID	#4					#5					#6				
	Duration (months)	108					16					18				
	Outcome	sNfL	NfL-CSF	ALS-FRS-R	ALS-PR	SVC	sNfL	NfL-CSF	ALS-FRS-R	ALS-PR	SVC	sNfL	NfL-CSF	ALS-FRS-R	ALS-PR	SVC
Disease course (months)	-9											271	6765	21	7.06	
	-7						90.3									
	-6								41	1.0						
	-5								39	0.9						
	-3	87.20		43	0.05	120			40	0.6						
	-4								36	0.9						
	-2						62.3									
	0	177.41	17490	45	0.03	96			35	0.8		390	6741	1	3.71	
	0.5	177.39	15607			116						352	6717	1	3.71	
	1	92.35	13663			103			32	0.9		315	5802	1	3.44	
	2	50.42	4817	45	0.03	96			31	0.9		284	4410	1	3.21	
	3	51.15	4187	42	0.05	96			33	0.8		252	3018	1	3.00	
	4	31.39	2493	45	0.03	89			32	0.8		248	3117	1	2.82	
	5	30.87	3566	45	0.03	104	29.3		32	0.8		249	2070	1	2.66	
	6								32	0.7						
	7								33	0.7						
Change*		-83%	-86%	0	0	8	-53%		-2	-0.1		-36%	-69%	0	-1.05	

ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS functional rating scale revised; ALS-PR, ALS progression rate; duration, disease duration in months; SVC, slow vital capacity as measured in percent of the predicted value (corrected for height, age, sex, and weight); sNfL, neurofilament light chain in serum in pg/ml; NfL-CSF, neurofilament light chain in CSF in pg/ml; *Change, change from time M0 to the last measured value; M0, month of initiation of tofersen treatment; background colour: gray, values before treatment; blue, values during treatment; white, no measurements available

Figure 1. Serum neurofilament light chain (sNfL) before and during treatment with tofersen. 1A Individual slopes of sNfL concentration during ALS disease course (patients #1 to #5). **1B I**ndividual slope of sNfL concentration (patient #6). **1C** sNfL pre-treatment (M0; except #5 M-2) compared to on treatment (M5). M0, month of initiation of tofersen treatment; M-2, 2 months before tofersen treatment; M5, 5 months of tofersen treatment. Significance level is indicated as *, p≤0.05.



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