Increased CSF APPs-α levels in patients with Alzheimer disease treated with acitretin

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ABSTRACT

Objective: We investigated induction of α-secretase A disintegrin and metalloprotease 10 (ADAM10) by the synthetic retinoid acitretin (Neotigason; Actavis, München-Riem, Germany) in patients with mild to moderate Alzheimer disease (AD) via measurement of CSF content of α-secretase–derived amyloid precursor protein (APPs-α).

Methods: Twenty-one patients clinically diagnosed with mild to moderate AD received acitretin (30 mg per day) or placebo in a 4-week double-blind study. Primary endpoint was the difference of CSF APPs-α ratios calculated from the APPs-α levels after treatment and at baseline. We monitored safety and tolerability of the treatment. In addition, we assessed biomarkers such as β-amyloid 42 ($A\beta_{42}$) under treatment conditions.

Results: The acitretin group showed a significant increase in CSF APPs-α levels compared with the placebo group (difference 0.38, 95% confidence interval 0.03–0.72, $p = 0.035$) within this rather short treatment period. The synthetic retinoid acitretin was overall safe and well tolerated.

Conclusions: Our pilot study highlights that acitretin is able to enhance the nonamyloidogenic APP processing in human patients. Clinical consequences of this regulation should be investigated in larger and longer trials in patients with AD to evaluate acitretin's potential to serve as a novel therapeutic drug.

Classification of evidence: This study provides Class III evidence that in patients with AD, oral acitretin increases CSF APPs-α levels. *Neurology*® 2014;83:1930–1935

GLOSSARY

Aβ = β-amyloid; **AD** = Alzheimer disease; **ADAM10** = A disintegrin and metalloprotease 10; **ANOVA** = analysis of variance; **APP** = amyloid precursor protein; **CERAD** = Consortium to Establish a Registry for Alzheimer's Disease; **CI** = confidence interval; **IZKS** = Interdisziplinäres Zentrum Klinische Studien; **NINCDS-ADRDA** = National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association.

The α-secretase A disintegrin and metalloproteinase 10 (ADAM10) catalyses nonamyloidogenic processing of the amyloid precursor protein (APP), giving rise to the neurotrophic and neuroprotective protein fragment APPs-α despite APPs-β and β-amyloid (Aβ) peptides. Overexpression of the major neuronal α-secretase ADAM10 (e.g., see reference 1) in an AD mouse model was accompanied by decreased Aβ synthesis and plaque load, increased production of APPs-α, and rescue of learning and memory deficits.[2] In aging rats, on the contrary, lowered amount of CSF APPs-α correlated with poor memory performance.[3] In addition, patients with mild cognitive impairment and Alzheimer disease (AD) have repeatedly been reported to show reduced amounts of α-secretase and enhanced amount or activity of β-secretase in the brain.[4] A Swedish family with AD revealed a strong correlation between low CSF levels of α-secretase–derived cleavage product and poor performance on neuropsychological tests while no correlation occurred for Aβ peptides.[5] We therefore consider induction of α-secretase ADAM10 as a valuable target for AD therapy by the enzyme's potential of interfering with amyloidogenic APP processing, and/or because of the synthesis of neuroprotective APPs-α.

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Retinoids are able to increase expression of ADAM10 in cell culture and animal experiments.[6] Acitretin, a synthetic retinoid that competes with all-trans retinoic acid concerning interaction with the intracellular binding protein CRABP,[7] displayed a similar antiamyloidogenic effect in human neuroblastoma cells as well as in an AD mouse model.[6] Use of all-trans retinoic acid itself as a therapeutic drug is prevented in humans by its toxicity; acitretin, on the contrary, is clinically approved for long-term treatment of psoriasis.[8]

Here, we hypothesized that the enhancement of the α-secretase ADAM10 activity via acitretin increases primarily the CSF APPs-α levels in patients with AD. Second, we expected a decrease of APPs-β levels because of the stimulation of the nonamyloidogenic APP pathway via α-secretase activation by acitretin, with a consecutive reduction of Aβ levels.

METHODS

The primary objective of this study was to analyze whether a 4-week treatment with the synthetic retinoid acitretin is able to increase CSF APPs-α levels in patients with mild to moderate AD (level of evidence: Class III).

Patients. We conducted this study as a prospective, randomized, placebo-controlled, parallel-group, 4-week treatment phase II study in 2 centers in Germany (University Medical Centre of the Johannes Gutenberg University, Mainz, and University Medical Centre, Rostock). Patients were enrolled and randomized into placebo or treatment group (acitretin, 30 mg per day). The Interdisziplinäres Zentrum Klinische Studien (IZKS) Mainz generated a separate randomization list for each trial center using standard software (SAS). Each investigator received patient kits containing medication for one patient labeled with the randomization number in consecutive order. Capsules containing 10 mg acitretin (Neotigason; Actavis, München-Riem, Germany) or placebo were produced and packed by the Pharmacy of the University Medical Center Mainz to achieve a blinding of the study. If a subject was included, the investigator chose the drug kit with the lowest provided randomization number. This number was communicated to the IZKS and also documented in the case report form and source data. Information about medication was kept in a sealed envelope, which was to be opened only in case of a medical emergency.

Men and women older than 50 years with mild to moderate dementia (Mini-Mental State Examination score 14–27) and a diagnosis of probable AD according to the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association) criteria were included[9] (for more details on inclusion and exclusion criteria, see the EU Clinical Trials Register: EudraCT No 2009-011881-27). Regarding the novel diagnostic criteria of probable AD dementia,[10] and beside the applied clinical diagnostic NINCDS-ADRDA criteria, biomarker evidence can increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiologic process. Regarding the CSF biomarker profile, all included patients had at least one pathologic biomarker finding ($A\beta_{42}$, phospho-tau, or total tau).

Standard protocol approvals, registrations, and patient consents. The study was initiated after approval by the ethic committees, and executed in accordance with the Good Clinical Practice guidelines (Declaration of Helsinki and International Conference on Harmonization). The trial was monitored by the IZKS (University Medical Centre, Mainz) and registered with ClinicalTrials.gov (NCT01078168). Patients provided written informed consent before enrollment.

Sample and data collection. Both groups were requested to attend 3 visits: visit 1 (before randomization) served for assessment of baseline values (lumbar and venipuncture), at visit 2 (after 2 weeks of treatment), blood was drawn for compliance control (as described in reference 11), and at visit 3 (after 4 weeks of treatment), samples for endpoint measurements were taken (CSF, blood). Mini-Mental State Examinations were done at screening, visit 1, and visit 3, and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery was performed at visit 1 and visit 3; CERAD total score was calculated according to Chandler et al.[12] Physical examination and psychiatric interviews as well as vital sign measurements were done at screening, visit 1, visit 2, and visit 3. Adverse events were assessed at visit 1 (baseline), visit 2, and visit 3 (follow-up). *APOE* genotypes were determined as described previously.[13]

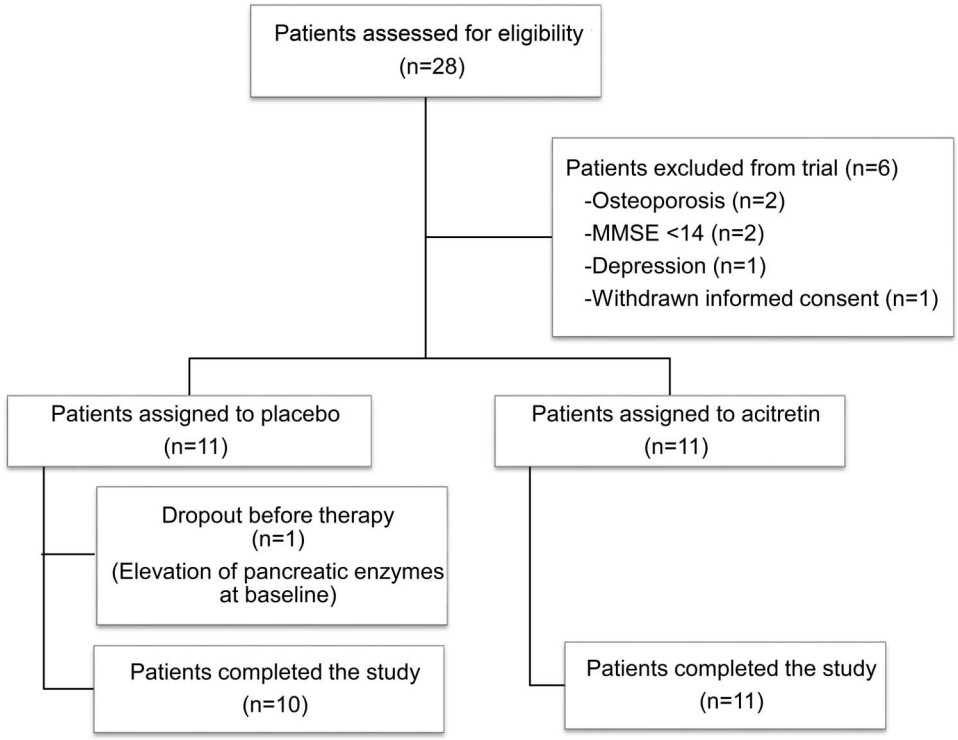
Quantitation of APP proteolysis products and biomarkers. Soluble APP protein species were detected in the CSF (visits 1 and 3) by Western blotting using anti–APPs-α or anti–APPs-β antibody (Covance, Princeton, NJ) and the appropriate HRP-labeled secondary antibody (Pierce). Membranes were reincubated for quantitation of human serum albumin (Abcam, 1:1,000) as a loading control. CSF biomarkers were analyzed by ELISA following the manufacturer's instructions (Innotest Aβ 1–42, Innotest-hTau-Ag, Innotest Phospho-Tau [181P]; Innogenetics, Gent, Belgium).

Data analysis. We used GraphPad Prism 6 (GraphPad, La Jolla, CA) and SPSS (version 21; IBM Corp., Armonk, NY) for statistical analyses performing analyses of variance (ANOVAs) and appropriate post hoc tests. An additional analysis of covariance analysis for our primary endpoint (APPs-α ratios treatment/baseline) including age as a covariate was performed to control for possible effects of between-group age differences. Categorical patient characteristics were analyzed using Fisher exact test. For the normally distributed data (Kolmogorov-Smirnov test >0.05), Student t test and repeated-measures ANOVAs were used for neuropsychological tests. Because of the small number of patients assigned to both groups, we calculated differences in biomarker values over the course of treatment as the quotient between the individual measurements at end of treatment (visit 3) and at baseline (visit 1) before treatment to control for interindividual variance. All samples from one patient (baseline and treatment) were analyzed together to avoid interassay variability.

RESULTS

Twenty-two patients were randomized to either placebo (n = 11) or acitretin (30 mg/d; n = 11) treatment (figure 1). Demographic and baseline characteristics were not statistically different between the 2 treatment groups (see table 1). For example, patients in the placebo group had a mean

Figure 1 Flow diagram with disposition to the 2 treatment groups



Patients were randomly assigned to placebo or acitretin. Randomization was performed by the IZKS (Interdisziplinäres Zentrum Klinische Studien, Mainz). One patient within the placebo group did not enter the treatment because of safety concerns regarding unclear elevation of pancreatic enzymes observed at screening. MMSE = Mini-Mental State Examination.

age of 73 years; patients in the acitretin group had an average age of 67 years ($t = 1.864$, $df = 19$, 95% confidence interval [CI] −12.93 to 0.75, $p = 0.078$). Sex did not differ between the groups (Fisher exact test: $p = 0.298$). Mini-Mental State Examination did not differ significantly between groups or over the course of treatment. At baseline and follow-up, CERAD total score test results differed between groups (Student t test: baseline $F = 1.2$, $p = 0.067$; follow-up $F = 0.039$, $p = 0.026$) but not over the course of treatment (no significant interaction effect) (repeated-measures ANOVA; visit 1 acitretin group average 55.8 ± 14.8 vs placebo group 45.1 ± 9.8; visit 3 acitretin group average 60.4 ± 14.6 vs placebo group 45.7 ± 13.0; $F_{1,19} = 5.00$, $p = 0.038$; see table 1). Post hoc testing of a treatment effect (visit 1 vs visit 3) within the acitretin group showed a trend toward an improvement in CERAD total score ($t = 2.221$, $df = 10$, 95% CI 0.015–9.105, $p = 0.051$).

Observed adverse events were in the range of known undesirable effects such as dryness of the skin and mucous membranes, skin scaling, and hair loss (see table 2).[14] No differences between the acitretin- and the placebo-treated patients in vital signs and blood and CSF chemistry were observed, and laboratory parameters were within the range of normal variations.

The primary outcome parameter (index test) was the increase of CSF APPs-α (given as increased ratio after treatment period/baseline) levels to demonstrate the activation of the nonamyloidogenic pathway of APP processing. We observed a significant APPs-α increase of 25% in the acitretin-treated patients when comparing individual starting point measurements with follow-up values ($t = 2.284$, $df = 18$, 95% CI 0.030–0.724, $p = 0.035$; figure 2) while APPs-α slightly decreased in the placebo group during the observation period (figure 2). The APPs-α increase was still significant ($F_{1,19} = 4.44$, $p = 0.050$) after controlling for a potential effect of between-group difference in age.

Moreover, because treatment and placebo groups were not properly matched regarding CERAD sum scores (differing between treatment and placebo group at baseline), we additionally included this variable as covariate into the analysis of covariance. Neither age ($p = 0.826$) nor baseline CERAD sum score ($p = 0.995$) had a significant effect on the primary outcome parameter (difference of CSF APPs-α levels between drug and placebo). The significance of the treatment effect disappeared in this model, but a trend remained ($F = 3.914$, $p = 0.065$). By contrast, APPs-β showed a trend to decline but did not reach significance.

Table 1 Demographics of the patients included in this study

	Placebo (n = 10)	Acitretin (n = 11)
Mean age, y, ± SD	73.0 ± 3.8	66.9 ± 9.6
Sex, F/M	6/4	9/2
APO ε4, noncarriers/carriers	2/8	4/6[a]
$A\beta_{42}$, ng/L		
b	625 ± 155	644 ± 156
t	641 ± 198	637 ± 133
Total tau, ng/L		
b	941 ± 320	572 ± 403
t	866 ± 300	632 ± 242
Phospho-tau, ng/L		
b	112 ± 39	77 ± 32
t	106 ± 34	78 ± 35
MMSE		
b	20.4 ± 4.2	23.9 ± 4.3
t	22.1 ± 4.0	24.0 ± 3.4
CERAD sum		
b	45.1 ± 9.8	55.8 ± 14.8
t	45.7 ± 13.0	60.4 ± 14.6

Abbreviations: $A\beta_{42}$ = β-amyloid 42; b = baseline; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; MMSE = Mini-Mental State Examination; t = after treatment.
Data are count or mean ± SD.
[a] One patient in the acitretin group did not consent to genetic testing.

There was no significant correlation of APPs-α and APPs-β, but patients with more APPs-α increase (median split) tended to have decreased APPs-β compared to those with low or zero increase (Student *t* test $F = 0.967$, $p = 0.072$).

Other biomarkers such as $A\beta_{42}$, phospho-tau, and total tau remained unchanged under acitretin medication when comparing intraindividual treatment with baseline values (Student *t* test: $A\beta_{42}$ $p = 0.735$; phospho-tau $p = 0.460$; tau $p = 0.593$).

Table 2 Adverse events

Category	Placebo (n = 10)	Acitretin (n = 11)	*p* Value
Adverse events	5 (50)	8 (73)	0.39
Severe adverse events	0 (0)	1 (9)	1.0
On-study death	0 (0)	0 (0)	1.0

Analyses were performed with Fisher exact test because of small group sizes. Numbers in parentheses are calculated percentages. Observed adverse events were as follows for the placebo group: headache, migraine, vertigo, muscular pain, aggressiveness, and unresolved increase in pancreatic enzymes. In the acitretin group, the following adverse events were frequently observed: dryness of skin, mouth, and lips, detachment of callus, desquamation of skin, and hair loss. One formal serious adverse event occurred in the acitretin group at the end of treatment period: diagnostic workup because of persistent diarrhea required hospitalization. The serious adverse event resolved without any serious findings or consequences.

DISCUSSION The most important finding of this study is the observation of a significant increase in CSF APPs-α ratios under acitretin treatment in patients with mild to moderate AD. Thereby, we report the first human in vivo evidence of enhanced ADAM10 activity by acitretin in AD. This proof of mechanism in humans provides both a new mechanistic avenue and a surrogate marker for a potential disease-modifying therapy.

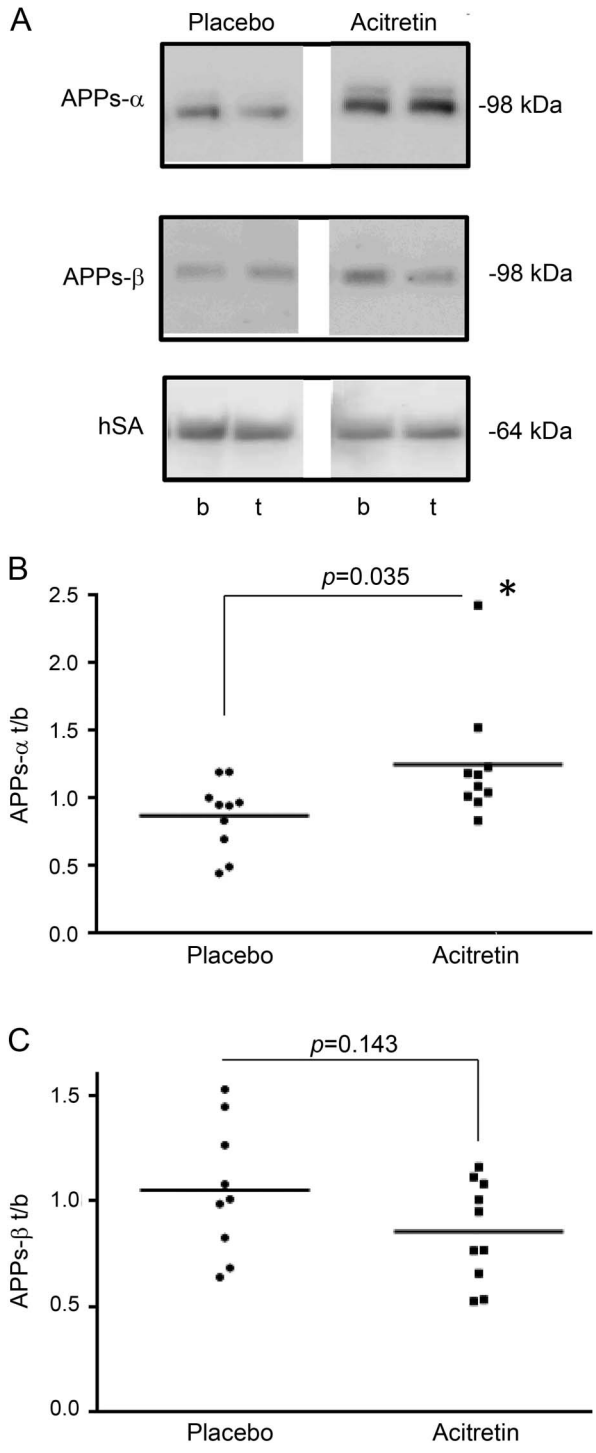
There was only a tendency observed for reduced amounts of the alternative cleavage product APPs-β measured in the CSF of patients in parallel to increased APPs-α and no changes in $A\beta_{42}$ levels. This might be attributable to different stability of the quantified cleavage products within the CSF and small sample size. Moreover, retinoids have been reported to influence Aβ oligomer and fibril stability in vitro.[15,16] It has been shown that administration of all-trans retinoic acid reduces Aβ deposition in an AD mouse model,[17] but it is not clear whether and to what extent the disaggregating properties contributed to this observation in vivo. If so, a short period of treatment with the synthetic retinoid acitretin would then initially result in increased soluble Aβ liberated from depositions while its synthesis rate might already be reduced by enhanced ADAM10 activity.

We assumed that by direct competition between α- and β-secretase, APPs-β should be lowered under acitretin medication as shown in the AD mouse model by direct application to the brain.[6] Such a competing outcome for the enzymes' activities has been repeatedly demonstrated in cell culture experiments and in animal studies: for murine primary neurons, for example, it has been found that knockdown of ADAM10 resulted in a mild upregulation of β-secretase activity.[1] However, there are conflicting data that indicate that depending on source of biological material and experimental parameters, a noncompetitive situation for the 2 proteases, α- and β-secretase, might occur.[18–20]

Nevertheless, a sole increase of APPs-α should inherit benefit by itself: de novo protein synthesis, e.g., increased in rat synaptosomes treated with APPs-α,[21] which might explain the long-lasting modulatory effects of the protein fragment on synaptic plasticity reported from numerous animal experiments (e.g., see references 22–25).

The limitation of our study clearly lies within the restricted number of patients who were not closely matched for age, sex, and disease severity, which does not allow speculating on the effect of acitretin on cognitive function and therefore therapeutic efficacy. However, acitretin, which has already been used for long-term treatment of elderly patients with psoriasis,[6] appeared to be safe in patients with AD. This

Figure 2 Changes of soluble APP species in CSF under acitretin treatment



(A) Western blot results for APPs-α and APPs-β detected in CSF demonstrate increase in APPs-α quantity under acitretin treatment whereas the APPs-β amount did not change significantly and control (human serum albumin [hSA]) remained unchanged. (B) A significant increase of CSF APPs-α under acitretin treatment could be observed compared with placebo treatment. One data point within the APPs-α determination was identified as an outlier (*); the *p* value obtained without this respective quotient is calculated as $p = 0.033$ (95% confidence interval 0.022–0.470). (C) No significant change of CSF APPs-β under acitretin treatment could be observed compared with placebo treatment. APPs data points are given as after treatment/baseline ratios (t/b). APP = amyloid precursor protein.

lays the groundwork for performing future trials of clinical effectiveness after a prolonged treatment.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting, interpretation, and critical revision of this manuscript. K.E., F.F., K.L., and A.F. were involved in study design. K.E. and O.T. wrote the paper. O.T. and S.T. coordinated recruitment and assessment of patients. K.E. and A.F. wrote the study protocol and supervised sample and data collection and reporting. K.E., C.H., and J.L. were involved in sample analysis. All authors had access to the study data and approved the submission.

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DISCLOSURE

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