An indirect response model with modulated input rate to characterize the dynamics of Aβ-40 in cerebrospinal fluid

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Introduction

The amyloid hypothesis suggests that increased production or reduced clearance of amyloid beta (Aβ) species (mainly Aβ-40 and Aβ-42) and their subsequent deposition as plaques in the brain play a critical role in the cascade of biological events involved in the pathogenesis of Alzheimer's disease. Biomarkers of brain Aβ amyloidosis include reductions of the Aβ level in the cerebrospinal fluid.

A number of clinical trials have shown a high intra-individual variability of CSF Aβ level which also tended to rise when sampled repeatedly by means of an indwelling lumbar catheter over a number of hours [2]. Some recent findings have associated the rise of CSF Aβ to the sampling frequency or sampling volume or both [2] while others postulated a diurnal change [3] in CSF Aβ to explain the intra-individual variability observed.

Objective

The objective of this study is to characterize the dynamics of Aβ-40 in cerebrospinal fluid to better understand its high intra-individual variability observed in clinical studies as illustrated in figure 1.

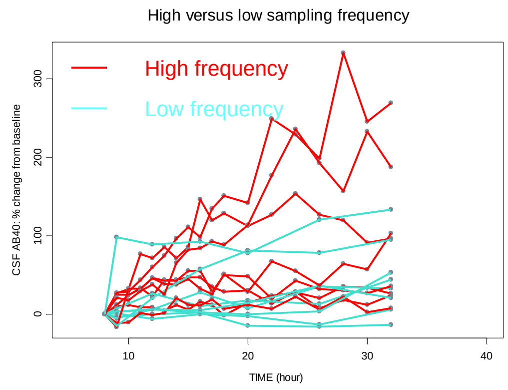

Figure1: Time-course of % change from baseline of CSF Aβ-40 of 8 healthy young men at high (in red: 18 samples of 6ml each) and low (in blue: 7 samples of 6ml each) sampling frequency. 10 days between the two sampling periods. **Data were obtained by digitizing plots from J. Li et. al. (2012)**

Methods

Study design

The data were from three different clinical studies. Data from studies 1 and 2 were literature data and were obtained by digitizing plots from J. Li et. al. (2012). Study 3 was phase 1 clinical trial.

<u>Study 1</u>: 7 healthy eldery men and women (58-83 years old) participated. 7 ml of CSF were collected for each subject at 0 (5:30 AM), 1, 4, 8, 12, 18 and 24.
<u>Study 2</u>: cross-over design. 8 healthy young men (24-45 years old) divided in 2 groups of 4.
group 1: 6 ml of CSF collected for each subject at 18 time points over 24 hours (high frequency) at 0 (8AM), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22 and 24 hours. 10 days later, 6ml of CSF were again collected from the same 4 subjects at 7 time points over 24 hours at 0 (8AM), 1, 4, 8, 12, 18, and 24 hours.
group 2: 6ml of CSF collected for each subject at the low frequency first followed 10 days later by the higher frequency collection of CSF.
<u>Study 3</u>: 10 young men (19-45 years olds) from the placebo group of a phase 1 clinical trial. 2 ml of CSF were collected at 19 time points every 2 hours over 38 hours at 0 (2AM), 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38.

Model

An indirect response model was used to characterize the dynamic of CSF Aβ 40.
<u>Testing hypothesis</u>: The rise of Aβ 40 in CSF is due to sampling frequency and/or sampling volume.
As the volume of CSF is relatively small its dynamic will reflect the effect of sampling frequency and volume.
<u>Assumption</u>: the rate of formation of Aβ 40 in CSF is (a decreasing) function of the total volume of CSF at any given time.
More specifically:

Dynamic of CSF volume: $$\partial \frac{dV}{dt} = prod - Ke * V - Vs * \delta t \qquad (1)$$

Rate of formation of CSF Aβ 40 $$K_{in} = Base * K_{out} * (V_0/V)^{\gamma} \qquad (2)$$

Dynamic of CSF Aβ 40 : $$\partial \frac{A\beta}{dt} = K_{in} - K_{out} * A\beta \qquad (3)$$

Equation 1: V is the tptal CSF volume at time t. Ke is the rate of elimination of CSF; *prod* is the rate of formation of CSF. This rate was fixed to 0.35 ml/min a value derived from the literature [4]. At steady-state: *prod* = Ke*V_0 where V_0 is the initial volume of CSF. Vs is the volume of aCSF sample. δt is an index function equal to 1 at sampling time and zero elsewhere.
Equation 2: K_{in} and K_{out} are respectively the production and elimination rates of Aβ 40 in CSF. *Base* is the concentration of Aβ 40 at baseline. *Base,* K_{in} and K_{out} and γ are estimated

Population data analysis

All data were modeled simultaneously using a nonlinear mixed effects modeling approach in NONMEM (version 7 Icon Development Solutions, Ellicott City, MD) for the parameters estimation and SPLUS (version 8.0; Insightful, Seattle, WA) was used for graphical analyses of the results.
Inter-individual and inter-occasion (for the cross-over design) variability was characterized. Residual variability was modeled with a proportional error model.
Model development and qualification were guided by goodness of fit plots and the precision of parameter estimates.

Results

The final population PK parameters are presented in Table 1 (covariance were aborted).

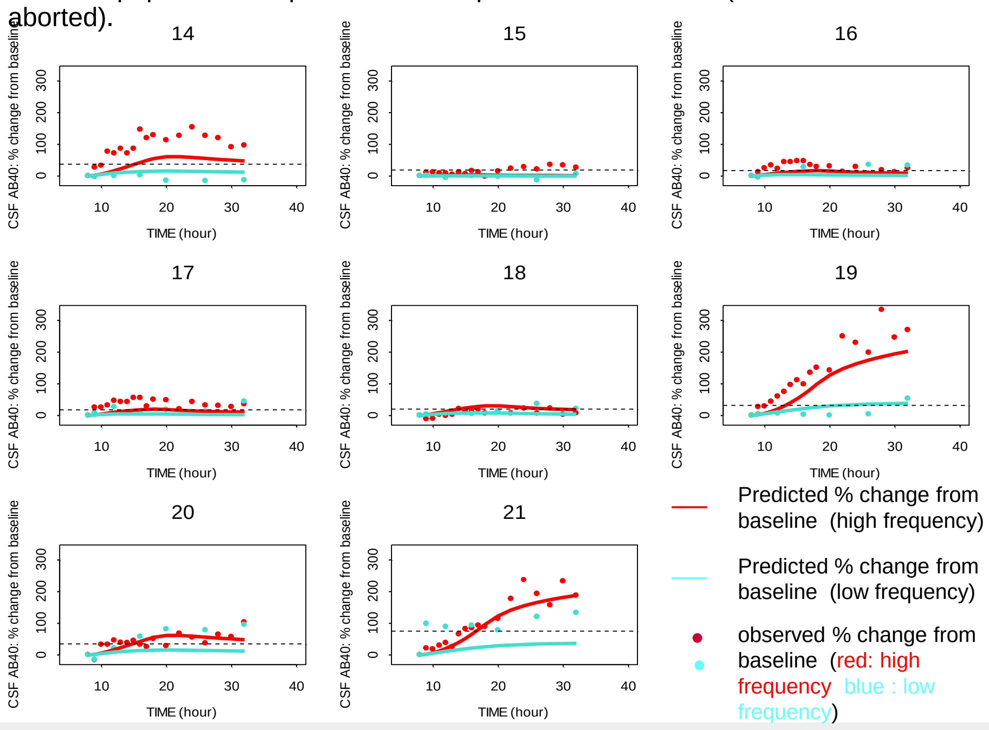

Figure 2: % change from baseline of CSF Aβ 40 from study 2. Observations (dots) of high sampling frequency (red) and low sampling frequency (blue) versus individual predictions (lines). The horizontal broken lines are the observed % of change of the baseline value for the same individual in 10 days.

Table 1: Final population parameter estimates

Parameter	Unit	Definition	Estimate	IIV*	IOV*
Base	ng/L	Baseline Aβ40	5940	9%	8%
K_{out}	1/h	elimination rate of Aβ40	0.268		
K_e	1/h	elimination rate of CSF	0.14 (not estimated)	69%	
V_0	ml	Initial CSF volume	150 (not estimated)		
γ		power	2.39		
error		Proportional error	12%	5%	

* IIV and IOV are respectively the inter-individual and inter-occasion variability

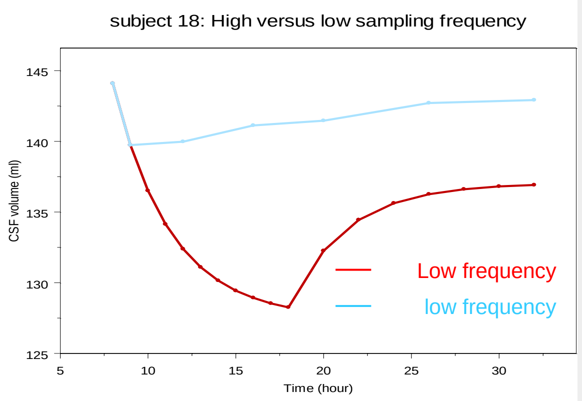

Figure3: Predicted time course of CSF volume. High sampling frequency (red) versus low sampling frequency (blue). The volume of CSF decreases with a high sampling frequency scheme, and increases again when the frequency is lowered. This substantiate the hypothesis that both sample volume and sampling frequency are impacting CSF Aβ levels.

Conclusions

An indirect response model with modulated input rate was used to describe the dynamic of CSF Aβ 40. The contributions of both the sampling frequency and the sampling volume to the high intra-individual variability of CSF Aβ40 were quantitated.
Although the goodness of fit plots were not perfect, the model supports the hypothesis that the rise of Aβ 40 in CSF is partly due to sampling frequency and sampling volume.
However further investigations are needed to validate the approach of this on-going work.

References:[1] E. Karran, M. Mercken and B. De Strooper. *The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics.* Nature Reviews - Drug Discovery. Vol. 10. Sept. 2011
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[3] Y. Huang et. al. *Effect of age and amyloid deposition on Aβ dynamics in the human central nervous system.* Arch Neurol. (2012) Jan: 69 (1) 51-8
[4] R.W.P. Cutler et. al. *The origin and turnover rates of cerebrospinal fluid albumin and gamma-globulin in man.* J. Neurological Sciences. Vol. 10, Issue 3, 1970.