# eTable 4. Summary characteristics of included open-label trials (N=3)

| **Study ID** | **n** | **Genetic diagnosis** | **Sex;**  **age (y)** | **Clinical presentation** | **L-arginine treatment** | **AEDs or other treatments** | **AEs** | **Response to treatment** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Koga et al. 2002 1 | 3 | m.3243A>G (87% hetroplasmy in muscle) | F; 17 | Periodic vomiting.Extensive basal ganglial calcification | 16  9;  IV L-arginine  0.5 g/kg as a 10% solution (over 15-min)  Placebo  4;  5% dextrose (0.5 g/kg)  3;  D-arginine (in a 10% solution)  Treatment within 1-h of symptom onset | NR | None | At 24-h, significant improvements (p<0.05) in L-arginine vs. placebo treated SLEs as follows:  headache (5/9 vs 1/7), clinical disability (5/9 vs 0/7), nausea (4/9 vs 1/7), vomiting (6/9 vs 1/7). Teichopsia did not improve (1/9 vs 0/7), persisting for several days.  At 30-min after L-arginine, uptake in the decreased rCBF in the ischemic region was improved on SPECT (↑ was < 13% of the increase on the contralateral side).  At 24-h, plasma lactate and pyruvate improved (no change in CSF). |
| m.3243A>G (74% hetroplasmy in muscle) | F; 18 | Generalized muscle W, periodic vomiting and hemiparesis. Extensive basal ganglial calcification |
| m.3243A>G (58% hetroplasmy in muscle) | M; 15 | Hemiblindness, hemiconvulsions, and vomiting. Extensive basal ganglial calcification |
| Koga et al. 2005 2 | 24 | m.3243A>G  (68 ± 16% heteroplasmy in muscle) | 8M, 16F;  19.6 ± 12.5 (8.2–30.3)  Control group compared at baseline n=72  27M, 45F;  21.5 ± 10.4 (4.3–35.4) | SLEs fulfilled the criteria the following criteria: migraine headache, vomiting, convulsion, and transient blindness  with brain image suggesting focal brain abnormality. | 34  22  IV L-arginine  0.5 g/kg as a 10% solution within 1-h of symptom onset  Placebo  8;  5% dextrose (0.5 g/kg)  4;  D-arginine (in a 10% solution)  Oral use in N=6 patients  4-24 g (0.15-0.3 g/kg/d) for 18-mo. | NR | Headache when L-arginine was infused too rapidly in 2 patients | *Acute:*  At 24-h, significant improvements (p<0.05) in SLEs were as follows: headache (21/22 vs 1/12), clinical disability (20/22 vs 1/12), nausea (22/22 vs 1/22), vomiting (22/22 vs 1/22), hemi-blindness (transient) (7/7 vs 1/4), teichopsia (19/22 vs 0/12)  *Chronic:*  Significant reduction in the frequency of SLEs compared to pre-supplementation (0.09 ± 0.09 vs 0.78 ± 0.42, p<0.05); significant reduction in the severity of SLEs after treatment (0.17 ± 0.18 vs 2.04 ± 0.34) |
| Koga et al. 2018 3 | 20 | m.3243A>G | *Acute:*  N=4 patients enrolled in IV L-arginine only (and who had taken L-arginine other than the study intervention prior to the study).  Additional N=5 patients enrolled in oral and IV L-arginine †  N=10 patients started and completed 2-y IV trial. 8M; 17.2 ± 5.1 (at baseline)  N= 2 patients died during follow up; N=8 completed 7-y follow up | Eligibility patients developed an ictus of SLEs within the previous 6-h. | 3 patients treated with IV L-arginine in 7 SLEs (unclear how many SLEs per patient)  IV  0.5 g/kg as a 10% solution (over 1-h) within 6-h of symptom onset  Additional dose of 0.5 g/kg after 2-h if symptoms did not improve  (received IV when developing an ictus of SLE) | Previous use:  N=10  1 AED:  N=2 (20%);  2 AEDs: N=4 (40%);  ≥ 3 AEDs:  N=4 (40%) | 6/10 patients had AEs. Fever: N=5/10 patients (50%); ↓ hematocrit (N=3; 30%); ↓ hemoglobinuria (N=3; 30%). Patients recovered without treatment.  6 episodes of moderate AEs:  fever (n=4), epilepsy (n=1), bleeding at the injection site (n=1); causality with L-arginine was denied.  1 episode of severe seizures developed in a patient who had been prone to develop seizures since before the trial.  2 patients died during 7-y follow up due to renal failure and sudden death | The improvement rates of the co-primary endpoints, H and nausea / vomiting, at 2, 6, 12, and 24-h after completion of the initial IV administration increased with time: for H, 25% (n=2/8), 12.5% (n=1/8), 50% (n=4/8), and 62.5% (n=5/8), respectively; nausea/vomiting, 50% (n=3/6), 40% (n=2/5), 80% (n=4/5), and 80% (n=4/5), respectively.  The changes in 4 other stroke-like symptoms were NR.  By the end of 7-y follow up:  clear progression of disease burden (JMDRS), 24.2 +/- 12.7 vs 10.2 +/-8.48).  The distribution of SLE frequency in patients was NR. |
|  |  |  | *Chronic:*  N=15 started the trial. However, baseline demographics presented for N=13.  N=3 discontinued;  N=12 completed 2-y trial [data presented for N=13, as N=1 intention-to-treat (ITT)].  Of these, 7M;  22.7 ± 12.5  N=2 patients died during follow up; N=10 completed 7-y follow up (data presented for N=11, as N=1 ITT).  Of these, 7M;  30.6 ± 12.7 | Eligibility patients if they developed SLEs in the last 2-y | 0.3-0.5 g/kg/d in 3 divided doses to maintain plasma arginine concentrations to 100 μmol/L (for 2-y) | Previous use:  1 AED:  N=8 (61.5%);  2 AEDs: N=3 (23.1%);  ≥ 3 AEDs:  N=2 (15.4%) | Nasopharyngitis, n=10/15 patients (66.7%).  7 episodes of severe AEs:  drug hypersensitivity, increased AST, ALT, CPK, metabolic acidosis, arrhythmias, and volvulus. All recovered or became alleviated due to the discontinuation or withdrawal (7 among a total of 10 patients)  3 discontinued (2-y) trial treatment due to the ↑ frequency of epileptic seizures, concurrent pneumonia, and unverified  efficacy.  N=2 patients died during 7-y follow up due to sudden death and renal and heart failure | By the end of 2-y:  The distribution of SLE frequency in patients was as follows: none (n=5), one (n=2), two (n=2), three or more (n=4).  The interictal phase was not significantly extended (p>0.05).  By the end of 7-y follow up:  clear progression of disease burden (measured by JMDRS; 24.2 +/- 12.7 vs 10.2 +/-8.48).  The distribution of SLE frequency in patients was NR. |

Abbreviations: AEs, adverse events; AST, aspartate aminotransferase; F, female; h, hour; JMDRS, Japanese mitochondrial disease rating scale; M, male; NR, not-reported; rCBF, regional cerebral blood flow; SLE, stroke-like episodes; W, weakness; y, year

**References**

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