A Third Case Report Regarding the Effects of "ASEA redox Supplement" in a ~3-year old boy with Duchenne Muscular Dystrophy from town Slobozia, Romania (preprint)

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1st motto: „ASEA works at some fundamental level in the body that we may never understand" (2011, Dr. Chase N. Peterson MD [1999-2014], the former president of the University of Utah from 1983 to 1991)

2nd motto: „ASEA is based on technology that the scientist don't yet understand." (2013, Dr. A.S. Narain Naidu MD Phd, microbiologist, immunologist and researcher, author of the reference volume „Redox Life")

3rd motto: „We didn't think that drinking ASEA would shift metabolites chronically. We thought it would do something during exercise, but not after a week of drinking it [without concomitant exercise: author's note]. After working with the bioinformatics statistical division, we were able to determine that drinking ASEA over one week caused a shift in 43 metabolites, not a little shift: it was a large shift that caught us by surprise." (David Christopher Nieman [URL2, URL3] PhD and full professor at the College of Health Sciences at Appalachian State University, and director of the Human Performance Lab at the North Carolina Research Campus (NCRC) in Kannapolis, NC) (video interview URL, from minute 5:40)

4th motto: „Pediatrics – what a joy, what a feeling of accomplishment when helping Nature heal its children or prevent their diseases and accidents!" (Andrei-Lucian Drăgoi, pediatrician specialist and independent researcher)

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Abstract

This paper argues that "ASEA redox Supplement" (**ARS**) may show comparable or even stronger beneficial effects (with less or none adverse effects) than corticosteroids in children with Duchenne Muscular Dystrophy (**DMD**) and Becker muscular dystrophy (**BMD**). This paper presents a **third** case report on the effects of an ionized "saline water" called "ASEA redox Supplement®" (**ARS**) oral solution in a ~3-year-old boy with DMD from town Slobozia [URL2], Romania. *In vitro* studies showed that ARS is a very potent selective NRF2 activator, thus a very potent (indirect) antioxidant and cytoprotective: the studies conducted *in vivo* also support this main pharmacological mechanism of ARS, with no toxicity up to high doses, in contrast with the much more toxic corticosteroids.

From the first months of ARS treatment, the main rhabdomyolysis markers (with very high initial serum levels) dropped significantly, with no found toxicity until the present.

Before starting adjuvant therapy with oral ARS, this boy-patient was already prescribed by his attending neurologist a combined therapy with: L-carnitine (1g/day) & Vitamin D3 (1000IU/day) & calcium-magnesium oral supplement (5ml/day) & plant-extracts hepatoprotective syrup (5ml/day) & coenzyme Q_{10} (30mg/day) from the last week of **February 2019** (thus from approximately **5 months earlier** than the moment in which ARS therapy was initiated). This previous combined therapy of dietary supplements (**DS**s) also showed a promising decrease in rhabdomyolysis serum markers (**RSMs**) (which is also an important fact with implications for other children with DMD who may potentially benefit from this combined set of DSs): however, when the calcium-magnesium oral supplement was replaced by a combination of ARS (30 ml/day ~ 2.5 ml/kg/day) & omega-3 fatty acids (185 mg/day with a DHA:EPA ratio of approx. 5-to-1) from **August 1st, 2019**, the **RSMs** decrease was quite spectacular (when compared to the anterior decrease) when measured in December 2nd, 2019 at "Victor Gomoiu" Pediatric Hospital (from Bucharest, Romania).

This paper continues the work of other past articles/preprints of the same author [**1**, **2**, **3**, **4**, **5**, **6**].

The main conclusions of this third case report (on ARS effect in boys with DMD) are essentially the same as those emitted in the preprint dedicated to the 2nd case report on ARS in another 5-year old boy with DMD:

(**1a**) ARS has remarkable antioxidant and immunomodulatory effects and should be studied on larger groups of children with DMD under the age of 4 years old (but also on other age groups of children and even young adults), as an alternative to early corticosteroids;

(1b) ARS should be studied as single adjuvant therapy, BUT ALSO in various combinations with other DSs (with cytoprotective and antioxidant properties) like: L-carnitine, vitamine D3, omega-3 fatty acids, coenzyme Q10 etc (given the potential beneficial synergy between these all these DSs [including ARS] on DMD);

(**2**) Given its immunomodulatory effect (NRF2 selective activation and NF-kB inhibition), ARS deserves future cohort studies on its potential to at least partially replace corticosteroids and other non-steroidal immunosuppressants in many types of pulmonary/renal/hepatic/ articular/skin autoimmune and even malignant diseases of both children and adults;

(**3**) Given its very strong antioxidant effects (by highly selective NRF2 potent activation), ARS deserves future cohort studies on acute/chronic diseases that imply high levels of tissular oxidative

stress, especially some acute/chronic cardiovascular and respiratory diseases like acute myocardial infarction with acute/chronic heart failure, stroke, Chronic Obstructive Pulmonary Disease (**COPD**), asthma etc. of both children and adults (so that ARS may help millions and even billions worldwide).

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For an introduction to DMD, NF-kB, NRF2, ARS and the 1st case report on ARS effects in DMD see the main references of this paper [1, 2]. **All the essential aspects of this 3rd case report on ARS effects in DMD are included in the next table (see next page).**

(Table 1. The essential aspects of this 3rd case report on ARS effects in DMD)

Table 1. The essential aspects of this 3rd case report on ARS effects in DMD

PEDIATRIC CONSULTS by Dr. Andrei-Lucian Drăgoi	Anamnestic and clinical essential aspects of this case	Paraclinical essential aspects of this case	Management -- essential measures recommended by dr. Dragoi
Consult no. 1 by dr. Dragoi on 31.07.2019 (home consult)	**Age**: 3 years old (**birth date**: **2.07.2016**) **Sex:** male **Birth location:** Slobozia, Romania * **Diagnosis**: Duchenne muscular dystrophy (**DMD**) (genetic testing in March 2019 with DMD genotype confirmation in **April 2019** [when he was 2 years and 9 months old]) * **Anamnesis**: - according to his mother, this DMD boy had a maternal uncle who "*walked on his toes until the age of 6-7 years old and lost his capacity to walk at the age of ~7 years old and died at the age of 20 years old*" **- ALTHOUGH the CK (2600U/l) and ASAT (780U/l) serum levels (SLs) of this boy were significantly increased from the first day after birth (according to the maternity medical file of the child), these marked RSMs and the suggestive history element (the deceased maternal uncle) were ignored by both the neonatologist and his family doctor until 22.01.2019 (Age: 2 years &months) when a dermatologist discovered (by routine screening) very high ASAT SL (970U/l) and ALAT SL (844.5 U/l); the boy was then sent on 30.01.2019 to the "Victor Babes" Infectious Diseases Hospital from Bucharest (Romania) for extensive screening on infectious liver diseases (with negative serology for hepatitis B&C and also negative for Toxocara); after ruling out these liver diseases, the infectionist send this boy on 27.02.2019 to "Victor Gomoiu" pediatric hospital for muscular dystrophy screening;** -first neurologic consult in 27.02.2019 at "Victor Gomoiu" pediatric hospital -last neurologic consult (until Dr. Dragoi's consult) in 22.05.2019 at the same "Victor Gomoiu" pediatric hospital -up-to-date vaccine status * **Clinical aspects (the essentials)**:	**Genetic test result (blood sample collected on 1.03.2019; Age:~2 years& 8 months; result ready on 19.04.2019 at ~2 years& 9 months)**: heterozygous complete deletion of 49th and 50th exons of dystrophin gene (dys-gene) (which is generally the most frequent type of exon-deletion from all known DMD cases worldwide): furthermore, exon-deletions are also the most frequent type of dys-gene mutation in DMD patients with more than 50% of all known DMD patients worldwide having various types of exon-deletions [URl1, URl2, URl3, URL4]); the boy's mother was also demonstrated to carry exactly the same 49th&50th exons deletion and also demonstrated with a slight elevation of both ASAT and ALAT serum levels (possibly caused by this same carried dys-gene mutation) and high total IgE serum levels; **Important note**: although not specified in the genetic test result, this 49th&50th exons deletion is probably an in-frame deletion: however, the clinical evolution (with loss of ambulation at 7 years old of age and death at 20 years old of age) of his maternal uncle clearly indicates that this boy has a severe DMD phenotype (as the very high serum levels of his rhabdomyolysis markers [**RMs**] also indicate); given all these previous arguments, the dystrophin of this boy is probably significantly shorter than the normal dystrophin [URL1, URL2, URL3]; * **Heart ultrasound (1) (Age: 1 week)**: "normal". **Heart ultrasound (2) (28.09.2016; Age: 7 months) (selection)**: ventricular septal defect (**VSD**) in the middle third of the interventricular septum (**IVS**) with diameters	**-should determine CK-MB and myoglobin SLs and myoglobin urinary concentration (because these rhabdomyolysis markers were not determined until the moment of this consult by dr. Dragoi)** * **-should start ARS P.O. 30+0+0 ml/day (=30 ml/day ~ 2 ml/body_kg/day) from the first week of August 2019**: the 30 ml fraction should be administered before meals; **after 1 month of ARS P.O., the daily dose may be increased to 30+30+0 ml/day (=30 ml/day ~ 4 ml/body_kg/day) (parents didn't apply this increase until the last week of January 2020)** * **- should continue the other combined DSs (all started from April 2019) with the same daily dosing as previously applied**: **Coenzyme Q10** (30 mg /day), **L-carnitine** (1g/day) & **Vitamin D3 (1000IU/day)** & plant-extracts hepatoprotective syrup (5ml/day); * **- may discontinue the calcium-magnesium oral DS** (initial dose:

	Body mass (BM): ~12.5 kg (percentile ~10: under average, but normal BM) **Body exam**: he can independently stand, walk and run; slight loss of muscular strength (predominantly in axial muscles) with mild kyphosis and lumbar hyperlordosis, slight pseudohypertrophy of calf muscles (both with 19.5 cm in circumference), marked psychomotor agitation (walks and runs with a slightly enlarged sustaining base [with higher than normal distance between his feet]), didn't collaborate for Gower's sign; no installed urethral and anal sphincter control (he doesn't announce his imminent micturitions nor defecations); normal cranial nerves; tight phimosis (with one smegma pearl) **Mental examination**: **Language skills**: language development delay (with predominant expressive language delay: he uses only aprox. 5 Romanian words ["mather" {"mama"}, "father" {"tata"}, "water" {"apa"} etc] which he clearly and correctly spells and uses them spontaneously; he only uses two verbs "give me" [distorted] and "bye", both correctly used; he doesn't build simple sentences, he doesn't even associate two or more words together); inconstant visual contact with examiner and parents when he is called by name; he can accomplish simple instructions (to stand on his potty or to take out his pampers by himself alone; he brings and offers various objects at request; he points various objects with his index finger or hand at request); **Social skills**: he doesn't get closer to smaller children but he sometimes wants to socialize with children older than his age; **Play skills**: he uses toys in normal ways (he doesn't prefer atypical toys like bottles, nor laces/cords/strings, leafs etc); he likes to play with ball; he likes to sprinkle water and sand and he generally likes a lot to play with water and in the water; **History**: the boy was born from mother's first gestation (as first and single child until present), born from a high risk pregnancy (because of his mother having unilateral kidney stone disease [**KSD**] and complicated with acute pyelonephritis and secondary fever and severe kidney colic/pain in the 6th month of gestation [and received antibiotics and specific medication for KSD in hospital]); Gestational age at birth 33 weeks; Body mass at birth: 2.15kg; Apgar score: 6 (1 minute)/6 (after 5 minutes) (he was born with respiratory insufficiency with	3/3.6mm (and secondary left-to-right cardiac shunt), without atrial septal defect (ASD) (formen ovale functionally closed), with normal cardiac valves; **Heart ultrasound (3) (age: 2 years & 7 months): normal (spontaneously healed VSD);** **Heart ultrasound (4) (age: 2 years & 10 months): normal (reconfirming the spontaneously healed VSD);** **Abdominal ultrasound (age: 2 years & 5 months): normal;** * **ANTERIOR LABS (2.07.2016 [day 1 after birth]; 4.07.2016 [day 3 after birth], 18.07.2016 [~ 3 weeks after birth])**: **Hgb: 12.8 g/dl (vs Hb=10.5g/dl in the 1st day after birth and after blood transfusion);** **ASAT serum level (SL): 162 U/l** **ALAT SL: 34 U/l (within normal range [wnr]);** **CK SL: 9949 U/l [2.07.2019] vs 2037 U/l [as repeated on 4.07.2019]** **CRP SL: 0.118 mg/l** **Total bilirubin: 4.36 mg/dl (~ 4 times higher than the superior limit of the normal range [slnr]);** **Direct bilirubin: 0.19mg/dl (wnr);** **Important note: Despite his increased RSMs (ASAT and CK), this boy wasn't recommended any neurological consult, nor determination of CK-MB SL until January 2019 (when he was 2 years and 5 months old).** * **ANTERIOR LABS (routine screening from 22.01.2019 conducted by a dermatologist and accomplished in private lab from Slobozia, screening done because of some allergic manifestations of the boy)**: **ASAT SL: 970.9 U/l (>20* slnr);** **ALAT SL: 844.5 U/l (>20*slnr);** * **ANTERIOR LABS (routine hepatitis screening from 30.01.2019 conducted by an infectionist from the "Victor Babes" Infectious Diseases Hospital from Bucharest)**: **-negative hepatitis B&C serologies;** **-negative Toxocara serology;** **ASAT SL: 685 U/l (>15*slnr)** **ALAT SL: 770 U/l (>15*slnr);**	5ml/day, started from April 2019) * -should start omega-3 fatty acids dietary supplement with 185mg/day (and may increase to 370mg/day after one month); * -should start physical therapy sessions -should start home physical therapy daily sessions (30-45 minutes/session and even 2 sessions/day when starting ARS P.O.) * -should continue periodic **neurological consults** (at least two consults per calendaristic year) * - while under ARS P.O., he should be tested with North Star Ambulatory Assessment (**NSAA**) and with the 6-minute walk test (**6MWT**) each 6 months; * -psychological extensive consult, for speech therapy and behaviour therapy * -other specific alergologic tests and alergologic consult * - screening the phenotype of the mother with GGT, CK and CK-MB SLs

	secondary marked cyanosis and altered general state, also associated with cloudy amniotic fluid: he needed oxygen therapy at birth), systolic heart murmur (grade III-IV/VI); he was also born with anemia (with hemoglobin level Hb=10.5g/dl) and he needed blood transfusion with two units of blood (after which hemoglobin increased to Hb=12.8 g/dl); he was kept in the lying-in hospital for about 3 weeks; **Other important information**: **Vaccination status**: vaccinated up-to-date (two doses of MMR vaccine [one 1st dose at 10 months of age and one 2nd dose at 12 months of age] because of the measles epidemic context in Romania); -**blood group**: AB Rh+ -**development quotient (DQ)=62%** from the normal for age and sex (according to the psychologist who evaluated the child at "Victor Gomoiu" children hospital) **Previous treatment (until 31.07.2019) (prescribed by his attending neurologist from the last week of February 2019)**: L-carnitine (1g/day) & Vitamin D3 (1000IU/day) & calcium-magnesium oral supplement (5ml/day) & plant-extracts hepatoprotective syrup (5ml/day) & coenzyme Q_{10} (30mg/day) *	**GGT SL: 10 U/l** (wnr) **CK SL: 27 713 U/l (>200*slnr)** **LDH SL: 5 317 U/l** (a non-specific marker for tissular damage, including rhabdomyolysis, especially myocardium damage) * **ANTERIOR LABS (routine DMD screening from 27.02.2019 conducted by a neurologist from the "Victor Gomoiu" pediatric hospital, BEFORE starting any therapy)**: **ASAT SL: 860 U/l (>20*slnr)** **ALAT SL: 770 U/l (>15*slnr);** **CK SL: 24 000 U/l (>200*slnr)** **LDH SL: 3 026 U/l** * **ANTERIOR LABS (routine check after the first ~ 3 months of treatment with DSs for DMD conducted by the same neurologist from the "Victor Gomoiu" pediatric hospital)**: **ASAT SL: 311 U/l (>7*slnr)** **ALAT SL: 356 U/l (>8*slnr);** **CK SL: 18 350 U/l (>200*slnr)** **LDH SL: 2 670 U/l**	

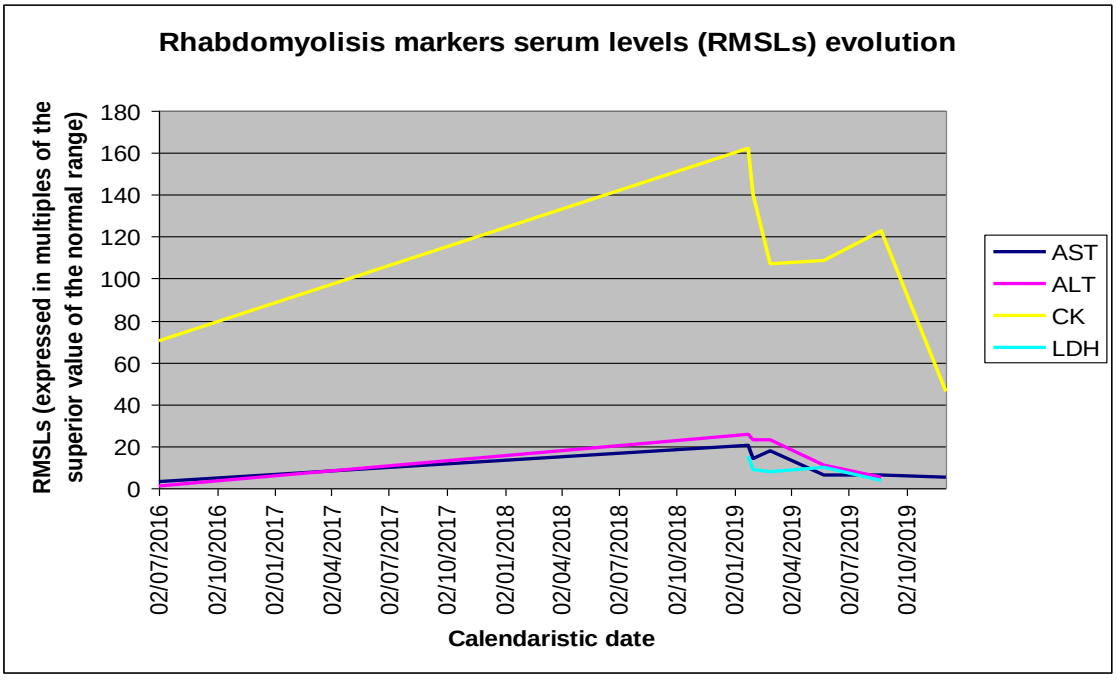
Consult no. 2 by dr. Dragoi (24.01.2020) (short online consult for minimal anamnesis and labs reading)	**Age**: 3 years & 3 months (**birth date**: 2.07.2016) * **Body mass (BM)**: ~13 kg (percentile ~15: under average, but normal BM) **Anamnesis**: -online consult after ~6 months of combined therapy with: **ARS P.O. (30ml/ day = 2.3 ml/ kgb/ day; parents didn't increase the ARS dose to 60ml/day after the 1st month of treatment with ARS) & L-carnitine (1g/day) & Vitamin D3 (1000IU/day) & plant-extracts hepatoprotective syrup (5ml/day) & coenzyme Q_{10} (30mg/day)** **-has also started** speech therapy and behaviour therapy from autumn 2019	**ANTERIOR LABS (21.08.2019) (after ~3 weeks of ARS P.O. 30 ml/day (~2.3 ml/body_kg/day):** **ASAT SL: 303 U/l** **ALAT SL: 175 U/l** **CK SL: 21 000 U/l** **LDH SL: 3 448 U/l** * **ANTERIOR LABS (2.12.2019) (after ~4 months of ARS P.O. 30 ml/day (~2.3 ml/body_kg/day):** **ASAT SL: 241.98 U/l** **CK SL: 7 885.7 U/l** **LDH SL: 1 318.65 U/l**	**-should determine CK-MB and myoglobin SLs and the myoglobin urinary concentration (because these rhabdomyolysis markers were not determined until the moment of this consult by dr. Dragoi)** * **-should continue ARS P.O. and increases its dose up to 45+15+0 ml/day (=60 ml/day ~ 4.6 ml/body_kg/day); the ARS dose may optionally be increased to 60+30+0 ml/day after the one month with 60 ml ARS/day** * **- should also continue the other combined DSs (all started from April 2019 and continued up to present) with the same daily dosing as previously applied**: **Coenzyme Q_{10}** (30 mg /day), **L-carnitine** (1g/day) & **Vitamin D3 (1000IU/day)** & plant-extracts hepatoprotective syrup (5ml/day); * -should continue omega-3 fatty acids dietary supplement with 185mg/day (and increase to 370mg/day at any time); * -should continue physical therapy sessions -should continue home physical therapy daily sessions (30-45 minutes/session and even 2 sessions/day when starting ARS P.O.) * -should continue speech therapy and behaviour therapy * -should continue periodic **neurological consult** (at least two consults per calendaristic year) * - while under ARS P.O., he should be tested with North Star Ambulatory Assessment (**NSAA**) and with the 6-minute walk test (**6MWT**) each 6 months; * -psychological extensive consult, for speech therapy and behaviour therapy

(Table 2. The rhabdomyolysis markers (serum levels) of this 3rd case report on ARS effects in DMD (presented in chronological order))

Table 2. The rhabdomyolysis markers (serum levels) of this 3rd case report on ARS effects in DMD (presented in chronological order)

Index of lab set	Date/interval of the lab set and aprox. age (A) of the boy	Location of lab	ASAT (U/l)	ALAT (U/l)	CK (U/l)	LDH
1	2-18.07.2016 A: 1-3 weeks	Slobozia (maternity)	162	34	9949 [2.07.2019] 2037 [4.07.2019]	-
2	22.01.2019	Slobozia (private lab)	970.9	844.5		
3	30.01.2019	"Victor Babes" National Institute of Infectious Diseases (Bucharest)	685	770	27 713	5 317
4	27.02.-05.03.2019	"Victor Gomoiu" Pediatric Hospital (Bucharest)	860	770	24 000	3 026
5	22-27.05.2019 (after ~4 months of L-carnitine & coenzyme Q10& Vitamin D3 & calcium-magnesium supplement & hepatoprotective syrup)	"Victor Gomoiu" Pediatric Hospital (Bucharest)	311	356	18 350	2 670
6	21-27.08.2019	"Victor Gomoiu" Pediatric Hospital (Bucharest)	303	175	21 000	3 448
7	2-5.12.2019 (after ~4 months of **ARS** & L-carnitine & coenzyme Q10& Vitamin D3 & hepatoprotective syrup)	"Victor Gomoiu" Pediatric Hospital (Bucharest)	241.98		7885.7	1318.65

(Image 1. The evolution of the rhabdomyolysis markers serum levels (RMSLs) of this 3rd case of DMD)



Results and Interpretations

1. The treatment with ARS P.O. in the first ~4 months (from the 1st week of August 2019 until the 1st week of December 2019) plus the anterior and concomitant treatment with other combined DSs (from the last week of February 2019 until the 1st week of December 2019) was associated with:
   a. ***** *a spectacular ~5-fold total decrease of ALAT SL* (from **844.5 U/l** [on 22.01.2019] to **175 U/l** [on 21.08.2019])
   b. ***** *a spectacular ~4-fold total decrease of ASAT SL* (from **970.9 U/l** [on 22.01.2019] to **241.98 U/l** [on 2.12.2019]) (with **normal GGT serum levels** on 31.01.2019 [**10 U/l**]: the only available determination until present)
   c. ***** a *spectacular ~3.5-fold total decrease of CK SL* (from **27713 U/l** [on 22.01.2019] to **7885.7 U/l** [on 2.12.2019])
   d. ***** *a spectacular ~4-fold total decrease of LDH SL (*a non-specific marker for tissular damage, including rhabdomyolysis, especially myocardium damage*)* (from **5317 U/l** [on 22.01.2019] to **1318.65 U/l** [on 21.08.2019])
   e. (all * markings): under the reserve that CK-MB and myoglobin (**MG**) serum levels were never determined for this boy and never specifically requested by any doctor except dr. Drăgoi;
   f. These significant decreases of the (previously) listed rhabdomyolysis markers may be explained by the fact that **ARS has strong global NRF2 activation effect (on all types of muscles/myocytes) and a very strong NRF2 activation effect on the myocardium**, where the expression of NRF2 is larger than in skeletal muscles, an additional indirect subtle potential "proof" that ARS acts via NRF2 pathway). These results suggest that *ARS may have very potent muscular (including myocardial) protective effects* (the basis of which *we propose the study of ARS on large cohorts with acute or chronic cardiac diseases*), *significantly limiting the muscular damage in DMD patients, with the potential of even stronger effects in (milder) BMD phenotypes*: this comes in the "same pack" with *no liver toxicity, no adverse effect on growth and development of the child* and *no other adverse effects* in other clinical spheres until the present. **Additional note**. ARS (combined with other DSs) actually tends to transform a severe DMD phenotype in a milder BMD phenotype.
   g. For extensive **interpretations** of ARS effects in all three DMD cases (published by the author) see reference [**Error! Bookmark not defined.**] (section "*Results and Interpretations*").
   h. The next labs scheduled for this child in spring 2020 were postponed due to Covid-19 pandemics.
   i. Because this DMD boy has no muscle biopsy until present (thus has no molecular studies on his mutant dystrophin)

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Discussions

1. For previous extensive discussions on ARS effects in all three DMD cases treated with ARS as adjuvant (published by the author) see reference [1] (section "*Discussion*").

2. The concomitant determination of myoglobin concentrations in both serum and urine would have been very useful in clearly differentiating between a lower loss of myoglobin from muscles cells into blood VERSUS a higher rate of myoglobin elimination in urine (which both may express by lower serum levels of myoglobin): two (out of the three families) didn't had the financial resources to determine serum myoglobin for their DMD boys and NONE of those three distinct families had the financial resources to accomplish both myoglobin tests concomitantly and that may be a significant drawback in studying DMD cases treated with ARS in Romania or other poor countries.

3. **Pathophysiology [4]**. The pathological mechanisms of DMD are generally complex and dramatic: the main hallmark of DMD is a very high oxidative stress (**OS**) level in DMD-phenotype myocytes including cardiomyocytes (leading to chronic muscle inflammation, repeated cycles of degeneration and impaired muscle regeneration) [URL1, URL2, URL3, URL4, URL5, URL5, URL6, URL7, URL8, URL9, URL10, URL11, URL12, URL13, URL14, URL15, URL16]
   a. OS is two sided: whereas excessive OS causes intracellular molecular damage, maintenance of a physiological level of oxidant challenge (mainly by superoxide molecules generation), termed "oxidative eustress" (**OES**), is essential for governing life processes through redox signaling. "Redox balance is maintained by prevention, interception, and repair, and concomitantly the regulatory potential of molecular thiol-driven master switches such as NRF2/Keap1 or NF-κB/IκB is used for system-wide OS response. Non-radical species such as hydrogen peroxide (H_2O_2) or singlet molecular oxygen, rather than free-radical species, perform major second messenger functions. Chemokine-controlled NADPH oxidases and metabolically controlled mitochondrial sources of H_2O_2 as well as glutathione- and thioredoxin-related pathways, with powerful enzymatic back-up systems, are responsible for fine-tuning physiological redox signaling. This makes for a rich research field spanning from biochemistry and cell biology into nutritional sciences, environmental medicine, and molecular knowledge-based redox medicine." [URL1, URL2, URL3].
   b. ARS contains both superoxide and H_2O_2 species (in small concentrations<1%) and not only hyper-activates NRF2, but also "injects" cells with various free radical

species, thus keeping OES while preventing a possible cytotoxic reductive stress (**RS**): that is what makes ARS unique from all known natural/artificial antioxidants; in contrast, common antioxidants may easily induce RS when given/administered in excess or when too strongly activating the NRF2 pathway [URL1, URL2, URL3, URL4, URL5, URL6, URL7, URL8] (although there may be cases in which a slight RS may prevent OS: see URL). **More specifically**, even if ARS is a solution in which there is a relatively good redox balance between free oxidant species (**FOS**) and free reductive species (**FRS**), ARS has an ~3-4 acid ph (as its superoxide and other FOS slightly predominate over FRS). The direct antioxidant effect of ARS is probably low, although "injecting" ARS in a cell under oxidative stress actually (and at least partially) restores the balance between FOS and FRS in that cell. In the same time FOS from ARS strongly (and very selectively) activates NRF2 and all the endogenous antioxidant enzymatic systems controlled by NRF2: apparently this may lead to RS, but this probably does not happen in case of ARS just because ARS ALSO "injects" cells with some additional FOS (which probably remain partially non-neutralized by endogenous antioxidant systems) and that is unique among all direct antioxidants and among all known NRF2 activators. In a cell under high OS, ARS strongly lowers the global oxidative level/potential from/of that cell (not mainly by direct mechanism, but mainly by NRF2 activation and consequent endogenous antioxidant enzymes genetic overexpression) and in the same time "injects" additional FOS species in the cell, thus preventing reductive stress. It is true that ARS also "injects" FRS in that same cell, but those FRS are in minority (when compared to FOS predominance in ARS). **Prudence is however advised so that ARS should be administered in progressively higher doses (correlated with the body mass of the patient) so that to effectively treat OS without causing RS: (explanation 1) RS may have also caused the slight re-increase of ASAT, ALAT, CK and CK-MB (in the lastly reported period of treatment) in the 1st published case of an ARS-treated boy with DMD [**Error! Bookmark not defined.**]**; **(explanation 2)** another possible explanation for this slight re-increase (of those rhabdomyolysis markers) may be an autoimmune response to a possible increase in the number of normal dys revertant fibers (plausibly induced by ARS) to which organisms with DMD phenotypes (**DPs**) haven't normally gained an immune tolerance because the low levels of normal dys in these DPs (a phenomenon already demonstrated after exon-skipping therapy in a mdx mouse model: see URL). Furthermore, there is a very high variability between human individuals in their cellular response to physical exercise (**PE**) (aka "redox individuality"): because ARS grossly contains the same redox molecules that are usually produced in cells by PE, the response to ARS is also expected to be very variable (concerning the possible induction of OS and/or RS) in general, and even more variable in DMD cases in which there is a very large spectrum of possible dys gene mutations (affecting dys structure and functions in the human cells). **Given its uniqueness in possibly preventing RS, ARS should replace common antioxidants in all those past studies (which should be redesigned by including ARS) in which those tested antioxidants or NRF2 activators were demonstrated to not help and even to induce RS.**

c. The strong stimulation of lipid metabolism induced by ARS through higher rate of tissular lipolysis [**1**,**2**] (with significantly higher energy production produced by partial switching from a glucidic to a lipidic metabolism) may very plausible help the skeletal and cardiac muscles to overcome the high oxidative stress (characteristic to DMD muscles) and help those muscles to repair and/or regenerate with significantly higher efficiency.

d. The spectrum of diseases (including genetic syndromes) which have an important component of acute and/or chronic OS is immense, that is why ARS has a significant potential to help in all these diseases, and that is why ARS deserves systematic extensive studies in many diseases from this OS-centered spectrum of diseases.

e. ARS is such a potent indirect antioxidant (via NRF2 pathway) that it can be also used as a research tool to indicate/verify if any disease has a significant oxidative stress component or not: for example, the significant decrease of all rhabdomyolysis markers (when under ARS P.O.) in these published cases of DMD clearly indicates that DMD has an important oxidative stress component. More specifically, ARS can be administered in any clinical case even when no specific/exact diagnostic is known: if there will be any clinical or paraclinical amelioration in that clinical case with unknown diagnosis, then OS is probably one important link in the pathophysiology of that unknown/undiagnosed disease.

4. **Additional lab/imaging and other tools for studying DMD cases treated with ARS in the future [4]**. Impaired muscle regeneration is a hallmark in DMD, that is why several indices of regeneration (centronucleation, fibre size, embryonic myosin, utrophin serum levels [URL]) can also be measured in ARS-treated DMD/BMD cases.

a. LDH [URL2], which is expressed extensively in almost all body tissues: it is released from the intracellular medium during tissue damage, it is a marker of common injuries

and disease such as muscles damage (from DMD/BMD), heart failure etc. [URL1a, URL1b, URL2, URL3, URL4, URL5]

b. Diaphragm ultrasonography may also be used in the future as a practical non-invasive assessment of the diaphragm function in ARS-treated DMD cases [URL].

c. Various questionnaires and scores can be used to quantify the quality of life in children and adults with DMD [URL].

d. FORT [URL2] and FORD [URL2] tests may also be used to periodically monitor the antioxidant properties in any ARS-treated patient (not only in ARS-treated DMD/BMD patients).

e. Hand-held myometry [URL1, URL2, URL3, URL4, URL5]

f. 6 Minute Walk Test [URL2] (**6MWT**) [URL1, URL2a, URL2b, URL3, URL4a, URL4b, URL5, URL6, URL7, URL8, URL9, URL10, URL11] and its 2MWT variant (URL1)

5. **Additional diets and molecules which may have synergic effects with ARS [4]**. Possible synergic combinations between ARS and other therapeutic molecules also deserve extensive studies:
   - **a.** Various diet-charts for DMD patients [URL]
   - **b.** Specific physical therapies [URL]
   - **c.** creatine monohydrate (URL)
   - **d.** simvastatin (URL1, URL2)
   - **e.** N-acetylcysteine (**NAC**) (URL; ARS may even be studied in combination with [or as a replaces of] NAC in paracetamol/acetaminophen intoxication/poisoning, because, similarly to NAC, ARS also increases the concentration of glutathione in all cells, including hepatocytes by activating glutathione synthase via NRF2 pathway)
   - **f.** melatonin [URL]
   - **g.** Medical laser [URL]
   - **h.** SIRT1 activators [URL]
   - **i.** Protandim® (a NRF2 activating combination of herbal dietary supplements) [URL]
   - **j.** various vitamins: vitamin C, vitamin E, vitamin D3, vitamins from the B complex etc.

6. **Other potential uses of ARS [4]**.
   - **a.** Given the spectrum of NRF2 cellular/tissular different concentrations (kidney > muscles > lungs > heart > liver > brain), ARS (as a very efficient NRF2 activator with excellent bioavailability in all these listed vital organs) has a significant therapeutic potential in renal, hepatic, pulmonary, heart, liver and even brain infectious and/or inflammatory and/or degenerative diseases (possibly also including mental disorders like depression, anxiety etc). Given that kidneys have the highest NRF2 tissular concentration, ARS deserves a special focus in studying the treatment with ARS PO in various nephrologic/kidney disease like: various types of (progressive) glomerulonephritis, nephrotic syndrome, urinary tract infections (**UTIs**) (especially pyelonephritis), chronic kidney disease (**CKD**) and even hemolytic-uremic syndrome (**HUS**) and even Covid-19 (which, by triggering endothelial inflammation, frequently has heart, renal and coagulation complications, not only pulmonary complications) so that to prevent renal scaring or other possible mild or serious complications of these kidney diseases.
   - **b.** Given its "hybrid" antimicrobial and anti-inflammatory effects (plus its demonstrated stability in nebulized form), ARS deserves extensive studies on its possible capacity to prevent airway tract infections similarly to inhaled antibiotics in recent specific studies on DMD patients with respiratory distress/insufficiency [URL] of various infectious or non-infectious etiologies.
   - **c.** ARS may be tested as adjuvant in various doses (2-3-4-5-..10 ml x 1-2-3/day) as adjuvant treatment with possible good results on pulmonary/airways inflammation (because of its anti-inflammatory properties via NRF2 pathway) and viral/bacterial infections (because of its direct bactericidal and virucidal properties).
   - **d.** Given its corticoid-like anti-inflammatory effects, ARS also deserves extensive studies (alone or in various combinations with inhalatory, oral or parenteral corticosteroids) in all diseases which usually respond to corticoids, like pulmonary sarcoidosis, primary or secondary pulmonary fibrosis, cystic fibrosis (because of its hybrid anti-microbial and anti-inflammatory mechanism), scleroderma with pulmonary determination (because ARS significantly diminishes chronic inflammation and thus may prevent fibrosis). The results may be even better when ARS nebulizations are associated with ARS consumption PO. Of course that ARS may be first tested on various mouse models of chronic pulmonary inflammation of various infectious, autoimmune, genetic and non-genetic diseases.
   - **e.** ARS may also have some interesting effects on extracellular matrix (**EM**) and interstitial (stromal) cells (**ICs**), especially on telocytes, which are a novel defined type of ICs (in the field of stem cells), with very long (tens to hundreds of micrometres) and very thin prolongations called "telopodes": these telopodes present an alternation of thin segments called "podomeres" (with caliber mostly < 200 nm, below the resolving power of light microscopy) and dilated segments called "podoms", which accommodate a relatively large number of mitochondria (on which ARS was proven to have some significant effects via NRF2 pathway but also via other

genetic pathways [see the 1st published case on ARS effects in DMD]), (rough) endoplasmic reticulum and caveolae - the so-called "Ca2+ uptake/release units".

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Final conclusions [4]

1. ARS is plausibly the strongest (artificial) NRF2 selective activator ever produced by humans in a lab: that is why ARS may be regarded as a very important discovery in redox medicine and human/animal medicine/biology in general.
2. ARS effects in DMD patients appear to be reproducible, because the response to ARS is quite similar in all these three published ARS-treated DMD cases: that makes ARS a very promising new strategy to be further studied in DMD and BMD treatment/management. Furthermore, we predict that ARS effects in BMD patients (which have a less affected phenotype) may be even more remarkable.
3. Obviously, further extensive studies are needed to better understand the cellular effects of various ARS dosages and ARS combinations with other (possibly synergistic) therapeutic molecules/drugs (as previously detailed).
4. ARS therapy is significantly more expensive than oral corticosteroids but ARS therapy has the advantage to have zero toxicity (in principle) and to be significantly less expensive than ataluren or exon skipping therapy for example.

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3. **Competing interests:** the author of this paper was invited a couple of times to present ARS and his clinical experience with ARS, but with no financial remuneration and no competing interests.

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(most of the references were already included as hyperlinks/URLs in the text)

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