

Lysine Therapy for SARS-CoV-2

Christopher Kagan, Alexander Chaihorsky, Rony Tal, Bo Karlicki.

Until treatments with wide universality across target viral families become a reality, pandemics will continue to inflict severe medical and economic losses on the world's population, as the current situation demonstrates. Both therapeutic and vaccine arms of viral defense should be developed with universality in mind, and our group, Bio-Virus Research, has been working on both universal vaccines and universal therapeutic approaches for decades. In this letter we report our current results using L-lysine therapeutically against SARS-CoV-2.

The first report of the clinical use of L-lysine, written by the lead author of this article, appeared in *The Lancet* in 1974. (1) The mechanism of action and clinical follow up confirming its effectiveness in the treatment of herpes was published in 1978 (2), and in-vitro confirmation of the inhibition of arginine by lysine was published in 1985. (3) Since then L-lysine supplementation with arginine restriction has become a recognized treatment worldwide, and the generally used dosage ranges between 100 mg to 4 grams a day; notably no toxicity has been reported with up to 8 grams per day. (4) Lysine therapy appears to apply universally across the entire family of herpes viruses with no exceptions reported. Examples in humans include cytomegalovirus and zoster. (2) Lysine has been shown to be suppressive in both RNA and DNA viruses, examples include the RNA-type mouse encephalomyelitis virus, and the DNA-type adenovirus type 1, SV 40, and polyoma, and the herpes virus in chickens that causes Marek's disease is known to be arginine dependent. (2) The action of lysine is complex with interference of L-arginine incorporation into the virus by L-lysine established. (2) (3) Lysine inhibits arginine absorption in the intestine competitively lowering arginine levels, as well as inhibiting arginine reabsorption in the renal tubules. (2) A more complex mechanism with respect to SARS-CoV-2 is strongly suggested in multiple references which lay a foundation for further investigation beyond the scope of this clinical report. (6) (9) (10) (11) (12) (17) (20) (23)

A report in 2016 which included L-lysine showed a positive clinical outcome against MERS-CoV in-vitro, although not SARS-CoV-2 which had not yet appeared. (5) Given that L-lysine appears to operate universally within the herpes viral family, it would be reasonable to expect it to work in the entire SARS viral family. Our clinical experience demonstrates effectiveness against SARS-CoV-2, and it is therefore likely to work in MERS-CoV and other members of the Coronavirus family in-vivo. Dietary lysine

deficiency is known to impair both antibody responses and cell-mediated immune response. (7) Lysine improves the immune system. (4)

We tested the clinical efficacy of lysine on SARS-CoV-2. Tabulated data from 40 + subjects, and non-tabulated data from 100+ subjects; 8 were in the United States, and the majority in the Dominican Republic. The age ranged between 16 to 77, with 55% of the tabulated group being female. Approximately 50% of the subjects were PCR or rapid test Covid confirmed. Approximately 50% were febrile, 30% had cough/throat, 35% anosmia, 50% CNS/muscle pain, and 45% had other symptoms.

The dose range administered was 1000 mg to 4000 mg, with the latter rarely given, and an average dose of 2000 mg. We do not recommend exceeding 3000 mg due to possible bradykinin buildup causing a cough or increasing coughing in some subjects. (19) The dosage schedule recommended based on our study for acute cases (less than 1 month with symptoms) is a base dose of 1000 mg twice on day 1, increasing, if needed, by 500 mg to 1000 mg for a total not exceeding 3000 mg on day 2. From day 3 forward, some patients may require as high as 3500 mg. The recommended treatment times are one hour before breakfast, and 3 pm on day 1 with the times advanced earlier in the afternoon on day 2 if needed, opening a 9 pm time slot for a third dose. All doses should be taken a minimum of 1 hour before a meal, and with two cups of water. Two cups of water aids in absorption, hydration, anticoagulation, and dampens appetite which results in a decrease in the quantity of unintended arginine ingestion. A first day emergency dose of 2000 mg together (try not to exceed 4 grams in total on day 1) or a few hours apart yields outstanding results. There are many charts available of the lys/arg ratios in various foods, and a dietary ratio of 2.0 to 3.0 lysine to 1.0 arginine for the first few days is recommended. The ratio can be lowered to 1.5 to 3.0 lysine to 1.0 arginine once near full symptom control is achieved. Restriction of coffee (and other high caffeine drinks), the importance of which cannot be stressed enough, and observing the arginine restricted diet is critical to the speed of recovery and success of treatment. Additional cautionary notes are listed at the bottom of the letter, and these cautions should be observed in follow-up clinical studies.

No trend was noted between sexes, ages, or co-morbidities in relation to lysine treatment. Approximately 80% of acute stage Covid-19 sufferers given lysine displayed a minimum 70% reduction in symptoms in the first 48 hours (not including long term symptomatic subjects). Excluding long term subjects, treatment times vary from 2 days to 3.5 weeks, with many variables at play. Patients who started lysine in the hospital were

discharged an average of 3 days after starting treatment. Treatment should be continued regardless of negative results, until low dose lysine is reached, and no symptoms are observed. Even when lysine was in short supply, subjects on 2 grams on day 1, and 1 gram the following days, while adhering to the dietary restrictions, had slightly delayed but timely recoveries. Resuming physical activity too early during recovery sometimes resulted in setbacks. Several of the inpatients, tabulated and non, after starting this protocol were RT-PCR negative on day 2 to 3, coinciding typically with their discharge. A larger sample size and randomized controlled trials with RT-PCR daily testing will be required to assess the true time to conversion to seronegative. Five patients who fasted on day 1, due to lack of appetite, were noted to have a significant reduction in the time and severity of febrile and non-febrile symptoms. It is assumed that zero food intake equated to no arginine consumed, and hence faster response time. For this group, the time to significant reduction in symptom varied from 4 hours to 18 hours (with only a few symptoms remaining). It is important to note that while the average subject may be completely asymptomatic on day 3 or 4, if they stop treatment/exhaust lysine supply, on many occasions, symptoms return, albeit usually reduced in severity. Typically for this group, symptoms abate within a few hours of resuming their lysine.

Lysine is a treatment, not a cure, and is dependent on the immune system response gathering momentum to further control the illness. All should remain on at least a maintenance dose of 1 gm for a minimum of a 1 week (preferably 2 weeks or more) after all symptoms have abated including following dietary restrictions for 3 weeks to prevent relapse. Evidence of asymptomatic clotting for those who stopped the regimen too early was observed. Coffee (associated arginine increase) can overwhelm lysine rendering it ineffective until the caffeine effect subsides. The caffeine effect displaces lysine from the metabolic pathways. (18) Coffee/high caffeine consumption was the most common behavior of long term symptomatic subjects, followed by a vegetarian/lysine deficient diet and exercising. Coffee/high caffeine drinks should be avoided during treatment and for 3 weeks after recovery at a minimum. Our treatment protocol has been used in more than 180 patients, with 40+ reported here. Only 1 subject was hospitalized after starting lysine for secondary bacterial infection. He was discharged 6 days later, with no long-term effects. One Covid-19 confirmed fatality due to secondary bacterial infection occurred. Obviously more studies, including randomized controlled trials, are required for full clinical understanding.

One of the most important observations in relation to lysine was the incredibly short time to eliminate/reduce fever presumably due to extinguishing the associated cytokine storm. Cytokine storm appears to be extinguished in hours, based on the 5 inpatients

who appeared to be in severe crisis when lysine was administered who showed very rapid reduction in symptoms and stabilization. CRP levels returned to normal, yet D-dimer levels were high in some subjects. Only a small percentage of subjects on lysine were febrile past 24 hours, and most were relieved in less than 12 hours with proper doses and dietary restrictions. IL-10 inhibits the synthesis of IL-6, TNF and IL-1 beta which are implicated in fever. (8) IL-10 serves as an endogenous antipyretic. (8) Lysine deficiency raises IL-6 inflammatory cytokine levels, so lysine potentially has an IL-6 inhibitory effect, and lysine also increases IL-10 anti-inflammatory cytokines as shown in the liver. (7) Therefore, it is logical to assume that supplementation with lysine could restore or augment IL-10 levels resulting in downregulating proinflammatory cytokines, in turn eliminating fevers and cytokine storms. IL-6 inhibitors for patients with severe Covid-19 are associated with decreased intubation, reduced mortality, and increased discharge. (13) L-lysine decreases nitric oxide production (14), thereby limiting a key role in the pathogenesis of inflammation, and thus lysine may serve an anti-inflammatory role (15) by reducing pro-inflammatory cytokines (24). These clinical results suggest that lysine appears highly suppressive of viral replication, and if these results are confirmed by further studies, lysine should significantly flatten the curve, reduce mortality and hospital bed utilization while we await a curative vaccine or vaccines, ideally one with universal application across the entire Coronavirus group.

It might be that the combination of suppressive lysine and vaccination is superior to either alone. There may be places in the world where even inexpensive lysine is unaffordable, but high lysine foods combined with arginine restriction might still serve the purpose. Our hope is that these findings will encourage those in a position to perform follow-up studies to do so, hopefully confirming its usefulness, and further refining our understanding of optimal dosage, mechanisms, routes of administration and how to maximize the efficacy of this therapy.

Cautionary note: Long term asymptomatic (over 1 month) and medically fragile patients should exercise caution and use low dose lysine for the initial days and incrementally raise their dose 500 mg every 4 to 5 days, until reaching 2500 mg daily and evaluate. Higher doses have been used, but the concern is that doses higher than 3000 mg could result in occult clots embolizing. No coffee, exercise, marijuana, or arginine rich foods during treatment is included in the recommended protocol. Lysine has been reported to nearly double serum zinc levels without supplementation. (16) Zinc and calcium should not be given with lysine since lysine also raises calcium levels. (22) Patients on pacemakers should be under close clinical observation since lysine might increase cardiac output (21) and increases pulmonary resistance. (14) Clinicians who are

interested in more details may contact us for additional information at Bio-Virus Research +1(775) 742 8811, xyz1953@gmail.com).

Bio-Virus Research Inc.
5774 Tappan Dr.
Reno, Nevada, USA
xyz1953@gmail.com
+1(775) 742-8811

1. Kagan, C.; Lysine therapy for herpes simplex. *Lancet* i: 137 (1974).
2. Griffith, R. S.; Norins, A. L.; Kagan, C.; A multicentered study of lysine therapy in herpes simplex infection. *Dermatologica* 156:257-267 (1978).
3. Griffith, R. S.; DeLong, D. C.; Nelson, J. D.; Relation of arginine-lysine antagonism to herpes simplex growth in tissue culture. *Chemotherapy* 27: 209-213 (1981).
4. PubChem (internet). Bethesda (MD) National Library of Medicine (US), National Center for Biotechnology Information; 2004- Pubchem compound summary for cid 5962, lysine; (cited 2020 aug. 28) available from:
<http://pubchem.ncbi.nlm.nih.gov/compound/lysine>.
5. Muller, C.; Kari, N.; Ziebuhr, J.; Pleschka, S.; D, l-lysine acetylsalicylate + glycine impairs coronavirus replication. *Journal of Antivirals & Antiretrovirals* 8(4) 142-150 (2016).
6. Riley, F. L.; Martin. L.; Morin, E. L.; Stephens, E.E.; Hilton, B. L.; Polyriboinosinic-polyribocytidylic acid-poly-l-lysine (poly(icl) without carboxymethylcellulose (cmc): a new primate-effective interferon inducer. *Proceedings of the Society for Experimental Biology and Medicine* 169: 183-188 (1982).
7. Han, H.; Yin J.; Wang, B.; Huang, X.; Yao, J.; Zheng, J.; Fan, W.; Li, T.; Yin, Y.; Effects of dietary lysine restriction on inflammatory responses in piglets. *Scientific Reports* 2451 (2018).
8. Leon, L.R.; Kozak.; W., Rudolph, K.; Kluger, M. J.; An antipyretic role for interleukin-10 in LPS fever in mice. *Am. J. Physiol.* 276 (1999).
9. Heurich, A.; Hofmann-Windkler, H.; Grier, S.; Liepold, T.; Jahn, O.; Pohlmann, S.; Tmprss2 and adam17 cleave ace2 differentially and only proteolysis by tmprss2 augments entry driven by the severe acute respiratory syndrome coronavirus spike protein. *Journal of Virology* 88: 1293-1307 (2014).
10. Saito, S.; Matsui, S.; Wantanabe, M.; Waga, T.; Kajiwara, Y.; Shirota, M.; Iijima, M.; Kitabate, K.; Matsushita Y.; Moriguchi, I.; Inhibitory activity and protein binding of L-lysine derivatives as angiotensin converting enzyme inhibitors. *Arzneimittelforschung* 1078-81, 1990.
11. Melen, K.; Kinnunen, L.; Julkunen I.; Arginine/lysine-rich structural element is involved in interferon-induced nuclear import of STATs. *J. Biol. Chem.* 16447-55 (2001).

12. Baral, R.; White, M.; Vassilliou, V. S.; Effect of renin-angiotensin-aldosterone system inhibitors in patients with covid-19; a systemic review and meta-analysis of 28,872 patients. *Current Atherosclerosis Report* 22, 61 (2020).
13. Sinha, P.; Mostaghim, A.; Bielick, C. G.; McLaughlin, A.; Hamer, D. H.; Wetzler, L. M.; Bhadelia, H.; Fagan, M. A.; Linas, G. P.; Assoumou, S. A.; Leong M. H.; Lin, N. H.; Cooper, E. R.; Brade, K. D.; White, L. F.; Barlam, T. F.; Sagar, M.; The Boston medical center covid-19 treatment panel.; Early administration of interleukin-6 inhibitors for patients with severe covid-19 disease is associated with decreased intubation, reduced mortality, and increased discharge. *International Journal of Infectious Diseases* 99: 28-33 (2020).
14. Carter, B. W.; Chicoine, L. G.; Nelin, L.D.; L-lysine decreased nitric oxide production and increases vascular resistance in lungs isolate from lipopolysaccharide-treated neonatal pigs. *Pediatric Research* 55: 979-987 (2004).
15. Sharma, J.N.; Al-Omran, A.; Parvathy S. S.; Role of nitric oxide in inflammatory diseases. *Inflammapharmacology* 15(6): 252-259 (2007).
16. Rushton, D.H.; Nutritional factors and hair loss. *Clin. Exp. Dermatol.* 27(5): 396-404 (2002).
17. Ismawati, R.; Wirdjatmadi, B.; Priyatna, Y.; Mertaniasih, N. M.; The effect of zinc, lysine, and vitamin A supplementation to increase cellular immune response of pulmonary tuberculosis patients. *Biochemistry & Physiology: open access* 55:2168 (2015).
18. Nikolic, J., Bjelakovic, G.; Stojanovic, I.; Effect of caffeine on metabolism of l-arginine in the brain. *Mol. Cell. Biochem.* 244:125-128 (2003).
19. Taddei, S.; Bortolotto, L.; Unraveling the pivotal role of bradykinin in ace inhibitor activity. *Am. J. Cardiovasc. Drugs* 16(5) 309-321 (2016).
20. Boldt, A.; Gergs, U.; Frenker, J.; Simm, A.; Silber, R-E; Klockner, U.; Neumann, J.; Intropic effects of l-lysine in the mammalian heart. *Naunym Schmiedebergs Arch. Pharmacol.* 380 (4): 293-301 (2009).
21. Li; Wenhui & Wong.; Fang & Kuhn.; Jens & Huang.; l-Chueh & Choe.; Hyeryun & Farzan, M.; Animal origins of severe acute respiratory syndrome coronavirus; insight from ace-s-protein interactions. *Journal of Virology* 80: 4211-4219 (2006).
22. Civitelli, R.; Villareal, D.T.; Agnusdei, D.; Nardi, P.; Avioli, L.V.; Gennari.; C. Dietary L-lysine and calcium metabolism in humans. *Nutrition* 8(6): 400-405 (1992).
23. Almansour, H.; <http://www.researchgate.net/publication/340334873coronavirus> prophylaxis (the role of lysine amino acid in the prevention of viral attachment to the human cells). 4 (2020).
24. Kankuri, E.; Hamalainen, M.; Hukkanen, P.; Salmenpera,P.; Kivilaakso,E.; Vappatalo, H.; Moilanen, E.; Suppression of pro-inflammatory cytokine release by selective inhibition of inducible nitric oxide synthase in mucosal explants from patients with ulcerative colitis. *Scandinavian Journal of Gastroenterology* 38: 186-192 (2003).