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General information

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<u>Common name</u>: Alpha-lipoic Acid (ALA)

Alternate names:

Thioctic Acid; Lipoic Acid; Acetate Replacing Factor; R-ALA; S-ALA; Thioctacid, 1,2-Dithiolane-3-pentanoic acid, 6,8-dithiooctanoic acid.

Routes of administration:

Intravenous (IV), oral, vaginal suppository (only IV will be reviewed in this monograph).

Reported uses in cancer care:

IV ALA has been used by integrative cancer care practitioners with goals of improving survival, tumor response and quality of life (QoL), and alleviating chemotherapy side effects such as peripheral neuropathy.

Summary

IV ALA is mainly used in integrative cancer care for its antioxidant properties, as a means to stimulate glutathione synthesis, strengthen the effects of other antioxidants (e.g., vitamin C and E), and enhance insulin signaling. In total, seven studies reporting on 46 patients were included in Monographs are created by the Patterson Institute for Integrative Oncology Research team and are updated approximately every two years, or when significant new literature is published. An update on a previous search was completed in Medline and Cochrane Library for IV ALA on January 20, 2023. The previous search was from database inception. Eligibility criteria included Englishlanguage human studies in cancer reporting on efficacy, QoL, safety, or feasibility. A scoping review was performed to identify missing papers and background information. The papers were screened by two reviewers independently. Data was summarized into healthcare provider and patient monographs.

Pharmacokinetics

ALA is synthesized in humans in small amounts and it is mainly obtained from dietary sources such as organ meat, red meat, vegetables (spinach, tomatoes, broccoli), and fruits.^{1,20,21} ALA glutathione.^{20,21} This antioxidant capacity has been demonstrated clinically in one study of patients with advanced cancer.³¹

Glucose and insulin metabolism

Most studies and systematic reviews looked at the impact of ALA on glucose find a significant reduction in blood glucose and insulin, although some studies have found minimal impact.³²⁻³⁵ Hyperglycemia, commonly seen in diabetes and cancer, potentiates oxidative stress that can lead to neuronal and endothelial damage.²¹ It is speculated that ALA plays a role in the treatment and prevention of chemotherapy-induced peripheral neuropathy (CIPN) by participating in insulin production and enhancing glucose uptake in insulin-sensitive and insulin-resistant muscle tissue.²¹

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ALA+LDN protocol.³⁰ One person was still alive and free of any signs and symptoms 39 months after initial diagnosis (at the time of publication) without any standard therapies. A second person was treated for six months and observed an increased QoL, improvement of all symptoms, and no signs of disease recurrence on a PET scan. A third person exhibited immediate improvement in symptoms and was well enough to undergo surgery.

An additional case report describes a 61 year old man with follicular lymphoma who was first treated with a series of nine IV ALA therapies followed by six months of LDN.⁴¹ After 6 months of therapy the patient had complete resolution of multiple large, metabolically active, pathologic lymph nodes, and remained symptom free at the time of publication (1-year).

Finally, a case series included 11 patients with advanced metastatic cancer, 10 of whom were considered chemoresistant and offered palliative care only.⁴⁰ They received what the authors described as a metabolic treatment of 600 mg/day IV lipoic acid, 500 mg 3x/day of hydroxycitrate (HCA), and 5 mg of LDN at bedtime. Two patients died due to cancer progression within two months. Another two patients were switched to chemotherapy combined with metabolic treatment, and of those, one reported a dramatic tumor response. The rest of the patients had either stable or slow disease progression. None of the patients experienced significant side effects. Case 11 in this series had advanced hormone-resistant prostate cancer and received anti-androgen therapy in addition to 600 mg IV lipoic acid and 500 mg of HCA/day and experienced a 90% decrease in PSA levels. Authors suggest these preliminary results imply a lack of toxicity and possible efficacy of metabolic treatment in advanced chemoresistant carcinoma.

ALA in combination with other natural health products (NHPs)

A case report described a 64-year-old man with stage 4 renal cell carcinoma (RCC) with lung metastases who progressed on conventional treatment and then received a multimodal treatment including IV ALA.⁴³ The treatment consisted of IV racemic ALA, IV vitamin C, oral LDN, oral NHPs (ALA, selenomethionine silymarin,

Fourteen patients were enrolled, of whom eight (57%) experienced an improvement in neurological symptoms. The median time to improvement was 4 weeks. Adverse events

should cautiously alongside used be chemotherapy and radiation therapy.

Other medications: ALA may interfere with thyroid metabolism and

17. Costantino M, Guaraldi C, Costantino D. Resolution of subchorionic hematoma and symptoms of threatened miscarriage using vaginal alpha lipoic acid or progesterone: clinical evidences. *Eur Rev Med Pharmacol Sci.* Apr 2016;20(8):1656-63.

18. Ambrosi N, Arrosagaray V, Guerrieri D, et al. -Lipoic Acid Protects Against Ischemia-Reperfusion Injury in Simultaneous Kidney-Pancreas Transplantation. *Transplantation*. Apr 2016;100(4):908-15. doi:10.1097/tp.00000000000981

 Casciato P, Ambrosi N, Caro F, et al. -lipoic acid reduces postreperfusion syndrome in human liver transplantation - a pilot study. *Transpl Int*. Dec 2018;31(12):1357-1368. doi:10.1111/tri.13314
 Biewenga GP, Haenen GR, Bast A. The pharmacology of the antioxidant lipoic acid. *Gen*

Pharmacol. Sep 1997;29(3):315-31. doi:10.1016/s0306-3623(96)00474-0

21. Gor ca A, Huk-Kolega H, Piechota A, Kleniewska P, Ciejka E, Skibska B. Lipoic acid - biological activity and therapeutic potential. *Pharmacol Rep.* 2011;63(4):849-58. doi:10.1016/s1734-1140(11)70600-4

22. Packer L. alpha-Lipoic acid: a metabolic antioxidant which regulates NF-kappa B signal transduction and protects against oxidative injury. *Drug Metab Rev.* May 1998;30(2):245-75. doi:10.3109/03602539808996311

23. Breithaupt-Grögler K, Niebch G, Schneider E, et al. Dose-proportionality of oral thioctic acid-coincidence of assessments via pooled plasma and individual data. *Eur J Pharm Sci.* Apr 1999;8(1):57-65. doi:10.1016/s0928-0987(98)00061-x

24. Uchida R, Iwamoto K, Nagayama S, et al. Effect of -Cyclodextrin Inclusion Complex on the Absorption of R- -Lipoic Acid in Rats. *Int J Mol Sci*. May 4 2015;16(5):10105-20. doi:10.3390/ijms160510105

25. Brufani M FR. (R)- -lipoic acid oral liquid formulation: pharmacokinetic parameters and therapeutic efficacy. 2014 Aug; . *Acta Bio-medica : Atenei Parmensis* 2014;85((2):):108-115.

26. Gleiter CHS, B.S.; Hermann, R.; Elze, M.; Blume, H.H.; Gundert-Remy, U. Influence of food intake on the bioavailability of thioctic acid enantiomers. *Eur J Clin Pharmacol* 1996;50:513–514.

27. Takahashi H, Bungo Y, Mikuni K. The aqueous solubility and thermal stability of -lipoic acid are enhanced by cyclodextrin. *Biosci Biotechnol Biochem*. 2011;75(4):633-7. doi:10.1271/bbb.100596

28. Hermann R, Niebch G, Borbe HO, et al. Enantioselective pharmacokinetics and bioavailability of different racemic -lipoic acid formulations in healthy volunteers. *European Journal of Pharmaceutical Sciences*. 1996/05/01/ 1996;4(3):167-174. doi:https://doi.org/10.1016/0928-0987(95)00045-3

29. Mantovani G, Macciò A, Madeddu C, et al. The impact of different antioxidant agents alone or in combination on reactive oxygen species, antioxidant enzymes and cytokines in a series of advanced cancer patients at different sites: correlation with disease progression. *Free Radic Res.* Feb 2003;37(2):213-23. doi:10.1080/10715760303849

30. Berkson BM, Rubin DM, Berkson AJ. Revisiting the ALA/N (alpha-lipoic acid/low-dose naltrexone) protocol for people with metastatic and nonmetastatic pancreatic cancer: a report of 3 new cases. *Integrative cancer therapies*. Dec 2009;8(4):416-22. doi:10.1177/153m1cn.04 682]TJETQq0.00000912 0 612 792 r

35. Jibril AT, Jayedi A, Shab-Bidar S. Efficacy and safety of oral alpha-lipoic acid supplementation for type 2 diabetes management: a systematic review and dose-response meta-analysis of randomized trials. *Endocr Connect*. Oct 1 2022;11(10)doi:10.1530/ec-22-0322

36. Ganapathy-Kanniappan SG, J.F. . Tumor glycolysis as a target for cancer therapy: Progress and prospects. *Mol Cancer*. 2013;12, :152.

37. Zhang C, Liu J, Liang Y, et al. Tumour-associated mutant p53 drives the Warburg effect. *Nat Commun.* 2013;4:2935. doi:10.1038/ncomms3935

38. Gedlicka C, Scheithauer W, Schüll B, Kornek GV. Effective treatment of oxaliplatin-induced cumulative polyneuropathy with alpha-lipoic acid. *J Clin Oncol*. Aug 1 2002;20(15):3359-61. doi:10.1200/jco.2002.99.502

39. Gedlicka C, Kornek GV, Schmid K, Scheithauer W. Amelioration of docetaxel/cisplatin induced polyneuropathy by alpha-lipoic acid. *Ann Oncol*. Feb 2003;14(2):339-40. doi:10.1093/annonc/mdg051
40. Schwartz L, Buhler L, Icard P, Lincet H, Steyaert JM. Metabolic treatment of cancer:

intermediate results of a prospective case series. *Anticancer research*. Feb 2014;34(2):973-80.

41. Berkson BM, Rubin DM, Berkson AJ. Reversal of signs and symptoms of a B-cell lymphoma in a patient using only low-dose naltrexone. *Integrative cancer therapies*. Sep 2007;6(3):293-6. doi:10.1177/1534735407306358

42. Berkson BM, Rubin DM, Berkson AJ. The long-term survival of a patient with pancreatic cancer with metastases to the liver after treatment with the intravenous alpha-lipoic acid/low-dose naltrexone protocol. *Integrative cancer therapies*. Mar 2006;5(1):83-9. doi:10.1177/1534735405285901

43. Berkson BM, Calvo Riera F. The Long-Term Survival of a Patient With Stage IV Renal Cell Carcinoma Following an Integrative Treatment Approach Including the Intravenous -Lipoic Acid/Low-Dose Naltrexone Protocol. *Integrative cancer therapies*. Sep 2018;17(3):986-993. doi:10.1177/1534735417747984

44. Han T, Bai J, Liu W, Hu Y. A systematic review and meta-analysis of -lipoic acid in the treatment of diabetic peripheral neuropathy. *Eur J Endocrinol*. Oct 2012;167(4):465-71. doi:10.1530/eje-12-0555

45. Ziegler D. Thioctic acid for patients with symptomatic diabetic polyneuropathy: a critical review. *Treat Endocrinol.* 2004;3(3):173-89. doi:10.2165/00024677-200403030-00005

46. Mijnhout GS, Kollen BJ, Alkhalaf A, Kleefstra N, Bilo HJ. Alpha lipoic Acid for symptomatic peripheral neuropathy in patients with diabetes: a meta-analysis of randomized controlled trials. *Int J Endocrinol*. 2012;2012:456279. doi:10.1155/2012/456279

47. Guais A, Baronzio G, Sanders E, et al. Adding a combination of hydroxycitrate and lipoic acid (METABLOCTM) to chemotherapy improves effectiveness against tumor development: experimental results and case report. *Invest New Drugs*. Feb 2012;30(1):200-11. doi:10.1007/s10637-010-9552-x

48. Guo Y, Jones D, Palmer JL, et al. Oral alpha-lipoic acid to prevent chemotherapy-induced peripheral neuropathy: a randomized, double-blind, placebo-controlled trial. *Support Care Cancer*. May 2014;22(5):1223-31. doi:10.1007/s00520-013-2075-1

49. Jeffrey S, Samraj PI, Raj BS. The Role of Alpha-lipoic Acid Supplementation in the Prevention of Diabetes Complications: A Comprehensive Review of Clinical Trials. *Curr Diabetes Rev.* 2021;17(9):e011821190404. doi:10.2174/1573399817666210118145550

50. Simone CB, Simone NL, Simone V. Antioxidants and other nutrients do not interfere with chemotherapy or radiation therapy and can increase kill and increase survival, part 1. *Altern Ther Health Med.* 2007;13(1):22-8.

51. Yasueda A, Urushima H, Ito T. Efficacy and Interaction of Antioxidant Supplements as Adjuvant Therapy in Cancer Treatment: A Systematic Review. *Integrative cancer therapies*. Mar 2016;15(1):17-39. doi:10.1177/1534735415610427

52. Sheikholeslami S, Khodaverdian S, Dorri-Giv M, et al. The radioprotective effects of alpha-lipoic acid on radiotherapy-induced toxicities: A systematic review. *Int Immunopharmacol*. Jul 2021;96:107741. doi:10.1016/j.intimp.2021.107741

53. Segermann J, Hotze A, Ulrich H, Rao GS. Effect of alpha-lipoic acid on the peripheral conversion of thyroxine to triiodothyronine and on serum lipid-, protein- and glucose levels. *Arzneimittelforschung*. Dec 1991;41(12):1294-8.

54. Khamaisi M, Rudich A, Potashnik R, Tritschler HJ, Gutman A, Bashan N. Lipoic acid acutely induces hypoglycemia in fasting nondiabetic and diabetic rats.