

Retinoic acid may significantly prevent lymphedema development

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A study conducted at the Keck School of Medicine of the University of Southern California (USC) showed that 9-cis retinoic acid (alitretinoin) could significantly prevent postsurgical lymphedema. Furthermore, the experiments were conducted with updated, easily reproducible mouse models that more accurately simulated lymphedema development in humans. The National Institutes of Health-funded study was published in the *Annals of Surgery*.

Lymphedema occurs when damaged lymph nodes are unable to drain properly, causing swelling and tissue buildup. Lymphedema affects 140 million individuals globally, including 5 million people in the United States whose lymphedema is related to cancer-related lymphadenectomy. As surgical developments continue to increase cancer survival rates, the prevalence of lymphedema is expected to rise. And with no known cure for post-surgical lymphedema, lymph node dysfunction can negatively impact long-term quality of life.

"Physically, lymphedema is both uncomfortable and inconvenient," said Alex Wong, MD, assistant professor of surgery at Keck School of Medicine and one of the co-corresponding authors of the study. "Some patients express frustration at things we take for granted, like getting dressed. And for many of them, the swollen and deformed extremity is an unwelcome reminder of the cancer they fought or are still fighting."

To examine the effect of alitretinoin, the research team induced lymphedema by making a small incision in the hind legs of mice rather

than the base of the tail, as previous studies had done. This updated model better simulated lymph node dysfunction in humans in that rodent tails are not subject to the effects of gravity to the same extent as human arms and legs. And more simply, humans do not have a tail.

"Developing a more effective model for lymphedema research is as much of an achievement from our research as illustrating the potential benefits of retinoic acid," said Young-Kwon Hong, PhD, associate professor of surgery at Keck School of Medicine and co-corresponding author of the study. Hong previously illustrated the potential benefits of alitretinoin on preventing lymphedema in petri-dish models before developing the mouse model.

After the hind paw incisions were repaired, the mice were divided into two groups. One group received daily injections of 9-cis retinoic acid, while the other received a vehicle solution as a control. The mice treated with the retinoic acid experienced less postsurgical edema and significantly less paw lymphedema compared to the control group. Moreover, the mice treated with the retinoic acid had much faster lymphatic drainage and increased lymphatic vessel density.

"Lymphatic drainage and maintenance of the integrity of the lymphatic vessels are two key factors in preventing lymphedema," Hong said. "9-cis retinoic acid's ability to accomplish both makes it a promising treatment option."

Alitretinoin is already approved by the Food and Drug Administration for the treatment of skin lesions in acquired immune deficiency syndrome-related Kaposi's sarcoma and eczema. If further studies prove fruitful, Wong hopes to establish a clinical trial for alitretinoin as a preventive measure against lymphedema.

"Our immediate next step is to experiment with timing," Wong said.

"Currently, physicians watch and wait for [lymphedema](#), but our study suggests that treatment at the time of surgery may be a more effective course."

More information: Athanasios Bramos et al. Prevention of Postsurgical Lymphedema by 9-cis Retinoic Acid, *Annals of Surgery* (2016). [DOI: 10.1097/SLA.0000000000001525](https://doi.org/10.1097/SLA.0000000000001525)

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