

DRAFT COPY

Focus



Allergy Research Group® Newsletter

April 2003

Long-term, Low-intensity Warfarin (Coumadin) Therapy Highly Effective Method of Preventing Recurrent Venous Thromboembolism: *Can Nattokinase Play a Role?* See page 2

New England Journal of Medicine, April 10th, 2003.

Dr. Ralph Holsworth on the use of Coumadin & Nattokinase with Practical Protocols See page 3

New Nattokinase Case Histories from Dr. Martin Milner, N.D. See page 3

Green Tea Components Stand Out for Enhancing Chemotherapy and Protecting Healthy Cells See page 4

Anti-Angiogenic Agents Treat Obesity See page 7

Bindweed Extract & MPGC* Reduce Plasma VEGF** in Cancer Patients See page 8

*Muramyl Polysaccharide-Glycan Complex

**Vascular endothelial growth factors

Rye Grass Extract & Asthma: Double-Blind, Placebo Controlled Study Demonstrates Dramatic Improvement See page 9

Dr. Freidrich Douwes, M.D. on the use of MPGC for Cancer See page 10

In This Issue

NEJM: Low-Dose Warfarin (Coumadin) Therapy Highly Effective Method of Preventing Recurrent Venous Thromboembolism: *Can Nattokinase Play a Role?* 2

Dr. Ralph Holsworth on the use of Nattokinase in Combination with Low-Dose Warfarin (Coumadin) . . . 3

Nattokinase: Case Histories from Dr. Martin Milner, N.D. 3

Green Tea Catechins & L-Theanine in Integrative Cancer Care Luke G. Huber, N.D. 4

Folkman's New Research: Anti-Angiogenic Agents Treat Obesity . . 7

Bindweed Extract & MPGC Reduce Plasma VEGF in Cancer Patients Daniel Rubin, N.D. 8

Rye Grass Extract & Asthma: Double-Blind Placebo Controlled Study; Evidence of Improvement Demonstrated 9

Dr. Freidrich Douwes, M.D. on the use of MPGC for Cancer . . 10

Abstract: Green Tea Extract Polyphenol May Have A Protective Effect On Parkinson's Disease . . 10

Allergy Research Group®
30806 Santiana Street, Hayward, CA 94544
Phone: 800-545-9960
Fax: 510-487-8682
www.AllergyResearchGroup.com



Long-term, Low-intensity Warfarin (Coumadin) Therapy Highly Effective Method of Preventing Recurrent Venous Thromboembolism

New England Journal of Medicine, April 10, 2003

The National Institute of Health recently discontinued what was to be a 5-year trial on the use of long-term, low-dose warfarin (Coumadin) therapy for the prevention of Recurrent Venous Thromboembolism (VTE). The "PREVENT" trial was stopped almost two years early, according to a recent report in the April 10th issue of the New England Journal of Medicine (see abstract below) because such strong benefits were observed that the study's independent Data and Safety Monitoring Board concluded that it was unnecessary to continue. **"This is an important finding for the estimated half million Americans who each year experience either deep vein thrombosis (DVT) or pulmonary embolism. These results suggest that low-dose warfarin is a safe and effective way to prevent future episodes of these potentially serious blood clotting problems."** - Claude Lenfant, M.D., NHLBI Director.

The randomized, double-blind PREVENT trial was designed to enroll 750 patients, aged 30 years and older, with documented idiopathic DVT or pulmonary embolism within the previous two years who had at least three uninterrupted months of treatment with full-dose warfarin.

The trial began in 1998 and was scheduled for completion in 2005, but instead was discontinued in December of 2002. When the study was terminated early, 508 patients at 52 clinical sites in the U.S.,

Canada, and Switzerland had been enrolled and followed for two years on average, with some patients followed for up to four years.

According to per-protocol and as-treated analyses, the reduction in the risk of recurrent venous thromboembolism was between 76 and 81 percent.

Recurrent DVT or pulmonary embolism occurred in 37 of 253 patients assigned to placebo (7.2 per 100 person-years) and in 14 of 255 patients assigned to low-dose warfarin with target international normalized ratio of 1.5 - 2.0 (2.6 per 100 person-years; risk reduction, 64%; hazard ratio, 0.36; 95% confidence interval, 0.19 - 0.67; $P < .001$).

The current standard of care for idiopathic DVT and pulmonary embolism is five to 10 days of intravenous or subcutaneous heparin followed by three to six months of full-dose warfarin. Often treatment is discontinued because of bleeding risk with long-term use of full-dose warfarin, leading to recurrent thrombosis in 6% to 9% of patients annually.

"The PREVENT results strongly suggest that long-term use of low-intensity warfarin should be considered a new standard of care for the management of venous thrombosis after stopping full-dose warfarin therapy," Dr. Ridker.

Abstract

Long-Term, Low-Intensity Warfarin Therapy for the Prevention of Recurrent Venous Thromboembolism

New England Journal of Medicine, April 10th, 2003.

Paul M Ridker, M.D., Samuel Z. Goldhaber, M.D., Ellie Danielson, M.I.A., Yves Rosenberg, M.D., Charles S. Eby, M.D., Steven R. Deitcher, M.D., Mary Cushman, M.D., Stephan Moll, M.D., Craig M. Kessler, M.D., C. Gregory Elliott, M.D., Rolf Paulson, M.D., Turnly Wong, M.D., Kenneth A. Bauer, M.D., Bruce A. Schwartz, M.D., Joseph P. Miletich, M.D., Henri Bounameaux, M.D., Robert J. Glynn, Sc.D., for the PREVENT Investigators

Background: Standard therapy to prevent recurrent venous thromboembolism includes 3 to 12 months of treatment with full-dose warfarin with a target international normalized ratio (INR) between 2.0 and 3.0. However, for long-term management, no therapeutic agent has shown an acceptable benefit-to-risk ratio.

Methods: Patients with idiopathic venous thromboembolism who had received full-dose anticoagulation therapy for a median of 6.5 months were randomly assigned to placebo or low-intensity warfarin (target INR, 1.5 to 2.0). Participants were followed for recurrent venous thromboembolism, major hemorrhage, and death.

Results: The trial was terminated early after 508 patients had undergone randomization and had been followed for up to 4.3 years (mean, 2.1). Of 253 patients assigned to placebo, 37 had recurrent venous thromboembolism (7.2 per 100 person-years), as compared with 14 of 255 patients assigned to low-intensity warfarin (2.6 per 100 person-years), a risk reduction of 64 percent (hazard ratio, 0.36 [95 percent confidence interval, 0.19 to 0.67]; $P < 0.001$). Risk reductions were similar for all subgroups, including those with and those without inherited thrombophilia. Major hemorrhage occurred in two patients assigned to placebo and five assigned to low-intensity warfarin ($P = 0.25$). Eight patients in the placebo group and four in the group assigned to low-intensity warfarin died ($P = 0.26$). Low-intensity warfarin was thus associated with a 48 percent reduction in the composite end point of recurrent venous thromboembolism, major hemorrhage, or death. According to per-protocol and as-treated analyses, the reduction in the risk of recurrent venous thromboembolism was between 76 and 81 percent.

Conclusions: Long-term, low-intensity warfarin therapy is a highly effective method of preventing recurrent venous thromboembolism.

Leading Nattokinase Researcher

Dr. Ralph Holsworth on the Use of Nattokinase in Combination with Low-Dose Warfarin

"New studies are indicating lower doses of warfarin (Coumadin). I believe a physician should use warfarin and nattokinase together and titrate the warfarin downward to maintain a prothrombin time of 18-20 seconds. This protocol will decrease the harmful effects of warfarin, while maintaining a safer level of blood anticoagulation with the positive effects of nattokinase. I suggest this protocol for physicians who are uncomfortable with eliminating warfarin completely, but who are interested in minimizing the negative effects of warfarin, and achieving the positive effects of nattokinase. This protocol could save thousands of patients from the harmful effects of warfarin."

Dr. Ralph E. Holsworth, Jr.
Leading nattokinase researcher

See Dr. Holsworth's Protocol on page 10.

Nattokinase:

Case Histories from Dr. Martin Milner, N.D.

Case 1 – Peripheral Vascular Disease

Case 1 is a female patient with an array of health problems including advanced peripheral vascular arterial disease. Her iliac artery was bypassed surgically due to full occlusion in 1999 with current occlusion of her popliteal artery. As a result, she was experiencing severe intermittent claudicating bilateral calf and thigh pain, worse at night and with exertion. She experienced cramps and pains throughout the night disrupting her sleep for years. Many therapies were unsuccessful in resolving her debilitating pain. She has a long history of using intravenous EDTA once monthly for five years and then once weekly for the last year without improvement. She is an avid and conscientious consumer of health supplements, having taken for many years an array of nutrients, none of which, in combination with intravenous EDTA improved her intermittent claudication. She began taking nattokinase in July of 2002, taking 2 caps 2x daily on an empty stomach. Within two weeks she reported that the heaviness and achiness on exertion in her left leg had improved 50-70%. Her muscles in her calves began to reduce in achiness and within 1-2 weeks she was sleeping through the night with no pain. After taking nattokinase for over 6 months, she had experienced only two episodes of waking at night with leg pain. She has reported no side effects throughout the course of therapy. In addition, with her history of mild hypertension, severe peripheral vascular arterial disease, left atrial enlargement she probably has some pulmonary hypertension and micro embolization in her lungs which has been helped significantly with nattokinase.

Case 2 – Pulmonary Emboli with Headaches

Case 2 is a 64 year-old female with a history of five prior episodes of pulmonary emboli (clots in the lungs), apparently due to lower extremity venous thrombi that mobilized into her lungs. The last episode was in 1977 with no new occurrences since vein stripping, which was performed in 1977. With her history, a possible chronic coagulation disorder aggravating her other conditions was suspected. Her other related conditions included migraine headaches and a long-standing seizure-like disorder. She began taking nattokinase 2 caps 2x daily upon rising and before bed in January of 2003. This reduced her headaches from 2-3x weekly to none for the first 30 days. When the first headache did occur in late February of 2003, she developed the pre-migraine symptoms of nausea and visual changes without ever developing head pain.

Case 3 – Fibromyalgia with Headaches

Case 3 is a female with a long standing history of chronic fatigue, fibromyalgia, persistent leg cramps, varicose veins, hypothyroidism, chronic migraines, GERD, colitis, mild osteoporosis, some degenerative disk disease (L 4-5), osteoarthritis in one knee, obesity, hypertension, aluminum and arsenic toxicity, severe adrenal insufficiency and food allergies. She has taken supplements extensively for many years. She began taking nattokinase in January 2003 2 caps 2x daily on an empty stomach, and then increased to 3 caps 2x daily in April 2003. After starting nattokinase her energy improved with complete resolution of her headaches and improved varicose veins. This are extraordinary a patient who has attempted a wide array of headache medications with no response.

Case 4 – COPD, Shortness of Breath, Pulmonary Microembolization with Pulmonary Hypertension, Essential Hypertension

Case 4 is a 49 year-old female with chronic fatigue, shortness of breath and stress-related illness. Patient is obese with a variety of cardiovascular conditions including heart palpitations, high blood pressure, Type IV Hyperlipidemia, Syndrome X, COPD with 30% airway obstruction, pulmonary hypertension, and reports swelling in feet. After taking nattokinase 2 caps 2x daily for 2.5 weeks, patient's breathing was dramatically improved as well as her fatigue. Patient is also able to walk around the block at a medium pace with no heavy breathing at all. She is also now able to grocery shop, and is even starting to walk longer distances wearing small ankle weights.

Case 5 – Peripheral Vascular Disease, possible TIA and DVT

Case 5 is a 63 year-old male with possible DVT and passive embolization, who reports a sensation of tightness in his legs and felt like he was standing for hours yet wasn't. He developed a suspected deep vein thrombus (clot) on physical examination, and was also blowing out bloody granules from his nose for three days. These bloody granules were of concern in assessing possible pulmonary microemboli. He also reports a history of pain in right leg, which was diagnosed as an inflamed vein, phlebitis. He also has possible transient ischemic symptom complex including cold nose, numbness around lips, cold upper extremities in paroxysms, intermittent cold tingling in his hands, face and feet. Reported coldness in hands, feet and back of head over into his face with a loss of sensation in hands, left foot slight loss of sensation. Patient began nattokinase, 2 caps 2x daily and all of the above symptoms resolved after one week.