JAOA LETTERS

As the premier scholarly publication of the osteopathic medical profession, *JAOA—The Journal of the American Osteopathic Association* encourages osteopathic physicians, faculty members and students at colleges of osteopathic medicine, and others within the healthcare professions to submit comments related to articles published in the *JAOA* and the mission of the osteopathic medical profession. The *JAOA*'s editors are particularly interested in letters that discuss recently published original research.

Letters to the editor are considered for publication in the *JAOA* with the understanding that they have not been published elsewhere and that they are not simultaneously under consideration by any other publication.

All accepted letters to the editor are subject to editing and abridgment. Letter writers may be asked to provide *JAOA* staff with photocopies of referenced material so that the references themselves and statements cited may be verified.

Readers are encouraged to prepare letters electronically in Microsoft Word (.doc) or in plain (.txt) or rich text (.rtf) format. The *JAOA* prefers that readers e-mail letters to jaoa@osteopathic.org. Mailed letters should be addressed to Gilbert E. D'Alonzo, Jr, DO, Editor in Chief, American Osteopathic Association, 142 E Ontario St, Chicago, IL 60611-2864.

Letter writers must include their full professional titles and affiliations, complete preferred mailing address, day and evening telephone numbers, fax numbers, and e-mail address. In addition, writers are responsible for disclosing financial associations and other conflicts of interest.

Although the *JAOA* cannot acknowledge the receipt of letters, a *JAOA* staff member will notify writers whose letters have been accepted for publication. Mailed submissions and supporting materials will not be returned unless letter writers provide self-addressed, stamped envelopes with their submissions.

All osteopathic physicians who have letters published in the *JAOA* receive continuing medical education (CME) credit for their contributions. Writers of original letters receive 5 AOA Category 1-B CME credits. Authors of published articles who respond to letters about their research receive 3 Category 1-B CME credits for their responses.

Although the *JAOA* welcomes letters to the editor, readers should be aware that these contributions have a lower publication priority than other submissions. As a consequence, letters are published only when space allows.

Graduating Osteopathic Medical Students' Perceptions and Recommendations on the Decision to Take the USMLE

To the Editor:

As an osteopathic physician who took the United States Medical Licensing Examination (USMLE) and an associate program director of one of the nation's largest allopathic internal medicine residency programs, I read the medical education article by Robert T. Hasty, DO, and colleagues[1] in the February issue with great interest. On the basis of a survey of graduating osteopathic medical students, Hasty et al[1] attempted to evaluate students' perceptions related to the USMLE. As the primary reason for taking the USMLE, 46% of the respondents cited keeping their options open, and 35.5% cited enhancing their chances of getting into an allopathic residency.[1]

It is important to point out that graduating osteopathic medical students need *not* take the USMLE to better their chances of being accepted into an allopathic residency—with rare exceptions. These exceptions include training programs in highly competitive fields, such as neurosurgery, ophthalmology, dermatology, and orthopedic surgery. The fact is that most allopathic residency program directors know nothing about the Comprehensive Osteopathic Medical Licensing Examination-USA (COMLEX-USA). They do not know about the general validity of COMLEX-USA, and they do not know what information is tested or how to accurately compare this test's scores to those of the more familiar USMLE. Thus, allopathic residency program directors typically make baseless, assumed, and subjective comparisons between the 2 examinations.

Osteopathic medical students who score higher on COMLEX-USA than the USMLE will foster a belief that the former is not as rigorous as the latter. As a result, some allopathic residency program directors may direct students to take the USMLE in order to be considered for residency training. The motivation for this recommendation is a lack of knowledge about COMLEX-USA, an unwillingness to accept osteopathic medical students (by using the test as an obstacle to overcome), or a lack of trust in the scores of COMLEX-USA.

I disagree with the contention of Hasty et al[1] that "the present study represents the first reasonably objective findings specific to this issue that might aid faculty in their ability to counsel osteopathic medical students on this topic." If their study described a survey of allopathic residency program directors—as they suggest be done in the future—then this statement could be valid. However, a survey of osteopathic medical students who have no role in making allopathic residency acceptance deci-

sions hardly makes the results objective. Rather, the results are incredibly subjective, replete with potential hearsay, second-hand knowledge, and supposition.

The American Osteopathic Association (AOA) should take a proactive role in ensuring that allopathic residency program directors understand the nuances of COMLEX-USA and that this test cannot be compared directly to the USMLE. The AOA should also work to ensure that osteopathic medical students not be disadvantaged if they do not take the USMLE. However, the AOA must accept the fact that a majority of osteopathic medical students seek allopathic residency training.[2,3] Between 2007 and 2011, the percentage of graduating osteopathic medical students who applied to the National Resident Matching Program varied between 52.4% (in 2011) and 56.3% (in 2010).[2,3] During that period, the number of osteopathic medical students who applied to the National Resident Matching Program increased from 1652 in 2007 to 2178 in 2011.[2,3]

Graduating osteopathic medical students want the best postgraduate training—regardless of whether it is osteopathic or allopathic. The osteopathic medical profession should attempt to understand why osteopathic medical students do not choose our own institutions for training, rather than continue to keep allopathic training programs in the dark about COMLEX-USA and its usefulness in student assessment.

I, along with most of the allopathic residency program directors at my institution, Jackson Memorial Hospital, suggest that osteopathic medical students not take the USMLE unless absolutely necessary. It is a costly, time-consuming, and stressful examination that the vast majority of osteopathic medical students need not take. Furthermore, taking parts of the USMLE series does not bolster one's chances at acceptance into an allopathic residency training program, but rather will stimulate the interviewer to ask about the rationale for so doing.

Osteopathic medical students should choose residency institutions at which they want to train. The AOA should make every effort to ensure that the osteopathic medical profession's examinations are understood by all—so that graduates of osteopathic medical schools can be privy to a quality education at any facility, even if it is allopathic.

Joshua D. Lenchus, DO, RPh
Associate Professor, Division of Hospital Medicine, Department of Medicine, University of Miami Miller School of Medicine; Associate Program Director, Jackson Memorial Hospital Internal Medicine Residency; Miami, Florida

References

1. Hasty RT, Snyder S, Suciu GP, Moskow JM. Graduating osteopathic medical students' perceptions and recommendations on the decision to take the United States Medical Licensing Examination. *J Am Osteopath Assoc*. 2012;112(2):83-89.

2. American Association of Colleges of Osteopathic Medicine. *Trends in Osteopathic Medical School Applicants, Enrollment and Graduates*. Chevy Chase, MD: American Association of Colleges of Osteopathic Medicine; March 2012. http://www.aacom.org/data/Documents/Trends-apps-enroll-grads.pdf. Accessed May 25, 2012.

3. National Resident Matching Program. *Results and Data: 2012 Main Residency Match*. Washington, DC: National Resident Matching Program; April 2012. http://www.nrmp.org/data/resultsanddata2012.pdf. Accessed May 25, 2012.

Response

Thank you for the opportunity to respond to the letter to the editor by Joshua D. Lenchus, DO, RPh, regarding the *JAOA* article I coauthored, "Graduating Osteopathic Medical Students' Perceptions and Recommendations on the Decision to Take the United States Medical Licensing Examination."[1] I agree with most of the comments made by Dr Lenchus, particularly with his assertion that "graduating osteopathic medical students need *not* take the USMLE [United States Medical Licensing Examination]." In addition, I agree that most osteopathic medical students are served well by their Comprehensive Osteopathic Medical Licensing Examination-USA (COMLEX-USA) scores as credentials for entry into residency programs accredited by either the Accreditation Council for Graduate Medical Education (ACGME) or the American Osteopathic Association (AOA). The COMLEX-USA scores are also essential credentials for licensure in all 50 states.[2-4]

Furthermore, Dr Lenchus brings an important perspective and his personal observations regarding the current practices of ACGME program directors. This perspective serves as an important contrast to the opinions of graduating osteopathic medical students, as reported in our study.[1]

I would like to point out that the AOA and the National Board of Osteopathic Medical Examiners (NBOME) are actively working together on educating residency program directors regarding COMLEX-USA.[5] The NBOME has made 6 major presentations on COMLEX-USA at national or regional meetings of residency program directors during the past year. The NBOME also includes a COMLEX-USA informational handout as part of the new residency program directors' orientation program. This handout was made available at the recent ACGME Annual Meeting, in March 2012, and can be obtained from the NBOME Web site[6] and in various graduate medical education newsletters. Since 2010, all ACGME residency program directors receive the NBOME Annual Report, and representatives from graduate medical education (eg, ACGME, Association of Osteopathic Directors and Medical Educators, Organization

of Program Directors Associations [of the Council of Medical Specialty Societies]) participate in a number of NBOME committees and activities, including NBOME's Liaison Committee. Upon the request of the NBOME, the AOA has added communicating with residency program directors about COMLEX-USA to its 2011-2013 Strategic Plan.[7]

I would further add that the discrepancies between the perceptions of graduating osteopathic medical students reported in our article[1] and the observations of Dr Lenchus articulate a need to better educate osteopathic medical students on these important issues.

Robert T. Hasty, DO
Program Director, Internal Medicine Residency, Nova Southeastern University College of Osteopathic Medicine (NSU-COM)/Palmetto General Hospital, Fort Lauderdale, Florida; Associate Professor, NSU-COM

References

1. Hasty RT, Snyder S, Suciu GP, Moskow JM. Graduating osteopathic medical students' perceptions and recommendations on the decision to take the United States Medical Licensing Examination. *J Am Osteopath Assoc.* 2012;112(2):83-89.

2. Burmeister JD. New COMLEX-USA-to-USML conversion formula needed [letter]. *J Am Osteopath Assoc*. 2011;111(2):119. http://www.jaoa.org/content /111/2/120.1.full.pdf+html?sid=3ca39401-f0e1-4ae9-9c43-fbcef72911d2. Accessed June 7, 2012.

3. Slocum PC. Response [letter]. *J Am Osteopath Assoc*. 2011;111(2):119-120.

4. Gimpel JR. Response [letter]. *J Am Osteopath Assoc*. 2011;111(2):120.

5. Gimpel JR. New COMLEX-USA-to-USMLE conversion formula needed [letter]. *J Am Osteopath Assoc.* 2010;110(10):577-578. http://www.jaoa.org/content /110/10/577.full.pdf+html?sid=3ca39401-f0e1-4ae9-9c43-fbcef72911d2. Accessed June 7, 2012.

6. COMLEX-USA at a glance: what residency program directors should know about COMLEX-USA. National Board of Osteopathic Medical Examiners Web site; 2011. http://www.nbome.org/docs/COMLEX-USA%20at%20a%20Glance%20for%20ACGME_Dually-Accredited%20Residency%20Programs.pdf. Accessed June 7, 2012.

7. American Osteopathic Association. *AOA Strategic Plan 2011-2013.* Chicago, IL: American Osteopathic Association; 2011:11-12. http://www.osteopathic.org/inside-aoa/about/leadership/Documents/aoa-strategic-plan-2011-2013.pdf. Accessed June 14, 2012.

Editor's Note: Dr Hasty is Vice Coordinator for Advanced Items, Chair of the Innovations in Testing Advisory Committee, and an item writer for the National Board of Osteopathic Medical Examiners.

The Failed Theratope Vaccine: 10 Years Later

To the Editor:

The year was 2002. There was excitement in the air. Immunology and oncology were finally coming together in what appeared to be the most novel agent in the field of breast cancer treatment since the revolutionary introduction of trastuzumab. A vaccine had been shown to stimulate antibody- and cell-mediated immune responses against tumor-associated antigens.[1] Phase I and II studies provided convincing evidence that this highly touted therapeutic breast cancer vaccine, dubbed Theratope (synthetic O-linked disaccharide, sialyl-Tn-keyhole limpet hemocyanin [STn-KLH]; Biomira Inc, Edmonton, Alberta, Canada), was the next big idea in the field.[1] Hundreds of researchers around the world were eager to see the results of phase III clinical trials of this promising agent.

One of the first studies describing the use of Theratope in clinical practice had been published in 1996 by MacLean and colleagues.[2] They described how Theratope produced clinically significant antibody titers and a marked increase in survival in patients with breast cancer.[2] Vaccine activity was also associated with expression of CD69+ lymphocytes and CA27.29 (MUC-1), a high-molecular-weight glycoprotein rich in serine and threonine residues.[3] Two phase II trials compared the use of low-dose cyclophosphamide with and without Theratope and found that there was a statistically significant increase in survival among patients treated with the STn-KLH vaccine (overall median survival, 19.1 months; n=50), compared with those patients not treated with the vaccine (overall median survival, 9.2 months; n=104).[4,5] The trials reported minimal toxic effects with mild injection-site reactions and flulike symptoms.[4,5] Sandmaier et al[6] tested Theratope in vitro in 33 high-risk patients with breast cancer after stem cell transplantation. The researchers reported in 1999 that they observed STn antigen-specific T-cell proliferation and peripheral blood lymphocyte lytic activity.[6,7]

The stage was set for mid-2003. Numerous in vitro and phase II studies had delivered encouraging results for Theratope. There was a wave of optimism in the air. One June day in 2003, however, there was breaking news[8]:

> Biomira Inc. (Nasdaq: BIOM) (TSX:BRA) and Merck KGaA of Darmstadt, Germany, announced today that the results from a large pivotal Phase III trial of Theratope(R) vaccine for women with metastatic breast cancer did not meet the two pre-determined statistical endpoints of time to disease progression and overall survival. However, one pre-stratified subset of patients in the treatment group, women on hormonal treatment following chemotherapy, appeared to show a favourable trend to improvement in survival. ... The Phase III randomized, double-blind trial was designed and powered primarily as a survival study. Enrolment [*sic*] in the trial totaled 1,030 women at more than 120 sites in 10 countries and, to date, is believed to be the largest trial of a therapeutic vaccine conducted in women with metastatic breast cancer.

In the study referred to in this June 2003 news report[8]—the final results of which were published in 2011[9]—week-12 antibody testing revealed high specific immunoglobulin G titers in the group treated with Theratope and no detectable anti-mucin antibodies in the control group.

However, median survival time between the treatment and control groups (23.1 months vs 22.3 months, respectively) was not significantly different.[9]

Researchers were shocked by the initial phase III results reported in 2003.[8,9] The idea that vaccines could be given to stimulate antibody- and cell-mediated immune responses against tumor-associated antigens made so much sense at the cellular level, and results of phase I and II clinical trials were so promising! Patients treated with the Theratope vaccine produced clinically significant antibody titers, but—for some reason—this result was not translating into increased survival for the patients. What had gone wrong? Researchers went back to the drawing board to elucidate a clear mechanism describing the efficacy of the vaccine.

Although interest and hope waned, further research was conducted during the next few years. Epidemiologic studies showed that STn expression was highly restricted in normal tissue and was seen in approximately 25% to 30% of breast cancer cases.[10] In 2005, Braun et al[10] reported that tumor cells treated in vitro with an aromatase inhibitor exhibited increased sensitivity to monocyte-medicated, antibody-dependent cellular toxicity. Gilewski and colleagues[11] found that the combination of 2 vaccines—STn-KLH and the immunologic adjuvant QS-21—produced clinically significant antibody titers in high-risk patients with breast cancer, with little or no resulting toxicity.

Today, almost 10 years after the disappointing report on the pivotal phase III clinical trial of Theratope,[8,9] therapeutic vaccines for metastatic breast cancer no longer hold the same promise as they once did. Multiple vaccines have failed to show any meaningful benefits. Despite some encouraging recent results for the use of combination vaccines in the treatment of hormone-sensitive patients,[11] these findings need to be verified in large randomized controlled trials. Meanwhile, vaccines have shown some success with other types of cancer, such as prostate cancer (sipuleucel-T)[12] and melanoma (ipilimumab).[13]

Only time will tell whether vaccines will ever have a permanent role in treating patients with breast cancer. However, the Theratope vaccine story has ultimately become a tale of caution in the field of breast oncology.

Simon B. Zeichner, DO
Department of Internal Medicine, Mount Sinai Medical Center, Miami Beach, Florida

References

1. Holmberg LA, Sandmaier BM. Theratope vaccine (STn-KLH) [review]. *Expert Opin Biol Ther*. 2001;1(5):881-891.

2. MacLean GD, Reddish MA, Koganty RR, Longenecker BM. Antibodies against mucin-associated sialyl-Tn epitopes correlate with survival of metastatic adenocarcinoma patients undergoing active specific immunotherapy with synthetic STn vaccine. *J Immunother Emphasis Tumor Immunol*. 1996;19(1):59-68.

3. Reddish MA, MacLean GD, Poppema S, Berg A, Longenecker BM. Pre-immunotherapy serum CA27.29 (MUC-1) mucin level and CD69+ lymphocytes correlate with effects of Theratope sialyl-Tn-KLH cancer vaccine in active specific immunotherapy. *Cancer Immunol Immunother.* 1996;42(5):303-309.

4. MacLean GD, Miles DW, Rubens RD, Reddish MA, Longenecker BM. Enhancing the effect of THERATOPE STn-KLH cancer vaccine in patients with metastatic breast cancer by pretreatment with low-dose intravenous cyclophosphamide. *J Immunother Emphasis Tumor Immunol*. 1996;19(4): 309-316.

5. Miles D, Papazisis K. Rationale for the clinical development of STn-KLH (Theratope) and anti-MUC-1 vaccines in breast cancer [review]. *Clin Breast Cancer.* 2003;3(suppl 4):S134-S138.

6. Sandmaier BM, Oparin DV, Holmberg LA, Reddish MA, MacLean GD, Longenecker BM. Evidence of a cellular immune response against sialyl-Tn in breast and ovarian cancer patients after high-dose chemotherapy, stem cell rescue, and immunization with Theratope STn-KLH cancer vaccine. *J Immunother*. 1999;22(1):54-66.

7. Hadden JW. The immunology and immunotherapy of breast cancer: an update [review]. *Int J Immunopharmacol*. 1999;21(2):79-101.

8. Biomira and Merck KGaA announce Phase III Theratope(R) vaccine trial does not meet primary endpoints. PR Newswire Web site. http://www.prnewswire.com/news-releases/biomira-and-merck-kgaa-announce-phase-iii-theratoper-vaccine-trial-does-not-meet-primary-endpoints-71326627.html. Accessed May 29, 2012.

9. Miles D, Roché H, Martin M, et al; Theratope(r) Study Group. Phase III multicenter clinical trial of the sialyl-TN (STn)-keyhole limpet hemocyanin (KLH) vaccine for metastatic breast cancer [published online ahead of print May 14, 2011]. *Oncologist*. 2011;16(8):1092-1100.

10. Braun DP, Crist KA, Shaheen F, Staren ED, Andrews S, Parker J. Aromatase inhibitors increase the sensitivity of human tumor cells to monocyte-mediated, antibody-dependent cellular cytotoxicity. *Am J Surg*. 2005;190(4):570-571.

11. Gilewski TA, Ragupathi G, Dickler M, et al. Immunization of high-risk breast cancer patients with clustered sTn-KLH conjugate plus the immunologic adjuvant QS-21. *Clin Cancer Res*. 2007;13(10): 2977-2985.

12. Kantoff PW, Higano CS, Shore ND, et al; IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363(5):411-422.

13. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma [published online ahead of print June 5, 2010]. *N Engl J Med*. 2010;363(8):711-723.