Yale University Open Data Access (YODA) Project

RESEARCH STUDY PROPOSAL

This form must be completed in its entirety for all research studies utilizing Medtronic's rhBMP-2 clinical trial data. Use as much space as necessary. Examples are included in blue font below. Send completed form and other supporting materials to yodap@yale.edu.

I. PROJECT TITLE

Provide a title and brief description of your proposed study.

Title:

A Re-evaluation of Carcinogenicity and rhBMP-2: A Meta-Analysis of the Individual Participant-Level Data from the Yale University Open Data Access (YODA) Project

This study will evaluate the individual patient data from the YODA study and evaluate carcinogenicity in light of patient age and related risk factors.

Keywords: carcinogenicity, tumorgenicity, BMP-2

II. PRINCIPAL INVESTIGATOR

Date submitted in Day/Month/Year format: 10/10/2013

Submitting Principal investigator(s):

Andrew Indresano M.D. Paul Anderson M.D

Previous YODA IDs (if applicable): NA

III. TARGET PUBLICATIONS

☒ Abstract: Scientific meeting: North American Spine Society

☒ Manuscript: *Target journal(s) (in order of preference):*

1. Spine

2. Journal of Bone and Joint Surgery - American

3. The Spine Journal

Anticipated date of submission: 3/15/2014

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Explain the background, rationale and significance for your research study. List references in the last section of this form.

Recently two meta-analysis studies by Fu et al. and Simmonds et al. of the Yale University Open Data Access (YODA) project have evaluated the risk of malignancy with the use of recombinant bone morphogenic protein-2 (rhBMP-2).[1,2] Both studies had similar methodology but used different YODA trials for their evaluated time-points. Furthermore, Fu et al. found at 24 months that the cancer risk was increased with rh-BMP-2 (risk ratio 3.45, CI 1.98-6.00) while Simmonds et al. found that there was no statistically difference (risk ratio 1.98, CI 0.86-4.54) at the same time point. These different conclusions regarding the potential carcinogenicity of rhBMP-2 affects a large population as its use markedly increased from 5.5% in 2002 to approximately 28% of spine fusion cases by 2008.[3]

There have been other clinical and basic science studies relating BMP and carcinogenicity in addition to Fu and Simmonds' meta-analyses. Information from preclinical safety data revealed no proliferative effect of rhBMP-2 on human tumor cell lines (including osteosarcoma) and no mutagenic activity.[4] In fact, rhBMP-2 has been shown to inhibit tumorous cell lines from prostate, ovarian, and breast cancer.[5] However, there are contradicting studies that have shown a link between cancer and BMP based on its down stream affects on the SMAD family of proteins[6,7] and the up regulation and expression of BMP protein receptors on the surface of certain cancer cells.[8,9]

In this study, we would like to perform a meta-analysis of all the YODA project individual patient data (IPD) in spine fusion. A thorough literature review of BMP and cancer by Thawani et al. concluded that there is no definitive association between BMPs and the promotion of tumorigenesis or metastasis.[10] Similarly, a recent paper of ours (pending publication) reviewed over 500,000 Medicare patients treated with rhBMP-2 and showed no association with cancer. Despite a large amount of conflicting data, our hypothesis is that rhBMP-2 does not statistically increase the relative risk of cancer.

List the objectives of this study. Clearly identify primary, secondary and tertiary aims. Be specific and concise.

1. To determine if rhBMP-2 increases the relative risk of cancer

Describe the specific study population. List all relevant inclusion and exclusion criteria.

All patients enrolled and included in the Medtronic randomized controlled trials of rhBMP-2 undergoing lumbar spinal fusion for which there is individual patient data (IPD) available for analysis
Intervention: Fusion attempted using any rhBMP-2 containing intervention
Comparator: Fusion utilizing iliac crest bone graft (ICBG)
Outcome measure: Surveillance Epidemiology and End Results (SEER) cancer events and their time point to intervention/comparator in light of age, sex and other relevant risk factors.

List <u>all</u> outcome measures to be studied. Identify primary, secondary and any exploratory outcomes.

Objective 1: SEER cancer events

1) Primary: Time point to SEER cancer events based on intervention, as defined using investigator – reported adverse events

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Statistical detail is not required; however, you should outline the general analytic approach and describe any conceptual models and causal relationships, potential confounders, subgroup and interaction analyses, etc. Instructions such as "adjust for all significant variables" and blind variable selection methods (e.g., stepwise selection) are strongly discouraged. Provide references for any novel or non-standard methods at the end of this proposal

We plan to pool the individual patient data using meta-analysis techniques. The main outcome will be relative risk of control to experimental group. Because relative risk cannot be estimated when no events are present in both groups which occurred in a number of the trials, we will also calculate the incidence per patient -year of exposure and compare between groups. We plan a meta-regression analysis using Comprehensive Meta-Analysis software to adjust for confounders such as age, gender, co-morbidities and smoking history (if available).

[redacted]

List all references cited in this proposal.

1. Fu R, Selph S, McDonagh M, et al: Effectiveness and Harms of Recombinant Human Bone Morphogenic Proetin-2 in Spine Fusion. *Ann Intern Med* 2013; 158: 890-902.
2. Simmonds M, Brown J, Heirs M, et al. Safety and Effectiveness of Recombinant Human Bone Morphogenic Protein-2 for Spinal Fusion. *Ann Intern Med* 2013; 158: 877-889.
3. Deyo RA, Ching A, Matsen L, et al. Use of bone morphogenic proetins in spinal fusion surgery for older adults with lumbar stenosis: trends, complications, repeat surgery, and charges. Spine (Phila Pa 1976) 37(3): 222-230.
4. Poyton DW Jr, Lane JM. Saftey profile for the clinical use of bone morphogenic proteins in the spine. Spine 2002; 27 S40-S48
5. Soda H, Raymond E, Sharma S, et al: Antiproliferative effects of recombinant human bone morphogenetic protein-2 on human tumor colony-forming units. *Anticancer Drugs* 1998;9:327-331.
6. Kokorina N, Lewis J, Zakharkin, S, et al. rhBMP-2 has adverse effects on human oral carcinoma cell lines in vivo. *Laryngoscopy*. 2012;122:95-102.
7. Bokobza S, Ye, L, Jiang W. When BMP signaling does wrong: the intracellular and molecular mechanisms of BMP signaling in cancer. *Curr Signal Transduct Ther*. 2009;4:174-195.
8. Kleeff J, Maryyama H, Ishiwata T et al. Bone morphogenic protein-2 exerts diverse effects on cell growth in vitro and is expressed in human pancreatic cancer. Gastoenterology. 1999; 116: 1202-1216.
9. Yoshikawa H, Rettig WJ, Lane JM, et al. Immunohistochemical detection of bone morphogenic proteins in bone and soft tissue sarcomas. Cancer. 1994; 74: 842-847.
10. Thawani K, Wang A, Than K, et al. Bone morphogenic protein and cancer: review of the literature. Neurosurgery. 2010; 66: 233-246.

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