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A Review and Analysis of the YODA Trials: What Can We Glean Clinically?

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Abstract Medtronic's biologic, Infuse (rhBMP-2), was approved by the FDA in 2002. Since its approval, a whirlwind of controversy developed culminating in an investigation by the Senate Finance committee. These events led to a landmark agreement between Medtronic and Yale University to perform a comprehensive and unbiased analysis of all patient related data. The project was named the Yale Open Data Access (YODA). The purpose of this article is to evaluate the results of the YODA project and determine what is clinically meaningful.

Keywords Infuse · rhBMP-2 · Yale Open Data Access · YODA

Introduction

The Food and Drug Administration (FDA) approved the use of Infuse (rhBMP-2) in the LT-Cage (Medtronic Inc., Minneapolis, MN) in 2002 for L4-S1 anterior lumbar interbody fusion (ALIF) procedures. The decision was based upon the results of multiple clinical trials that demonstrated its equivalence to autologous iliac crest bone graft (ICBG) in achieving a solid fusion. The product rapidly gained acceptance by spine surgeons. In short order, Infuse was used in both anterior and posterior cervical fusion as well as posterior thoracic and lumbar fusion procedures. In 2010, Ong et al evaluated the Nationwide Inpatient Sample (NIS) and reported that the use of rhBMP-2 had increased 4.3 fold from 2003 to 2007 and that 85 % of its use was off-label [1].

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Following the expanded use of Infuse, several clinical studies began to surface regarding its safety profile. The FDA subsequently received 38 reports of adverse events related to the use of Infuse in cervical spine surgery highlighted by soft tissue swelling of the neck causing airway compromise, dysphagia, and neural compression [2]. These sequelae of Infuse use prompted a public notice from the FDA in 2008 stating, "the safety and effectiveness of rhBMP in the cervical spine has not been demonstrated and these products are not approved for (off-label) use" [3]. In June 2011, Senate Finance Committee Chairman, Max Baucus (D-Mont), and senior committee member, Chuck Grassly (R-Iowa), sent a letter to the Chairman and Chief Executive Officer of Medtronic, Omar Ishrak PhD, requesting the release of all documents related to adverse events associated with Infuse. Baucus and Grassly were also concerned about the relationship between the lead investigators and Medtronic. In their letter, the senators also asked for all records of payments made by the Minneapolis based company to clinical investigators. Chairman Baucus stated "we need to do everything we can to insure companies are not concealing serious medical complications from patients just to increase profits." It has been reported that the original authors received benefits ranging from $10 to $35 million in relation to consulting, royalties, and licensing for various Medtronic products in addition to Infuse. The same month, the Spine Journal (the official journal of the North American Spine Society [NASS]), published a special focus edition on rhBMP-2. The Editor-in-Chief, Eugene Carragee, MD, compared the adverse events data from the original industry published studies with FDA data summaries, follow-up studies, and administrative databases. Carragee et al reported the risk of adverse events associated with the use of rhBMP-2 to be 10–50 times higher than what was reported in the clinical trials [4]. The same edition included a review of the available FDA data due to growing reports of complications and concluded, "morbidity in the original industry-sponsored publications did not fully reflect

the data available from those trials as reviewed in FDA documents and subsequent clinical reports" [4].

Yale Open Data Access (YODA)

As a result of the controversy surrounding the use of rhBMP-2, Medtronic commissioned Yale University to perform a groundbreaking independent review of all documents and data related to the product. The Yale Open Data Access (YODA) project evaluated clinical trials data, as well as post-market medical device safety reports and published literature up to 2012. Medtronic provided a $2.5 million grant to support the project. Other than providing product specific information, Medtronic had no further involvement in the project.

The YODA project created a model enabling increased access and independent review of clinical trials data. The goal of this novel approach is to provide clinicians and patients with an objective and fair analysis of data related to drugs and medical devices. As overseer of the project, Yale University selected 2 independent institutions to perform the review. Yale also appointed an independent steering committee and a clinical advisory committee of industry experts to advise on the project. The company under review had contact with the Yale project leadership but not with the selected institutions or committees.

In the case of the Infuse review, Rongwei Fu at Oregon Health and Science University (OHSU) and Mark Simmonds at the University of York in the United Kingdom were selected to perform the review. Analysis was performed on twelve randomized controlled trials and over 30 observational studies. The reviews evaluated the safety and effectiveness of Infuse as well as the scientific process utilized. Fu et al and Simmonds et al published their reviews blinded to each other's findings.

YODA Findings

The results of the 2 independent reviews were published in the June 18, 2013 issue of *Annals of Internal Medicine*. The reports from OHSU and York to YODA as well as multiple commentaries are also available on the Yale School of Medicine website in the Center for Outcomes Research and Evaluation (CORE) section (medicine.yale.edu/core).

Effectiveness

Both institutions evaluated the effectiveness of rhBMP-2 compared with ICBG with respect to fusion, pain, and outcomes. Fu et al reported similar effectives between rhBMP-2 and ICBG in ALIF and posterolateral fusion (PLF) procedures. The authors were not able to draw meaningful conclusions regarding the effectiveness in other surgical techniques [5•]. In contrast, Simmonds et al demonstrated a significantly higher fusion rate with rhBMP-2 (RR: 1.12, CI: 1.02–1.23) at 24 months [6•]. However, the York group reported that increased fusion rate did not translate into a meaningful reduction in pain or improvement in outcomes.

Safety

The findings of the 2 institutions were more consistent with regards to the adverse events profile of rhBMP-2. Both groups reported trends towards increased complications with rhBMP-2. However, the number of adverse events tended to be small making it difficult to draw any meaningful conclusions. Some of the more highlighted adverse events, heterotopic bone formation, retrograde ejaculation, and osteolysis were not well captured in the individual patient data (IPD), thereby precluding analysis. The exact reason as to why these adverse events were not recorded is unclear. Conversely, the risk of cancer was well captured in the IPD. Both groups reported an increased risk of cancer associated with the use of rhBMP-2. The OHSU group found a significantly increased risk at 24 months (RR: 3.45, 95 % CI: 1.98–6.00) [5•]. The risk was no longer significant at 48 months. The York group reported a relative risk of 1.98 (95 % CI: 0.86–4.54) but did not find it to be significant due to the small sample size [6•]. Both institutions did discuss the difficulty in interpreting these findings due to the heterogeneity of the cancers and the low overall absolute risk.

Reliability of the Evidence

The reliability of the data was also analyzed at both institutions. OHSU and York found that the published literature on effectiveness (fusion, pain, outcomes) was consistent with the IPD. In contrast, the results in the published literature on the adverse events profile of Infuse differed significantly from the data in the clinical study reports (CSR). The York group stated, "we found adverse events to be incompletely and inadequately described in the trial publications. Published papers provided far less information than was available in the confidential CSRs (or in the supplied IPD). The way in which the adverse event data were presented in the literature was highly inconsistent and the rationale for presenting some adverse events and not others was rarely clear." Similarly, the OHSU group found, " there was serious selective reporting and underreporting of adverse events in the published articles for both rhBMP-2 and ICBG groups, especially in the Medtronic trials published early" [5•, 6•].

Discussion

Since its approval by the FDA in 2002, the use of Infuse in spinal fusion procedures has skyrocketed. The majority of its use has been off-label in cervical fusion and posterior thoracic and lumbar fusion procedures. In 2008, after reports of

increased tissue swelling causing airway compromise, dysphagia, and neural compression, the FDA issued a public notice stating that rhBMP-2 was not approved in cervical spine surgery as it had not been adequately studied. While spine surgeons heeded this advice, the use of Infuse in thoracic and lumbar fusion procedures continued to grow. Sales of the product peaked at $221 million in the first quarter of 2009.

The analyses performed by Oregon Health and Science University and the University of York on behalf of YODA have resulted in a number of important findings. From a clinical perspective, the reports concluded that rhBMP-2 is associated with a higher complication rate than ICBG in anterior cervical fusion procedures. This finding is well accepted in the spine community. The use of rhBMP-2 in anterior cervical surgery has been largely abandoned except for salvage procedures.

The reports also noted no significant difference in the effectiveness of rhBMP-2 when compared with autologous ICBG in spine fusion procedures. There was a difference in the radiographic fusion rate (rhBMP-2 81 % vs ICBG 69 %) but this did not correlate with improved outcomes [5•, 6•]. The comparable outcomes are consistent with the general opinion of the spine community. However, the published literature supports a fusion rate with ICBG of 80 %–100 %. [7, 8]. The 69 % fusion rate reported in the YODA project brings into question the methodology used to assess fusion. However, seeing as this would lead to an underestimation, a minimum of an 81 % fusion rate associated with rhBMP-2 is certainly acceptable.

The results of the adverse events analysis do not provide meaningful conclusions. The data regarding retrograde ejaculation and heterotopic bone formation was not collected. The risk of cancer, which was well documented, was increased with rhBMP-2 utilization. However, the number of patients with cancer and the overall absolute risk were small. In addition, within the data there was a heterogeneity of cancer types, which brings into question the validity of the association.

Despite the number of studies evaluated by the YODA Project, it is not surprising that the adverse events results are not meaningful and, in many cases, the data was not collected. The studies were designed to evaluate the effectiveness of rhBMP-2. As we have seen, the effectiveness results are consistent between published studies and the IPD. The studies were not designed or powered to assess adverse events. If the complications are not well defined in advance it is easy to miss important findings. Investigators will often have differing opinions as to what constitutes an adverse event, and therefore, not capture the data. Additionally, studies that are not powered to detect specific adverse events may encounter type II error (false negatives) whereby a meaningful difference exists but the study does not have enough subjects for detection.

Both institutions provided consistently negative remarks regarding the finding of underreporting of data when comparing the published literature and the IPD. Although one cannot rule out intentional misdirection, the problem can certainly be explained, in part, by the relatively small sample sizes in the individual studies. As Kevin Bozic (chair of the YODA Clinical Advisory Committee) stated, "I don't see this as a matter of people being dishonest. It was more a matter of individual investigators being unaware of the potential adverse consequences associated with rhBMP-2 due to small numbers of patients included in individual trials, lack of communication among investigators, and poorly defined categories of adverse events."

The most meaningful finding related to the adverse events results from the YODA Project was stated by Simmonds et al: "In common with other trials undertaken for regulatory purposes, the numbers of adverse events recorded in this dataset are considerably higher than would be expected in routine clinical practice" [6•]. This is in the setting of studies, which were not designed to assess adverse events and, therefore, are on the low end of data capture. This can partially be explained by the expectations of spine surgeons and the published literature chronically under estimating adverse events associated with spine surgery. The literature strongly supports a long history of surgeons overrating the outcomes of their patients [9].

Potentially the most important implication of the YODA project is the creation of a new model for evaluating drugs and medical devices. The YODA model provides a comprehensive and objective evaluation of the data by independent entities. Published data and IPD are analyzed individually and are compared. The results of this type of analysis should serve as the highest level of data in the literature. The YODA model should produce conclusions on which patients, physicians and industry can rely. Increasing adoption of the YODA model, however, will be a challenge. It requires companies that are willing to voluntarily subject themselves to an unprecedented level of scrutiny. It also requires a substantial amount of resources and money, $2.5 million in this case. This current model, therefore, may not be scalable. Evaluating one product every couple of years is unlikely to have a significant impact. In addition, even after all the money, time, and energy have been spent, the conclusions are not guaranteed to be meaningful. As we have seen with Infuse, the 2 institutions had some inconsistencies in their results regarding fusion rate and the relative risk of cancer.

Conclusion

The YODA trial was a ground-breaking approach to evaluating patient related data. Medtronic should be commended for its participation. Yale, OHSU, and York should be applauded for their hard work. The trial produced 3 important findings. First, rhBMP-2 causes dangerous soft tissue swelling in the neck and should not be used, except possibly in salvage situations, in anterior cervical spine surgery. Second, ICBG and rhBMP-2 are equally effective in thoraco-lumbar spine surgery. Third, there was a trend toward increased adverse events with rhBMP-2 but conclusions cannot be made with

the currently available data. Despite this novel approach to data analysis, at the end of the day we have to ask ourselves; did the YODA project really teach us anything? The authors of this article would argue, probably not. Infuse certainly has a role in spine surgery but that role is still being defined. Clinicians must use the available data on the benefits and sequelae of the product and communicate this to patients so that educated, informed decisions can be made collaboratively between the physician and the patient.

Compliance with Ethics Guidelines

Conflict of Interest Michael E. Le and Mark F. Kurd declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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