HHS Public Access

Author manuscript

J Am Coll Surg. Author manuscript; available in PMC 2020 October 12.

Published in final edited form as:

J Am Coll Surg. 2019 August ; 229(2): 217–219. doi:10.1016/j.jamcollsurg.2019.03.002.

Abrupt Discontinuation of the Codman Hepatic Artery Infusion Pump: Considerations in the Era of Precision Medicine

Ryan J Ellis, MD, MS[1,2], **Peter Angelos, MD, PhD, FACS**[3], **William R Jarnagin, MD, FACS**[4], **Nancy E Kemeny, MD**[5], **Ryan P Merkow, MD, MS**[1,2]

[1:]Surgical Outcomes and Quality Improvement Center (SOQIC), Department of Surgery, Feinberg School of Medicine, Northwestern University, Chicago IL

[2:]Northwestern Institute for Comparative Effectiveness Research in Oncology, Feinberg School of Medicine, Northwestern University, Chicago, IL

[3:]Department of Surgery and MacLean Center for Clinical Medical Ethics, Pritzker School of Medicine, University of Chicago, Chicago, IL

[4:]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

[5:]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

As development of personalized and precision therapies accelerates, an increasing number of treatments will be targeted at small patient populations. Research and development in rare diseases has been supported for decades by initiatives such as the Orphan Drug Act and the Safe Medical Devices Act, which provide protections and regulatory considerations for therapies designed for uncommon indications. Nonetheless, these treatments are a challenging economic proposition for manufacturers, who often resort to high prices to offset costs of therapies servicing small patient groups.[1] As the number of individualized therapies continues to expand, mechanisms to ensure sustainability of these treatments are essential.

Issues with economic viability in narrow-indication medicine are illustrated by the history of hepatic artery infusion devices and the recent discontinuation of the Codman Hepatic Artery Infusion Pump (HAIP), an effective but uncommonly used treatment primarily for patients with colorectal cancer metastatic to the liver. Following the previous withdrawal of the Medtronic (Minneapolis, MN) HAIP, the Codman HAIP had sole possession of the market for this therapeutic indication and was the only FDA approved device for this therapy. While only implanted in a fraction of patients with hepatic colorectal metastases (approximately 300 patients annually), recent acceptance and utilization of the pump had been expanding

Corresponding Author: Ryan P. Merkow, MD MS, Surgical Outcomes and Quality Improvement Center (SOQIC), Department of Surgery, Feinberg School of Medicine, Northwestern University, 633 N. St. Clair Street, 20th Floor, Chicago, IL 60611, ryan.merkow@northwestern.edu.

Disclosure Information: Nothing to disclose.

following excellent results in both phase I/II randomized trials and well-designed, high-impact observational studies.[2–7] More widespread expansion of HAI therapy has largely been limited by bottlenecks in pump availability over the years. Most recently, production of the pump was permanently halted on April 1st, 2018 and announced in a letter to physicians three days later. The pump was manufactured by Cerenovus, a subsidiary of Johnson & Johnson (J&J, New Brunswick, NJ), which cited raw material shortages as the primary reason for device discontinuation. Despite media coverage and pleas from clinicians to continue manufacturing, J&J discontinued production as scheduled.[8] Clinicians were left scrambling for alternative, and potentially less effective options, including after-market alterations of existing Medtronic Synchromed pumps (approved for intrathecal use) using still-produced Codman beaded arterial catheters. Moreover, the discontinuation negatively impacted ongoing clinical trials evaluating liver-directed pump therapy. In this article, we will discuss widely generalizable ethical and industry-specific considerations surrounding the discontinuation of the Codman HAIP, and offer potential solutions to prevent the occurrence of similar situations in the future.

The Codman Hepatic Artery Infusion Pump: A Cautionary Example

The discontinuation of the Codman HAIP highlights important ethical and economic considerations. Pharmaceutical and medical device companies have an ethical responsibility to provide safe, high-quality products for patients. In a vacuum, discontinuation of a life-saving therapy without warning or viable alternative is almost unquestionably outside the bounds of acceptable ethics. However, the situation surrounding the Codman HAIP is more nuanced and highlights the complexity of the intersection between the free market economy and healthcare in the US. In the Codman HAIP example, J&J cited part and raw material shortages leading to unsustainable production. It may be unreasonable to expect a company or its suppliers to significantly alter production or redesign a device simply because it occupies a therapeutic space with few alternatives. Additionally, a company producing multiple devices that treat uncommon diseases may face tradeoffs in producing multiple therapies. If a company decides that its limited resources should be concentrated in other areas rather than in revamping production of an existing technology, that may be ethically defensible.

A more glaring concern in the discontinuation of the Codman HAIP is the surprising lack of warning to clinicians that made investigation of alternative options exceedingly difficult. J&J did not officially announce discontinuation of the pump until after manufacturing had already stopped. If J&J was held to the same ethical standards as clinicians, this would constitute improper termination of a patient relationship and a violation of a well-accepted tenet of medical ethics.[9] The reasoning for the failure to alert physicians of the impending termination of pump production is unclear. Such disregard for patients who might depend on the pump and those anticipating receiving it gives the impression that the company did not prioritize these patients. Although there may have been complexity and uncertainty in securing parts, the company’s lack of transparency is a striking disregard for the impact that discontinuation of the pump would have on patients.

A Path Forward: Supporting Collaboration and Strengthening Patient Protections

The abrupt removal of Codman HAIP from the market and the subsequent fallout highlights the need for the healthcare industry to examine how to manage narrow-indication drugs and devices. The ethical and economic underpinnings that led to removal of this promising device from the market persist, and such a scenario is likely to repeat itself without systemic changes. Potential solutions to ensure continued availability of other therapeutics will require efforts from at least three major stakeholders: manufacturers, regulatory bodies, and clinicians. First, drug and device manufacturers must reaffirm their commitment to the small groups of patients whose lives might depend on the availability of their products. This space may often operate on thinner margins than large-indication drugs making them susceptible to rapids swings into non-viability. An independent ethical watchdog group, potentially under the auspices of the Food and Drug Administration, should be established to evaluate and approve moves into and out of the precision medicine market, ensuring that patients relying on these therapies do not abruptly lose access to care. Ideally, this would include both drugs and devices aimed at relatively small and vulnerable patient populations. This suggestion is not intended to demonize or shame industry, but rather to recognize that when a product is a lifeline to even a small group of patients, there exists a strong moral and ethical responsibility to avoid sudden life-threatening interruptions in access to drugs and devices that patients depend upon.

Second, common sense regulatory changes should occur. A minimum amount of time should be required between announcement of therapy discontinuation and actual cessation of production. Such regulatory requirements must also apply to the entire supply chain. Companies often forecast years in advance, and in almost all circumstances advance notification before therapy discontinuation should be an achievable obligation. This simple change could have avoided much of the negative reaction associated with the withdrawal of the Codman HAIP. The device industry would also likely benefit from additional economic incentives aimed not at research and development, but at maintenance and updating devices serving small populations of patients.

Third, barriers to partnerships between industry (e.g., device and pharmaceutical companies), the academic community (e.g., industry and university researchers) and government should be minimized. In the current climate, these sorts of partnerships are often discouraged for both economic and ethical considerations, especially those between academia and industry. In the example of the Codman HAI pump, if a fledgling drug company attempting to expand an indication to HAI were to partner with Johnson & Johnson, perhaps the Codman pump would not have been discontinued. Alternatively, academic institutions may need to take on a more active role in lobbying for narrow-indication therapeutics to ensure that manufacturers understand the important role of their products in the care of small patient populations. Certainly, without these partnerships many of the groundbreaking advances in cancer care in the past decade would not have been realized. Additional ethically and legally appropriate incentives to strengthen these

relationships should be pursued in a careful and thoughtful manner to ensure that patients benefit from such partnerships.

Finally, clinicians managing patients with rare conditions must work together more effectively to build the body of evidence. In this case, randomized trials supporting HAI pump use were performed prior to the emergence of many modern chemotherapeutic regimens, and HAI use decreased with the rise of these newer therapies. In more recent years, there has been significant heterogeneity in the oncology community on the best approach to metastatic disease and a dearth of comparative effectiveness trials involving older therapies such as the HAI pump. Thus, many of the economic underpinnings of the Codman HAIP discontinuation came from lack of consensus within the medical community. Alternative therapies such as newer systemic chemotherapy options were employed for similar indications, such that the pump was not routinely used for its already narrow indication. This fragmented usage can push economically tenuous medical therapies into non-viability.

Building consensus and defining preferred treatment options for patients with uncommon conditions can be challenging. In the future, expansion of large, multi-center collaboratives managing rare diseases could improve the quality of evidence guiding clinical decision making. Even with expansion of collaboratives, randomized comparative effectiveness studies will rarely occur for these indications. Clinicians managing patients with rare conditions will need to more readily embrace high-quality observational research as the best evidence that is logistically feasible.[10] Regional, national, and international working groups will likely be required to evaluate various levels of evidence and work towards establishing preferred treatment options. Importantly, establishing registries for rare populations, technologies and drugs or leveraging the power of existing registries is essential to overcoming barriers.[11] The clinician contribution to this solution will ultimately be to use all levels of evidence to more concretely define treatment algorithms, maximizing the economic viability of preferred therapeutics even when they have narrow applications.

Conclusions

Withdrawal of the Codman HAIP from the market without notice or plans for replacement raised several ethical and industry-specific concerns. As modern medicine continues to rely on more precision, patient tailored therapies, important regulatory changes will need to occur to support drugs and devices with narrow indications. Commitment from industry, government and clinicians will be necessary to more thoroughly support therapies for rare diseases so that patients are not left without access to life-prolonging therapies.

Acknowledgments

Support: Dr Ellis is supported by a postdoctoral research fellowship (AHRQ 5T32HS000078). Dr Merkow is supported by the AHRQ (K12HS023011) and an Institutional Research Grant from the American Cancer Society (IRG-18-163-24).

References

1. Bach PB, Giralt SA, Saltz LB. FDA Approval of Tisagenlecleucel: Promise and Complexities of a $475000 Cancer Drug. JAMA 2017;318:1861–2. [PubMed: 28975266]
2. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. N Engl J Med 1999;341:2039–48. [PubMed: 10615075]
3. Groot Koerkamp B, Sadot E, Kemeny NE, et al. Perioperative Hepatic Arterial Infusion Pump Chemotherapy Is Associated With Longer Survival After Resection of Colorectal Liver Metastases: A Propensity Score Analysis. J Clin Oncol 2017;35:1938–44. [PubMed: 28426374]
4. Dhir M, Jones HL, Shuai Y, et al. Hepatic Arterial Infusion in Combination with Modern Systemic Chemotherapy is Associated with Improved Survival Compared with Modern Systemic Chemotherapy Alone in Patients with Isolated Unresectable Colorectal Liver Metastases: A Case-Control Study. Ann Surg Oncol 2017;24:150–8. [PubMed: 27431415]
5. Dhir M, Zenati MS, Jones HL, et al. Effectiveness of Hepatic Artery Infusion (HAI) Versus Selective Internal Radiation Therapy (Y90) for Pretreated Isolated Unresectable Colorectal Liver Metastases (IU-CRCLM). Ann Surg Oncol 2018;25:550–7. [PubMed: 29181682]
6. Karanicolas PJ, Metrakos P, Chan K, et al. Hepatic arterial infusion pump chemotherapy in the management of colorectal liver metastases: expert consensus statement. Current oncology 2014;21:e129–36. [PubMed: 24523610]
7. Liver-directed chemotherapy device is saving lives. The Globe and Mail, 2013 (Accessed 1/21, 2019, at https://www.theglobeandmail.com/life/health-and-fitness/advsunnybrook/healing-the-future/liver-directed-chemotherapy-device-is-saving-lives/article12379031/.)
8. Grady D, Kaplan S. A Lifesaving Pump for Cancer Patients Is Being Phased Out. The New York Times 4 25th, 2018.
9. Code of Medical Ethics. (Accessed May 28th, 2018, at http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics.page.)
10. Merkow RP, Ko CY. Evidence-based medicine in surgery: the importance of both experimental and observational study designs. JAMA 2011;306:436–7. [PubMed: 21791695]
11. Snyder RA, Hu CY, Cuddy A, et al. Association Between Intensity of Posttreatment Surveillance Testing and Detection of Recurrence in Patients With Colorectal Cancer. JAMA 2018;319:2104–15. [PubMed: 29800181]