Transplantation Publish Ahead of Print
DOI: 10.1097/TP.0000000000001763

Causes and Consequences of the Worldwide Belatacept Shortage

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Disclosure: authors declare no conflict of interest

Medication shortages can create considerable disruptions in patient care depending on the availability of suitable therapeutic alternatives. Recently, the manufacturer of belatacept announced an impending shortage which could impact patient management at many transplant centers worldwide. Belatacept received Food and Drug Administration (FDA) and European Medicines Agency approval in 2011, with an indication for de-novo use following renal transplant. However, in many transplant centers, it has found use off label in conversion from calcineurin inhibitor (CNI)-based therapies. Although the use of belatacept in the US is not reported in the most recent OPTN/SRTR Kidney Annual Data Report, it is believed by the authors that this agent is gaining traction in all approved countries as an alternative to or in conjunction with reduced doses of traditional maintenance immunosuppressants.(1)

Like most biologic agents, the manufacturing of belatacept is difficult, time-consuming and expensive. To this end, the manufacturer of belatacept has been transitioning to a more efficient and higher yielding manufacturing process. Unfortunately, this transition has experienced a significant delay, but the reasons for this setback are unknown. It is important to note that the FDA mandates that when a change is made in drug manufacturing, prior to its approval for distribution, the manufacturer must validate any changes in identity, strength, quality, purity,

and potency of the drug to assure there is no change in pharmacokinetics, safety or efficacy.(2) Based on the belatacept manufacturing delay, along with the growth in new prescriptions, the manufacturer anticipates that the current supply of belatacept will not be adequate to facilitate its use in new patients. To preserve the current supply for existing belatacept-treated patients, the manufacturer established a restrictive distribution program. All patients currently receiving belatacept must be registered with the distribution program to continue to have access to this drug after March 15, 2017. The manufacturer anticipates that, subject to regulatory approval, the transition to the new manufacturing process will be successfully completed in late 2017, resulting in a significant increase in supply that will be able to sustain both existing and new patients starting in 2018.

Despite its slow up-take in many transplant centers since its regulatory approval, belatacept has positioned itself as an alternative to both CNI and mammalian target of rapamycin (mTOR) inhibitors. Patients that have used belatacept de-novo or via conversion may have experienced similar graft survival, however with better kidney transplant function. Treatment with belatacept is also associated with improved blood pressure and lipid profiles, as well as less diabetes when compared to CNI based regimens.(3, 4) Not having belatecept available as an alternative to traditional immunosuppression, even for several months, could therefore

significantly impact the management of transplant recipients. It is understood why the manufacturer felt the need to implement the belatacept distribution program, but such a program places a burden on transplant clinicians and center personnel. Managing the proper movement of patient-specific supplies and communication with transplant physicians, pharmacists, coordinators, infusion centers and patients will provide a challenge to transplant centers.

Overall, it has been well documented that both the United States and Europe have experienced an increased frequency of drug shortages, which have resulted in difficulties for patients, practitioners, health care facilities, and even federal regulators.(5-7) There are many factors that contribute to drug shortages, including reduced availability of raw materials, manufacturing difficulties, regulatory issues, and manufacturer marketing decisions, to name a few. Importantly, tendering, as a method of cost-containment, has also been identified as a cause of drug shortages. Tendering is a process in which payers (ie, private or government insurance), negotiates the lowest price for a medication with multiple producers. The supplier offers the lowest price has their medications available on the payers' insurance plans for the duration of the contract. The low drug prices resulting from tendering can reduce the number of suppliers, making drugs more susceptible to shortages.

Production of pharmaceuticals is becoming more and more concentrated, to increase efficiency. Thus, there may be only 1 active producer worldwide. If this sole production site has a problem, it immediately becomes a global issue. Additionally, due to the complexity of the production process, high quality requirements and small margin for errors, injectable drugs may be more susceptible to manufacturing problems or quality issues than capsules or tablets.(5-7)

Currently, drug shortages span across all major therapeutic areas, and medications used in solid organ transplantation are no exception. In the United States over the past 10 years alone, almost every major transplant immunosuppressant has been affected by a drug shortage (8):

Intravenous methylprednisolone (2000-2011; frequent shortages due to decreased production by several manufacturers)

Intravenous cyclosporine (2011; shortage due to manufacturer discontinuation)

Cyclosporine modified capsules (2012; shortage due to manufacturing delays)

Enteric-coated mycophenolic acid tablets (2012; no known reason for shortage)

Alemtuzumab (2012; shortage due to the drug being voluntarily withdrawn from the market and a restrictive distribution program being initialized for its use in organ transplantation)

Azathioprine tablets (2015; shortage due to manufacturer discontinuation)

Tacrolimus capsules (2015; shortage due to manufacturer discontinuation and manufacturing delays)

Intravenous azathioprine (2016; shortage due to discontinuation by the lone manufacturer)

Over a similar period, transplant centers have also experienced shortages in sulfamethoxazole-trimethoprim, ganciclovir, acyclovir, and intravenous immunoglobulin.

One of the biggest differences between many of the shortages listed above and the current belatacept shortage is the up-front communication of this issue by the

manufacturer to transplant practitioners and the institution of a restrictive distribution program to ensure that preexisting belatacept-treated patients remain on this medication. Although not being able to use belatacept in new transplant patients until the manufacturing transition is complete is far from ideal, with the steps taken by the manufacturer, transplant practitioners have had the time to take care of existing patients and plan for future patients.

In June 2013, the International Pharmaceutical Federation convened an International Summit on Medicine Shortage. A large number of solutions and best practices to prevent and mitigate shortages are suggested, both on the demand and supply side.(9) However, it is to be expected that drug shortages will continue to have a significant impact on patient management, including organ transplant recipients. Moving forward, manufacturers can help mitigate drug shortages through proper communication with federal agencies when changes in manufacturing processes or shortages in raw materials are noted. For practitioners, it is imperative that they be cognizant of current shortages, and adequately respond to new shortages of transplant immunosuppressants.

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