VIEWPOINT

The Ethical Challenges of Compassionate Use

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Granting access to drugs, vaccines, biologics, and devices that have not yet been approved by governmental regulatory authorities is a growing challenge for physicians, public officials, patient advocacy groups, institutional review boards (IRBs), and patients.[1] Although the issue of rapid access to investigational agents is not new, tracing back to the early days of the human immunodeficiency virus pandemic, the pace of requests has increased. This is attributable to many factors, including greater awareness of compassionate use on the part of patients and their physicians; more information available through the Internet and websites describing clinical trials; an increase in promising interventions, including genetic markers, immunotherapies, and recombinant vaccines; threats from potential epidemics such as Ebola, cholera, and influenza; and an increased willingness to try novel agents by patients who are chronically ill or dying.

Requests for rapid access to agents still under investigation fall into 2 categories—requests for groups of persons with the same disease and requests by individuals. The former are often described as requests for expanded access, the latter as requests for compassionate use. Regulatory bodies in various countries have created various programs for providing greater access to requests from groups, including the creation of expanded-access programs and emergency use waivers for patients who do not qualify for clinical trials. Compassionate use requests have proven to be more difficult to resolve.

Compassionate use requests can occur at any time in the research process—from product testing in animals, to early human safety trials, to the period nearing the end of clinical trials. Requests can come from patients who are dying, those facing disability and pain for which no approved agent has proven effective, those in the midst of lethal disease outbreaks and those newly affected, those who are chronically ill, and those who have limited access to therapies.[2]

Until recently, the main strategy for patients seeking compassionate use was to try to locate a possible treatment for their disease, often but not always with the help of their physician. Once a potential therapy is found, patients seeking compassionate use might try to make direct contact with the researcher testing the agent, most often at a private company, or to use a connection with an individual to make a request to a corporate official. Sometimes patients try to interest the traditional media in their plight or launch campaigns using social media to draw attention with the hope that public pressure might be brought to bear on the private parties who own the agent to provide it.[3]

In the United States, some have claimed that the key obstacle for those seeking compassionate use is the Food and Drug Administration (FDA). Even though the application process can be cumbersome, the FDA grants approval for 99% of compassionate use requests.[4] The major pathway for patients is to secure approval by a company moving the agent through the regulatory approval process. Unless that happens, the FDA plays almost no role in responding to compassionate use requests. However, granting compassionate use requests can at times compete with development of the agent for a larger group of patients. Companies have no legal obligation to offer access to experimental treatments, are often uncertain how to respond to requests, and may be uncomfortable in determining how to respond fairly to requests from the well connected or those using social media campaigns.[1] Historically, evaluating compassionate use requests depended exclusively or predominantly on assessments from company employees.

A Patient-Focused Approach to Compassionate Use

Janssen is one of the many companies grappling with compassionate use requests. One promising drug, daratumumab, then in late-stage clinical trials in the United States, had shown evidence of efficacy for patients with multiple myeloma refractory to other agents. However, because of a rapidly progressing clinical trial program and manufacturing constraints, most of the available supply of the drug had been allocated to clinical trials or expanded-access programs, with only a small amount available for compassionate use.

Early in 2015 Janssen contacted the Division of Medical Ethics at NYU Langone Medical Center to request a method for reviewing compassionate use requests that would be transparent, fair, beneficent, evidence-based, and patient-focused. Based on prior work involving the allocation of cadaver organs for transplantation, an independent 10-person committee was formed, the Compassionate Use Advisory Committee (CompAC),[5] consisting of physicians, bioethicists, patients, and patient advocates from 5 countries. The pilot model was to objectively advise Janssen on compassionate use requests for daratumamab.

Janssen provided funding for organizing and staffing the CompAC to the NYU Langone Medical Center. Some members serving on the committee, including the chair and deputy chair, chose not to be compensated.

How the CompAC Works

The Janssen company website receives requests for the pilot drug from physicians around the world. After company physicians identify requests that are medically inappropriate or eligible for clinical trials and expanded-access programs, remaining requests for compassionate use are transmitted to the CompAC for its independent recommendation to provide or not provide access to daratumumab. Janssen is legally bound to take final re-

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sponsibility for decisions to grant its agent and committed to inform the CompAC of any variation from the recommendations.

Although the committee spent a good deal of time discussing what if any criteria it would use in making decisions about which patients should receive access to the investigational agent, it quickly became evident that the key ethical requirement the CompAC had to achieve was fairness—making unbiased, even-handed decisions that would elicit patient and physician trust.

Several strategies were implemented to help ensure fairness involving compassionate use requests. For example, the CompAC advised Janssen to enhance access to information on company websites.

The CompAC developed approaches for evaluating requests fairly, including that requests from physicians be standardized so that all persons seeking compassionate use would present similar information and that all requests would be anonymized so as to allow no preference based on income, nationality, sex, race, or celebrity status. The committee also engaged both Janssen's and external subject matter experts to provide them with scientific insights from the development program and technical facts to aid their evaluation.

The CompAC created an appeals process by which a physician whose request for compassionate use was denied could reintroduce further standardized information about the patient. The CompAC also committed to respond to all requests within 5 business days, thereby ensuring that appropriate concern was shown to all patients and that no patients would be left without an expeditious answer—a source of ongoing frustration about compassionate use requests for patients and families.

Last, Janssen was committed to seek appropriate and prompt regulatory approval for the agent, as well as to provide it for compassionate use at no charge to patients.

After the creation of the committee in May 2015, these policies were implemented. Further discussion among CompAC members led to an agreement about principles of justice that would be used to guide decisions among specific requests. These included not harming patients, needing to exhaust all existing approved treatments, the scientific likelihood of an efficacious response, patient functionality, and, with lower priority, prior participation in clinical trials, length of coping with the disease, support for dependents, and patient age.

Lessons to Date

Between July 1 and December 31, 2015, Janssen received 160 preapproval access requests for daratumumab. Of these, company physicians determined that 43 had a benefit-risk profile that was not favorable, 28 requests had not exhausted all approved alternative therapies or were eligible for expanded-access programs or clinical trials, and 13 were excluded for other reasons (eg, incomplete data for assessment). Of the remaining 76 compassionate use requests evaluated by the CompAC, the committee recommended granting compassionate use for 60 requests and Janssen approved 62. The additional 2 patients approved by Janssen were a result of supplemental medical information provided by the requesting physician that addressed the CompAC's concerns. Review is ongoing for geographic regions in which daratumamab has not been cleared for marketing.

The major lesson from this review process in rationing a novel agent is that fairness (due process that seeks to ensure no bias, ensuring that all requests are heard), as much as justice (the actual outcome of distributions from the process[6]), is crucial for the effectiveness of the process of evaluating compassionate use requests. The ability of the CompAC to promote fairness and consistency, and by anonymization avoid patients, families, advocates, or advantaged parties from influencing decisions, limits bias and favoritism.

Companies, patient advocates, institutional review boards, and government officials have expressed interest in extending the CompAC model to other agents and settings. The CompAC model requires resource commitments, involves many different groups to support its activities, and is certainly not beyond criticism for its composition, principles, and decisions. But what is clear from this innovation in translational bioethics is that fairness must be secured if justice is to have any chance to flourish.

ARTICLE INFORMATION

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