Review Article

Compassionate drug use: Current status in India

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Abstract

The World Health Organization defines compassionate use (CU) as a "program that is intended to provide potentially life-saving experimental treatments to patients suffering from a disease for which no satisfactory authorized therapy exists and/or who cannot enter a clinical trial. For many patients, these programs represent their last hope." Over the years, an increasing number of requests and isolated cases have paved the way for more robust CU programs by pharmaceutical companies and guidelines by eminent regulatory bodies globally. In India, although there is no formal mention of the term "Compassionate Use" by the Central Drugs Standard Control Organization, there are provisions in the Drugs and Cosmetics Act 1940 and Rules 1945 to allow drugs to be imported as and when necessary. Such applications can be submitted to the Drug Controller General of India by a hospital, patient, or a pharmaceutical company. The evidence of such use of drugs is underlined by the availability of bedaquiline and delamanid for extensively drug-resistant tuberculosis (TB) and multidrug-resistant TB patients, respectively. CU is in its nascent stage in India owing to the lack of policies and laws needed to govern it. There is a need for regulatory bodies and pharmaceutical companies to work together to extend the spectrum of CU of drugs for the betterment of needy patients.

Keywords: Bedaquiline, delamanid, expanded access, preapproval access, special access

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INTRODUCTION

What does a family go through, when their loved one, suffering from a terminal illness or a rare disease, runs out on all available options? There are perhaps millions of families across the world today, who are living this nightmare, at this very moment. The past decade has been a testimonial to the fact that a single such case is enough to stir up a storm and bring about, even, changes in the laws of a country.

COMPASSIONATE DRUG USE

Conventionally, a drug could only be made available to a patient after it has been proved to be safe enough and efficacious, through the long and arduous process of clinical trials. However, desperate needs call for desperate measures, and it was soon realized that the time had come, to divert from the conventional path. Thus, came into existence, the concept of use of investigational drugs, which were still pending approval.

It all began, with the human immunodeficiency virus (HIV) epidemic of the early 1980s. It was during this time that sheer compassion allowed patients to access unapproved antiretroviral drugs as their last hope for survival.[1,2] The pharmaceutical giant "Glaxo-Wellcome" had generously donated its anti-HIV drug, zidovudine, free of charge to

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22,000 patients in the 1990s, when it was still undergoing phase III trials.[3] Ever since, use of drugs on compassionate grounds has been only growing stronger.

Today, several terms such as "Compassionate drug use," "Compassionate use," "Expanded access," "Preapproval access," "Special access," "Aaccess," and "Treatment use" are used interchangeably to refer to the use of such drugs. While the term "Compassionate drug use" is usually used in a colloquial sense for individual requests, "Expanded access" is an official term, which is designated by the United States Food and Drug Administration (US FDA).[4]

According to the US FDA, "Expanded access" is the use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient's disease and not primarily intended to obtain information about the safety or effectiveness of a drug.[5]

The World Health Organization (WHO) defines compassionate use (CU) as a "program that is intended to provide potentially life-saving experimental treatments to patients suffering from a disease for which no satisfactory authorized therapy exists and/or who cannot enter a clinical trial. For many patients, these programs represent their last hope."[6]

GLOBAL REGULATIONS

Over the years, an increasing number of requests have paved the way for more robust CU programs by pharmaceutical companies and guidelines by eminent regulatory bodies globally.[1]

The expanded/early access program was established by the US FDA in 1987.[7] Since then, few other laws have also come into existence. Under the FDA, there are three main categories under which drugs are made available on the compassionate ground: Expanded access for individual patients, including for emergency use; Expanded access for intermediate-size patient populations; and Expanded access for widespread use.[8]

Recently, FDA has further simplified the process by introducing an application form (Form FDA 3926) that enables doctors to request for drugs on compassionate grounds for their patients more easily.[9]

The European Union (EU), on the other hand, has the CU program and the named patient program in place. The European Medicines Agency (EMA) provides nonlegally binding recommendations through the Committee for Medicinal Products for Human Use.

Until May 2015, there were no equivalent mechanisms in Japan, and unapproved products were used under a physician's discretion via the Japan Medical Practitioners' Act or Advanced Medical Care B.[10]

COMPASSIONATE DRUG USE IN TERMINAL ILLNESS: ISOLATED CASES

Following the preapproval access of antiretroviral drugs on compassionate grounds, cancer activists in the United States soon followed suit. These activists aimed at obtaining investigational drugs for terminally ill cancer patients who were unable to be part of clinical trials due to any reason.[1]

One such organization that was formed with this mindset was the "Abigail Alliance." This organization was formed after the death of a 21-year-old Abigail Burroughs diagnosed with terminal squamous cell carcinoma of the head and neck. She lost her life in 2001, after being denied access to two investigational drugs: Erbitux (Cetuximab) from "Imclone System" and Iressa (Gefitinib) from "Astra Zeneca."[1,11]

COMPASSIONATE DRUG USE IN NONLIFE-THREATENING CONDITIONS

CU is not restricted to cancerous conditions alone. Requests for such access are also received for nonlife threatening, but disabling conditions. One such example which drew much attention in the US was that of the LeClaire brothers, Austin and Max. The brothers were born with a genetic disorder called Duchenne Muscular dystrophy, which made them progressively unable to walk. The family was fast losing out on options, but finally found hopes in a new experimental drug, called Eteplirsen which was being developed by the company "Sarepta Therapeutics."

Max, who is now 14 years old, was enrolled in an ongoing trial in 2011. However, Austin, who is now a 17-year-old boy was refused enrollment at the time. This was because he was already confined to a wheelchair and hence failed to qualify the enrollment criteria. However, Austin was enrolled into another trial for the same drug, 3 years later. Since then, the boys have noticed a significant improvement in their condition. Eteplirsen was later approved in September 2016 by the US FDA following a White House petition, which was signed by >100,000 people.[12,13]

COMPASSIONATE DRUG USE IN LARGE POPULATIONS

Isolated cases are not the only ones who place requests for CU. At times, situations arise when communities as a whole may need access to these drugs. An example is the

recent Ebola outbreak in West Africa from 2014 to 2016. To save lives and curb the epidemic, the WHO resorted to providing "ZMapp," a monoclonal antibody developed by "Mapp Biopharmaceuticals." The drug which was still under investigation managed to save four lives out of six Ebola-infected patients who received this drug.[14]

MAGNITUDE OF THE PROBLEM

The brunt of any public uproar following sensitive health issues is inevitably borne by the pharmaceutical company and the regulatory authority of the particular country.[1] During the initial years, FDA was perceived to be the biggest hurdle to patient access. However, the most common hurdle was in fact, not the FDA but the drug manufacturer.[2]

PHARMACEUTICAL COMPANIES: DILEMMAS

During the earlier years, companies responded, by invariably declining individual requests for investigational drugs, citing several reasons.[4]

1. Limited safety and efficacy data
2. Limited supply of medication
3. Judicious use of financial, personnel, and other resources: Unapproved drugs are not covered by insurance companies. Hence, small companies may not have funds to provide drugs free of charge. Expanded access requires special protocol for every single patient. Companies, especially smaller ones, may not have the manpower to carry out this task within a reasonable amount of time
4. Potential poor outcomes: FDA requires the reporting of any adverse event that may occur in an expanded access patient, irrespective of the cause. This requirement, however, could potentially adversely affect an ongoing clinical trial and make the manufacturer liable for damages
5. Potential impact on clinical trial enrolment
6. Ethical dilemma of expanding access to one or more patients versus an entire community.

PHARMACEUTICAL COMPANIES: CHANGE IN TREND

Times have changed, and companies are beginning to acknowledge such requests and treat them as a marketing opportunity to accumulate additional clinical data from a "real world" patient population scenario and a way to create patient interest in a drug after a clinical trial is successful. For example, the biotechnology company, "Genentech" encourages patients to apply for expanded access to their drugs.[4]

SCENARIO IN INDIA

India has eradicated several diseases such as polio, guinea worm disease, yaws, and tetanus; however, endemic diseases such as HIV infection and acquired immune deficiency syndrome, tuberculosis (TB), malaria, dengue, acute encephalitis syndrome, and many more continue to be huge public health problems.[15]

India is also laden with several rare diseases. Rare diseases lie at one end of the spectrum with the other end being occupied with highly prevalent diseases such as TB. Nonetheless, CU of drugs in either case is indispensable.

BURDEN OF MULTI DRUG-RESISTANT TUBERCULOSIS IN INDIA

According to global TB report 2016, India has the largest number of multidrug-resistant TB (MDR-TB) cases. An estimated 1.3 lakh new MDR-TB patients are added annually to the existing burden.[16] The densely populated urban city of Mumbai is the first to report cases of resistance to all first-line and second-line drugs.[17]

COMPASSIONATE DRUG USE: BEDAQUILINE FOR MULTIDRUG-RESISTANT TUBERCULOSIS

After almost 5 decades of treating TB with the same drugs, a new and effective antitubercular drug, bedaquiline, was approved for MDR-TB on December 28, 2012, by the US FDA. "Janssen," the parent company of Bedaquiline, had already initiated a preapproval access program in 2011, even while the drug was in phase IIb trials. Bedaquiline was made available for CU for MDR-TB patients in India since 2012; however, access to this drug has not been easy.[17-19]

In March 2016, Janssen India and Revised National Tuberculosis Control Program (under the aegis of the Director General of Health Services) came together and started a conditional access program (CAP). As per this program, 600 patients across six sites in India were to receive bedaquiline free-of-charge. In April 2017, it was announced that CAP would be expanded to cover 156 sites across India.[16,20]

COMPASSIONATE DRUG USE: DELAMANID FOR MULTIDRUG-RESISTANT TUBERCULOSIS

The Japanese pharmaceutical company "Otsuka Novel Products GmbH" (ONPG) conducted several trials during the last decade to prove the safety and efficacy of their new drug called Delamanid, against MDR-TB. It received its first global approval by the EMA on April 28, 2014, after an initial "conditional approval" on November 21, 2013.

Delamanid was to be used in combination with optimized background anti-TB regimen.[21,22]

Otsuka Pharmaceuticals has had a patent on delamanid in India for the past 8 years. In April 2017, the company held talks with the Indian government to make 400 courses of delamanid available at select treatment centers after approval under a CAP.[23,24]

COMPASSIONATE USE PROGRAMS: A BOON FOR INDIA

The importance of free access of these drugs, through CU programs, cannot be understated. This can be gauged by the fact that a 6-month course of bedaquiline and delamanid would cost a patient INR 29,000 and INR 18,00,000–25,00,000, respectively, in international market. Not to forget, the nonavailability of both the generics until the year 2023. Currently, these drugs are being made available in India for free, through GDF and USAID support.[25]

As almost 60% of TB patients in India are treated by private clinics, the actual number of patients who would benefit from these drugs remains elusive. Health experts opine that expanded access to these drugs is the key for India to achieve its ambitious goal of eliminating TB by 2025.[23]

NOTEWORTHY CASES IN INDIA

In May 2015, an anonymous 2nd-year postgraduate medical student from a well-to-do family was diagnosed with extensively drug-resistant TB. Experts came to consensus that she would be a good candidate for bedaquiline under CU. As the drug was unavailable in the public sector, she obtained the drug through a private facility and later reported significant improvement in her health.[26]

In January 2017, the case of an 18-year-old girl suffering from MDR-TB gathered the attention of local media. The girl, who hailed from Patna, Bihar, had contracted TB in 2014. After 3 years of treatment and dropping out of school, she turned to her last hope, bedaquiline. However, she was denied treatment at a Delhi TB hospital as she was not a resident of Delhi. The Hon'ble Delhi High Court later ruled in favor of the family, citing that domicile or residence of a patient is not a criterion for eligibility of bedaquiline under the government's CAP.[27]

REGULATIONS IN INDIA FOR COMPASSIONATE USE

The supreme authority for affairs of drugs and medical devices in India is the Central Drugs Standard Control Organization (CDSCO). According to CDSCO, a new drug approved outside India can receive a waiver of clinical trial in the Indian population only in cases of national emergency, extreme urgency, epidemics, for orphan drugs in rare diseases, and conditions which have no therapy.[28]

CDSCO complies with the Drugs and Cosmetic Act 1940 and Rules 1945 (as amended up to December 31, 2016). Although terms such as CU do not figure in the Act, provisions are in place to allow drugs to be imported as and when necessary. Applications can be submitted for the same to the Drug Controller General of India by a hospital, patient, or a pharmaceutical company.

Rule 33A and 34A of the Drugs and Cosmetic Act, 1940 and Rules, 1945 allow import of small quantities of new drugs by a government hospital or autonomous medical institution for the treatment of patients suffering from life-threatening diseases or diseases causing serious permanent disability, or such disease requiring therapies for unmet medical needs.[29]

CONCLUSION

Majority of the citizens in economically challenged countries like India struggle for survival on a day-to-day basis. Hence, the diagnosis of a health condition, with no available treatment, leaves the patient and the family in a hapless situation. Without the generous aid by large organizations such as the USAID, it is next to impossible for these patients to get a second chance at life. Even though compassionate drug use is nothing but preapproval access to drugs, many a times, it is supported on monetary terms by organizations, nongovernmental organizations, and patient health groups.

At present, India seems to be at its nascent stage with regard to CU. Even though necessary steps are being taken toward the right direction, India still lags behind in policies and guidelines in comparison to the rest of the world. There is no doubt that pharmaceutical companies and regulatory bodies need to work hand-in-hand to bring about changes in the system. However, greater awareness toward all diseases in general, especially aspects of prevention, is crucial for better health of communities in countries like India. Changes in guidelines and laws, not only pertaining to CU but also other issues, need to be addressed. For example, better laws for early detection of genetic disorders and change in currently strict laws for abortion in India may surprisingly reduce the burden of rare genetic disorders in the country.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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