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SAN DIEGO | JUNE 23-27

Perspectives on Benefit, Risk and Access

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AIDS Crisis: Patients Demand Access



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FDA Headquarters, Oct. 11, 1988; Photo source: FDA

1980s: Ripe for Patient-Driven Reform

- ▶ U.S. drug approvals among world's slowest
- ▶ Underfunded FDA has huge backlog of drug applications
- ▶ Reviews take years



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1990s: System Resets for Access

- ▶ PDUFA I eliminates “drug lag”
- ▶ Accelerated Approval speeds access in high-need settings
- ▶ FDAMA (which includes PDUFA II) expands FDA mandate from “protecting” to “promoting” public health



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Patient Perspectives

“There still is not a cure, but because of some of the new drugs, **a lot of us have been able to get back to work.**”

James Swire, AIDS Activist and Health Educator

June 1997



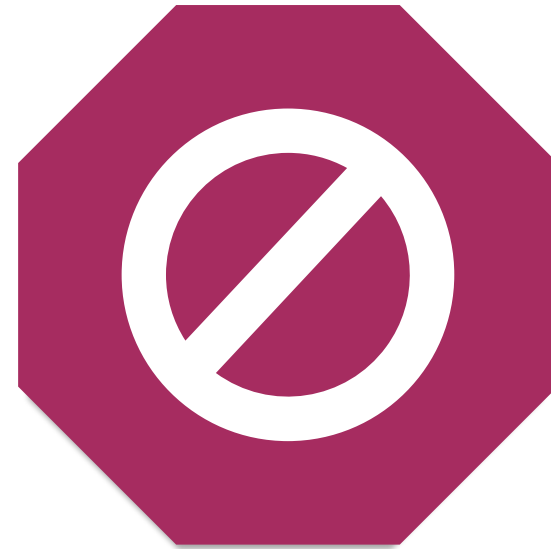
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2004: Risk Tolerance Plummetts

- ▶ Chiron flu vaccine suspended
- ▶ Rofecoxib withdrawn
- ▶ Antidepressants get black box warning
- ▶ Congress pressures FDA to require proof of the absence of risk
- ▶ Investment and access suffer



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Natalizumab Sparks Patient-Driven Change

- ▶ Accelerated Approval in November 2004 based on reduced relapse rate
- ▶ Withdrawn February 2005 due to one confirmed fatal case and one suspected case of PML in trials
- ▶ By 2006, 3 confirmed cases in ~3,500 patients treated in trials
- ▶ Confirmatory data showed
 - Significant reductions in progression of disability (primary endpoint vs. placebo)
 - Sustained reductions in relapse rates ~2x better than other drugs (based on cross-trial comparisons)



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Patient Perspectives

“Roughly 25% of us have been failing on medication, progressing. The aggregate risk of us not having the drug on the market is **far greater** than the risk of PML.”

*Mike Barron, Patient with MS
February 2006*



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Patient Perspectives



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“If someone tells me Tysabri will take 10 years off my life but I'll have the quality of life I had a year ago when I was taking it, **I'd take it.**”

Bartira Tiburtius, Patient with MS

March 2006

Patient Perspectives



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"People with MS have **the right to decide** what risks are acceptable to us."

Cheryl Bloom, Patient with MS
March 2006

Today: System Resets Around Patients



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“Patients are the experts in living with their disease or condition, the outcomes that are most important to them, and **how they weigh benefits and risks.**”

Jeff Shuren, Director of FDA's CDRH

May 2, 2019

C3G Patients Express Risk Tolerance



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REGULATION

FOUNDATION FOR INCLUSION

BY EMILY CUKIER-MEISNER, SENIOR WRITER

Hosting a patient-focused drug development workshop was the National Kidney Foundation Inc.'s first step in assuming the role of facilitator to collect patient perspectives that will shape R&D for kidney disease.

On Aug. 4, the advocacy group hosted a meeting of patients and caregivers, senior FDA leaders and drug company executives to discuss patient perspectives on C3 glomerulopathy (C3G). C3G is a rare condition caused by deposition of fragments of complement 3 (C3) protein in the kidneys.

"The patients with C3G and caregivers who courageously shared their stories provided a unique opportunity for the patient voice to be incorporated into drug development from the beginning," said CMO Joseph Vassalotti.

Vassalotti said the foundation chose C3G for its maiden effort because the condition affects a small yet engaged patient population that has a poor prognosis despite standard treatments. He said the patients tend to be knowledgeable because the road to diagnosis may be long and frustrating.

"The diagnostic journey for the person with C3G is often prolonged, requiring multiple kidney biopsies and visits with many different clinicians over years," he said.

There are no approved treatments for C3G. Standard of care includes the off-label use of steroids, which can have side effects, according to Alexion Pharmaceuticals Inc. and Novartis AG. Biogen and Amgen also have programs in anti-C3 and in inhibiting the complement system, respectively, according to Novartis AG.

hemolytic uremic syndrome (aHUS). CellCept is a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) that is approved to prevent transplant rejection.

About half the meeting participants who mentioned Soliris said it had helped stabilize or improve their kidney function, but the other half did not benefit.

Roughly half of patients with C3G progress to end-stage renal disease (ESRD) within 10 years of diagnosis, and disease recurrence leads to kidney failure in over 50% of patients who receive kidney transplants.

Vassalotti said another important factor in the choice of C3G as a starting point was that the disease mechanism is well enough understood to suggest several targets for intervention.

C3G can arise from several possible causes that converge on a common pathology: dysregulation of the alternative pathway of the complement system that leads to overproduction of C3 and deposition of C3 fragments in the glomerular basement membrane of the kidney.

Finally, he noted pharma has expressed interest in the indication. Achillion Pharmaceuticals Inc., which plans to study ACI-4471 in C3G, was lead sponsor of the workshop.

Novartis AG also contributed. The pharma would not say whether it has programs in C3G, but Richard Smith, chief medical officer, said the company has tested programs in anti-C3 and in inhibiting the complement system, respectively, according to Novartis AG.

Foundation spokesperson Julie Kim said she was not involved in developing the content, but the companies declined to disclose how much they contributed.

Vassalotti said the foundation expects to work together with regulators and companies to develop C3G therapies. Options the foundation is exploring include a patient registry, hosting conferences, disease and forming a coalition with other rare disease organizations. Vassalotti also is co-chair of the drug development (PFDD) meetings for rare diseases, but declined to give examples.

"I WILL GO TO PRETTY GREAT LENGTHS TO PRESERVE MY KIDNEY FUNCTION. IT IS MY NUMBER ONE PRIORITY."
LINDSEY FULLER, PATIENT

DAMAGE CONTROL

Some of the challenges the foundation faces include patient recruitment and enrollment in a small number of treatment centers that are geographically dispersed, and collection of consistent biomarkers and endpoints across different companies' trials to generate comparable data.

There are no established efficacy outcomes for C3G, so there is an opportunity for patients to help define them.

In a poll conducted at the workshop, patients rated fatigue, swelling, and difficulty breathing as their most problematic symptoms. But for some participants, alleviating symptoms took a back seat to altering the course of the disease.

"I will go to pretty great lengths to preserve my kidney function. It is my number one priority," said Lindsey Fuller. "Once you have your kidneys functioning, life is never the same again." Fuller, 37, was diagnosed with C3G nearly five years ago.

A minority of participants said preserving quality of life would be more important to them than altering progression. Across the group, patients were willing to accept increased risks from treatments in exchange for benefits on either front.

When polled about a hypothetical new treatment that could significantly slow progression or improve quality of life, but came with more severe side effects than their current regimen, slightly more than half of patients said they would "absolutely" take it. The remainder said it would depend on the benefit-risk profile.

None said they would not take the treatment.

"Across the group, patients were willing to accept increased risks from treatments in exchange for benefits on either [quality of life or altering progression]."

Source: Cukier-Meisner, E., BioCentury 2017

Patient Perspectives

“I will go to pretty great lengths to preserve my kidney function. That is my **number one priority**.”

Lindsey Fuller, Patient with C3G
August 2017



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Patient Perspectives

“I am home-bound and bed-bound 80% of the time. I am **willing to accept significant risks** to escape from this disease.”

Matina Nicholson, Person with CFS
April 2013



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Patients Quantifying Preferences

Clinical Therapeutics/Volume 36, Number 5, 2014

A Community-Engaged Approach to Quantifying Caregiver Preferences for the Benefits and Risks of Emerging Therapies for Duchenne Muscular Dystrophy

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¹Parent Project Muscular Dystrophy, Hackensack, New Jersey; and ²Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

ABSTRACT

Background: There is growing agreement that regulators performing benefit-risk evaluations should take patients' and caregivers' preferences into consideration. The Patient-Focused Drug Development Initiative at the US Food and Drug Administration offers patients and caregivers an enhanced opportunity to contribute to regulatory processes by offering direct testimonials. This process may be advanced by providing scientific evidence regarding treatment preferences through engagement of a broad community of patients and caregivers.

Objective: In this article, we demonstrate a community-engaged approach to measure caregiver preferences for potential benefits and risks of emerging therapies for Duchenne muscular dystrophy (DMD).

Methods: An advocacy oversight team led the community-engaged study. Caregivers' treatment preferences were measured by using best-worst scaling (BWS). Six relevant and understandable attributes describing potential benefits and risks of emerging DMD therapies were identified through engagement with advocates (n = 5), clinicians (n = 9), drug developers from pharmaceutical companies and academic centers (n = 11), and other stakeholders (n = 5). The attributes, each defined across 3 levels, included muscle function, life span, knowledge about the drug, nausea, risk of bleeds, and risk of arrhythmia. Cognitive interviewing with caregivers (n = 7) was used to refine the attributes and levels.

who were recruited in the United States through an advocacy group and snowball sampling. Caregivers were presented with 18 treatment profiles, each with a main-effect orthogonal experimental design, in which the dependent variable was the respondent's judgment as to the best and worst feature of the profile. Preference weights were estimated by dividing the relative number of times a feature was chosen as best and as worst, which were then used to calculate relative attribute importance.

Results: A total of 119 DMD caregivers completed the BWS instrument; they were predominately mothers (67.2%), married (89.9%), and white (89.9%). Treatment effect on muscle function was the most important among experimental attributes (28.4%), followed by risk of heart arrhythmia (22.4%) and risk of bleeding (21.2%). Having additional postoperative complications was relatively the least important attribute (2.1%).

Conclusions: We present a model process for community-engaged drug development for advocacy organizations aiming to promote patient-centered drug development. The community-engaged approach was successfully used to identify and implement a survey to measure caregiver preferences. Caregivers were willing to accept a serious risk when balanced with a noncurative treatment, even absent improvement in life span. These preferences should inform the Food and Drug Administration's benefit-risk assessments of emerging therapies.

“Caregivers were willing to accept a serious risk when balanced with a noncurative treatment, even absent improvement in life span.”

Source: Peay, H. et al., *Clinical Therapeutics* 2014



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Intense Desire for Access



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BioCentury, THE BERNSTEIN REPORT ON BIOBUSINESS

MARCH 31, 2014

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Regulation

Josh Hardy chronicles

By Steve Usdin
Washington Editor

The Josh Hardy story puts a human face on both the lifesaving potential of compassionate use programs and the wrenching decisions company executives must make about who receives access to compounds in clinical development.

The Hardy family's social media campaign to gain access to an experimental therapy has apparently saved the seven-year-old boy's life.

But along the way, television news programs depicted the situation as a simple case of corporate bad behavior that was corrected by the righteous attention of the media combined with the power of millions of people who became aware of Josh

marketed by Gilead Sciences Inc. to treat cytomegalovirus (CMV) retinitis in AIDS patients. Potentially fatal nephrotoxicity caused by Vistide has limited its use.

Chimerix created brincidofovir using a technology that makes it possible to create oral formulations of IV drugs with improved potency and reduced systemic exposure (see BioCentury, Feb. 24, 2003).

Chimerix started approving compassionate use applications in 2009, CEO Kenneth Moch told BioCentury. Using funding from HHS's Biomedical Advanced Research and Development Authority (BARDA), between 2011 and 2012 the company provided the compound to more than 200 patients under emergency INDs in the U.S. or equivalent regulations outside the U.S.

"Our extremely high-risk patient exhibited complete response to treatment with CMX001."

Journal of Clinical Virology



Whitehouse.gov

6:08 PM PST | FEB 10, 2017 | BIOCENTURY | POLITICS, POLICY & LAW

Right to try prairie fire

WHY INDUSTRY CAN DO LITTLE ABOUT RIGHT-TO-TRY LEGISLATION

BY STEVE USDIN, WASHINGTON EDITOR



EDITORS' COMMENTARY

DON'T SKIP DMD PATIENTS

BY STEVE USDIN, WASHINGTON EDITOR
AND SUSAN SCHAEFFER, EDITOR, BIOCENTURY

The skimpy NDA for eteplirsen to treat Duchenne muscular dystrophy has FDA wedged between the rock of inconclusive data and the hard place of a well-informed patient community that understands the limitations of the data and still demands access to the compound. There are very good arguments for rejecting eteplirsen, but they are outweighed by the possibility that the compound might help and is very unlikely to harm boys who have no other hope.

In the interest of patients, FDA should grant accelerated approval to eteplirsen for DMD that is amenable to exon 51 skipping. The agency should couple the approval with stringent requirements for Sarepta Therapeutics Inc. to rigorously confirm clinical efficacy, as well as an unambiguous understanding that approval will be withdrawn if efficacy is not confirmed.

At the eteplirsen advisory committee meeting on April 25, Janet Woodcock, director of FDA's Center for Drug Evaluation and Research (CDER), was correct to highlight the impact of regulatory decisions on patients, and the imperative to give patients a greater say in how the



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PHOTO: SHUTTERSTOCK/STEFANO BERTI

REGULATION

FDA TO FACILITATE ACCESS TO UNAPPROVED DRUGS

BY STEVE USDIN, WASHINGTON EDITOR

Patients' Academy Perspective

- ▶ Decisions with respect to benefit-risk should rest with patients
- ▶ Patients should be consulted early on in R&D, as partners with unique knowledge that can improve programs
- ▶ Patients with life-threatening or debilitating illness **OFTEN** prioritize access over risk
- ▶ **BUT** preferences and risk tolerance change over time in ways that cannot be assumed
- ▶ Patients must be properly informed in order to make benefit-risk decisions



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Thank You

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