

# The Most Expensive Drug in the World: To Continue or Discontinue, That Is the Question

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Tailoring treatment based on genetics and medical history may be preferable for patients with atypical hemolytic uremic syndrome who face lifelong therapy on an expensive medication and increased risk of infection.

**A** 59-year-old man with a 20-year history (1994) of HIV well controlled on highly active antiretroviral therapy (HAART) therapy (baseline viral load undetectable, CD4+ cell count 781), presented to a community hospital (May 7, 2014) with abdominal pain. The patient's girlfriend reported unusual behavior for 1 week before admission, including decreased appetite, binge drinking, and nonadherence to HAART therapy.

There was no history of fever, illegal medication use, or diarrhea. In addition to HIV, his past history was remarkable for hepatitis B, hypertension, and left lower extremity amputation secondary to a motor vehicle accident. He had a remote history of cocaine, PCP (phencyclidine), LSD (lysergic acid diethylamide), marijuana, and alcohol misuse and a 50 pack-year smoking history. His family history was remarkable for a mother who died of pancreatic cancer.

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During his hospitalization, he developed pronounced expressive aphasia and lethargy but was able to follow simple commands. A computed tomography (CT) scan of the head revealed a left lacunar infarction, and he was transferred to the VA Long Beach Healthcare System in California for further care of a possible stroke.

Shortly after arrival, he developed a fever of 100.9° F. His pulse was 100 bpm and regular, blood pressure was 164/92 mm Hg, and respiratory rate was 14 breaths per minute. A physical examination was remarkable for somnolence, disorientation, and aphasia. He was grimacing to light palpation in all 4 quadrants of the abdomen and had diffuse purpura on skin examination. Laboratory results showed worsening thrombocytopenia, acute kidney injury with proteinuria and hemoglobinuria, and hemolysis (schistocytes, low haptoglobin level, and elevated lactate dehydrogenase [LDH]).

The patient's changes in baseline laboratory results were platelet count 206,000 mm<sup>3</sup> to 64,000 mm<sup>3</sup>, serum creatinine level 0.98 mg/dL to

1.55 mg/dL. His hemogram showed normochromic normocytic anemia (hemoglobin [Hb] level 10.2 g/dL) with schistocytes. Serum samples were initially unreportable by the laboratory due to severe hemolysis, but his haptoglobin level was found to be low and, conversely, LDH remarkably high. Fifteen days after admission, his CD4+ cell count was 141. An abdominal CT scan showed right lower quadrant abdominal free fluid and thickening of the terminal ileum with surrounding stranding, suggestive of terminal ileitis, and he was started on piperacillin-tazobactam. A lumbar puncture was unremarkable, and HAART medications were resumed. The patient required intubation and a ventilator for acute respiratory failure.

Empiric treatment for presumed thrombotic thrombocytopenic purpura (TTP) with plasmapheresis and methylprednisolone was ineffective, and the patient required mechanical ventilation and hemodialysis.

In refractory cases of TTP-hemolytic uremic syndrome, rituximab, a monoclonal antibody directed at CD20 present on B

lymphocytes, is added empirically as effective salvage therapy and was therefore tried in this case.<sup>1</sup>

However, the addition of rituximab failed to improve the patient's condition, and he developed further seizure activity and evidence of new lacunar infarctions as seen on magnetic resonance imaging of the brain. His hospital course was complicated by recurrent hemoptysis and respiratory failure, requiring assisted ventilation and eventually tracheostomy.

A normal ADAMTS13 level (72%) and negative Shiga toxin test changed the diagnosis to atypical hemolytic uremic syndrome (aHUS). Mean complement C3 (74 mg/dL) and C4 (9 mg/dL) levels were low. Plasmapheresis was discontinued, and treatment with eculizumab (Soliris, Alexion Pharmaceuticals) was initiated. Meningococcal vaccine was administered post-eculizumab, aimed at reducing but not eliminating the risk of meningococcemia.<sup>2</sup> Two weeks later, the patient's platelet count normalized, renal function improved, hemolysis resolved, and the patient regained full mental status. Eight weeks after initiating eculizumab, he no longer required dialysis.

## DISCUSSION

Generalized thrombosis of smaller blood vessels (thrombotic microangiopathy [TMA]) occurs in 3 uncommon syndromes—TTP, HUS, and aHUS—all with similar clinical presentations but distinct pathologic etiologies and treatment. These syndromes share a clinical picture of thrombocytopenia, hemolytic anemia, and renal failure. Hemolysis in these conditions is manifested by schistocytes, elevated lactate dehydrogenase from damaged cells, decreased haptoglobin, anemia, and hemoglobinuria.

## Thrombotic Thrombocytopenic Purpura

Thrombocytopenic purpura occurs in about 3 cases per 1,000,000 adults per year.<sup>3</sup> It occurs when the metalloproteinase enzyme ADAMTS13 activity is impaired, interrupting its function to cleave large sticky von Willebrand factor (vWF) multimers, resulting in coagulation in microvasculature by increased platelet aggregation, hemolysis from shearing of red blood cells, and compromised circulation to the highly vascularized kidney and other vital organs.<sup>4</sup> The hallmark of TTP is a severely decreased ADAMTS13 activity (< 5% of normal) secondary to coexisting conditions, such as cancer, pregnancy, HIV infection, adverse effects (AEs), or antibodies to ADAMTS13.<sup>5</sup>

The TTP pentad of thrombocytopenia, hemolytic anemia, neurologic symptoms, renal failure, and fever were present in our patient. The patient had a known HIV infection but no exposure to medications associated with TTP (such as acyclovir, quinine, oxymorphone, platelet aggregation inhibitors, or immunosuppressants). Prior to obtaining ADAMTS13 level, the patient was treated empirically for TTP with early and daily plasma exchange to remove the inhibitor of ADAMTS13 and replace it with fresh frozen plasma. Rituximab also was used to inhibit production of antibodies to ADAMTS13 from CD20 B lymphocytes. These empiric clinical measures were not effective in stopping his decline in renal and neurologic functions.

## Hemolytic Uremic Syndrome

Like TTP, HUS is also a consequence of thrombotic microangiopathy. However, in contrast to TTP, which is more commonly seen in adults,<sup>3</sup> HUS

is usually seen in young children secondary to Shiga toxin-producing *Escherichia coli* (STEC).<sup>6</sup> Hemolytic uremic syndrome, also referred to as STEC-HUS or typical HUS, is a rare disease affecting 10 to 20 people per million annually. About 10% of these patients are classified as having aHUS because STEC is not implicated in their disease. It is of interest that, unlike aHUS, STEC-HUS is usually a self-limited disease of children, the majority of whom recover without relapse, and evidence that eculizumab improves prognosis in STEC-HUS is not compelling.<sup>5</sup>

## Atypical Hemolytic Uremic Syndrome

Atypical HUS is a complement-mediated disease. The usual function of complement proteins is to destroy foreign cells and activate immune cells. However, in aHUS this protective defense system goes awry resulting in a pathologic thrombotic milieu. Specifically, aHUS is a continuous complement mediated attack on vascular endothelial beds due to the failure of protein regulators to terminate the complement cascade. Unlike typical HUS, which is usually associated with a Shiga-toxin producing gastrointestinal infection, the trigger in aHUS is unknown and thought to be associated with a genetic predisposition.

Atypical HUS distinguishes itself from TTP and HUS in that it does not respond to plasma exchange, corticosteroids, rituximab, or other immunosuppressants. This is due to the distinct underlying pathophysiology of aHUS in which the problem is the unbridled activation of the alternate arm of the complement system.

The complement system is part of the innate immune system, which acts with or without the adaptive immune system it “complements” by

amplifying a cascade of responses to eliminate the trigger pathogen. There are 3 complement pathways—classical, lectin, and alternate. The alternate complement pathway, whose activation generates C5a complement (anaphylotoxin), was most pertinent to this case. This precipitates a number of downstream protein cleaving events that lead to the cell lysing membrane attack complex (MAC), which creates a pore in the cell membrane of pathogens seen as foreign. In aHUS, the patient's own cells come under attack by their own complement, which is no longer inhibited due to mutations in regulatory proteins of the alternate pathway.

With the foot off the complement brake (the hallmark feature underlying aHUS), endothelial cells, leukocytes, and platelets become hyperactive and thrombogenic, thereby resulting in microangiopathy and ischemia of involved organs.<sup>7</sup> These mutations may be sporadic or familial and occur in a genetically susceptible host.<sup>8</sup> It should be emphasized that genetic testing in complement mediated HUS is a specialized and slow process (weeks); the initial clinical diagnosis is one of exclusion and does not rest on genetic testing. Furthermore, serum complement levels may be normal in cases of complement mediated aHUS.<sup>9-11</sup>

This patient had a life-threatening condition that required distinguishing it from 2 rare diseases with very similar presentations; failure to do so in a timely fashion could easily have resulted in his demise. TTP or HUS was the important question, and ADAMTS13 level was one of the determining diagnostic tests. The usual interventions for TTP and HUS (plasmapheresis/plasma exchange and, in some cases, rituximab) were ineffective in this patient with aHUS.

The patient achieved full recovery of neurologic, renal, and hematologic impairments after treatment with eculizumab, the recombinant humanized monoclonal antibody that binds to the complement protein C5 brake and inhibits its enzymatic cleavage, thereby interfering with the production of the MAC and cell lysis.

Although the patient did not have an identifiable mutation in the panel of complement regulatory genes tested, the rather dramatic efficacy of the orphan drug eculizumab was in a sense confirmation of his complement related hemolytic uremia. Left undecided are the questions of how long to continue eculizumab, the potential risk of relapse with discontinuation, and the ethical dilemma of proper length of treatment with the most expensive medication in the world given its total cost and no clear discontinuation criteria.<sup>12-15</sup> The cost of medications for rare and ultra-rare orphan drugs have approached unsustainable levels, posing ethical challenges to many developed countries.<sup>16</sup>

### ECULIZUMAB AND ORPHAN DRUGS

Several months before his assassination, President Kennedy awarded Frances Kathleen Oldham Kelsey, MD, PhD, the President's Award for Distinguished Federal Civilian Service (August 7, 1962) for her insistence that more safety evidence for thalidomide be presented before she would approve its use in the U.S. As a result of the thalidomide tragedy, the Kefauver Harris amendment was passed unanimously by Congress and signed into law by President Kennedy on October 10, 1962. It required stringent evidence of safety and efficacy for FDA approval of a new medication, reporting of AEs to the FDA, truth in drug advertising, rules gov-

erning generic drugs, and informed consent from patients participating in clinical trials.

An unintended consequence was that the development of medications for uncommon diseases became fiscally unattractive to the pharmaceutical industry, ie, "orphaned." The Orphan Drug Act was enacted by Congress in 1983 to encourage development of drugs to treat less common diseases (diseases/disorders affecting fewer than 200,000 people in the U.S.) through incentives such as exclusive use approval for 7 years, reduced taxes, grants, and favorable laws. Ironically, thalidomide was designated an orphan drug on October 14, 1998 for treatment of multiple myeloma. Since its enactment in 1983, more than 400 orphan drugs and biologic products have been marketed. There may be as many as 7,000 orphan diseases to target for drug therapy, and the 17 of the 20 most expensive drugs in the world in 2013 were for rare orphan diseases.<sup>16</sup>

Paroxysmal nocturnal hemoglobinuria (PNH) is one of those rare diseases. Mutations of hematopoietic stem cells produce red blood cell membranes deficient in the glycoprotein to which signaling proteins attach (glycosyl phosphatidylinositol) and serve to inhibit complement-induced lysis. This results in intravascular hemolysis (increased LDH and decreased haptoglobin) and increased thrombosis. The FDA approved the orphan drug eculizumab for the treatment of the orphan disease PNH on March 16, 2007.

Eculizumab is a humanized mouse monoclonal antibody that gained FDA orphan drug approval (and exclusivity rights until 2019) for the treatment of aHUS on September 23, 2011, based on 2 industry-sponsored small trials of

17 and 20 patients, and it remains the primary and only known effective treatment for this disease.<sup>17-19</sup>

Eculizumab has raised many interesting questions. Its mechanism of action wets the appetite of pharmacologists and unveils more basic science questions regarding other related mechanisms of disease, recognition of foreign vs self, genetic influences, virulence of organisms, and more. National and international dilemmas have arisen because of the extreme cost of eculizumab, its position as the only effective treatment for this rare and often fatal disease, and the manufacturer's recommendation and promotion that it be continued indefinitely. How should the price of a drug, developed in large part by government-supported research and tax incentives, and without competition, be determined and justified?

### Pharmaceutical Inflation

A marketplace for pharmaceuticals is simply not analogous to other industries. Advances in pharmacotherapy, some miraculous, have come at a substantial cost. The high cost of drugs became newsworthy with the AIDS pandemic and the approval of the lifesaving azidothymidine (AZT) in 1989 (Burroughs Wellcome—also the developer of pyrimethamine [Daprim]) and its then record price. Cancer treatment that used to cost \$10,000 per year now costs \$10,000 per month while the oncology community extolls a 2- or 3-month progression free survival benefit. Patients must now deal with the shock of a cancer diagnosis followed by the shock of an exorbitant copayment.

Recent media attention focused derision on Martin Shkreli, chief executive officer of Turing Pharmaceuticals, for purchasing pyrimethamine and then raising the price of

the 62-year-old treatment for protozoan infection toxoplasmosis from \$13.50 to \$750 per pill. The debacle may also serve to highlight the complexities and ethical issues involved when profit intersects with health care. Some drug costs have dramatically increased in the U.S. because of greed, a belief that a marketplace can control costs, and the lack of regulation. The usual suspects, such as cost of research, length of development, stimulus to innovation, and return on investment, are difficult to apply to old medications whose marketing rights were acquired by purchase of another company. Can marketplace economics be applied in health situations where there is no competition, legal protections afforded manufacturers, consumers unable to make an informed decision?

While pharmacy and therapeutics committees were debating treatment of hepatitis C with either of 2 drugs approved in 2011, boceprevir (Victrelis, Merck) or telaprevir (Incivek, Vertex and Johnson & Johnson), Gilead Pharmaceuticals acquired Pharmasset Inc. and its hepatitis C drug sofosbuvir (Sovaldi) for a whopping \$11.2 billion in 2012. It received FDA approval April 8, 2013, under Breakthrough Therapy Designation.

While economists argued over the wisdom of such a high-cost acquisition, Gilead generated \$9 billion in sales during the first 3 quarters of 2014, surpassing adalimumab (Humira), which had been the highest earning drug in 2014. Hepatitis C could now be quickly treated with truly unprecedented efficacy and without the AEs of interferon. The oft-quoted cost \$1,000 per pill or about \$84,000 per treatment in the U.S. drew international attention. Prior options for hepatitis C treatment, which preceded sofosbuvir by a mere couple of years, fell into

pharmaceutical extinction. Telaprevir succumbed to competition and ceased to be manufactured on August 12, 2014. Shortly after approval of sofosbuvir, Gilead also gained approval of its combination product for hepatitis C ledipasvir 90 mg/sofosbuvir 400 mg (Harvoni) on October 10, 2014.

### The Most Expensive Drug in the World

Although there are no shortages of contenders for the coveted most expensive title, eculizumab is the current champion. Drugs that offer a cure, such as antibiotics, usually involve a relatively short, onetime course. Lack of return on the cost of development of curative agents may have reduced industrial incentives to develop antibiotics. On the other hand, the extent of infectious diseases, such as malaria, Ebola, tuberculosis, HIV, hepatitis, and the proliferation of drug-resistant organisms, continues to fuel industrial interest for this lifesaving class of medications.

Cancer medications touting a brief interruption of the race to death have raised questions of affordability, equitable access, and quality vs quantity of life. The \$11,000 per month endothelial growth factor inhibitor aflibercept (Zaltrap, Regeneron, and Sanofi) was approved by the FDA in November 2012 for colorectal cancer and was followed by a historic rejection by Memorial Sloan-Kettering Cancer Center, since its cost was nearly double that of a similar medication bevacizumab (Avastin) with similar meager benefit of a median progression free survival of 1.4 months.<sup>20</sup> Moreover Medicare is mandated to cover the price the manufacturers charge plus a 6% cushion for any cancer drug that the FDA approves.<sup>21</sup> Patients with private insurance, often

elderly and on a fixed income, are burdened with a copayment requirement of 20% of the cost of the drug. The nonnegotiation clause of Medicare has not reduced cost of medications, particularly for cancer, which many of the elderly will likely face.

The VA, a single-payer system distinguished by bipartisan congressional support, can directly negotiate with pharmaceutical companies, resulting in lower drug prices than discounts guaranteed by federal law; but what if there is no competitor? Biosimilar drugs are currently being debated by those seeking to prolong their patent protection. Stem cell therapies that offer a cure for some rare diseases or hope for common diseases are certain to command astronomical prices. Gene therapy offers hope for cure of both rare and common afflictions but at astounding prices.

The medication alipogene tiparvovec (Glybera, UniQure) delivered by adenovirus, for example, has been approved for use in the rare disorder lipoprotein lipase deficiency and is anticipated to cost \$1.6 million for a onetime curative treatment. The pharmaceutical industry has joined the gene therapy race. While this is indeed a record acquisition sum for alipogene tiparvovec, at least it offers a cure. Eculizumab, although unique and effective, offers indefinite administration at a cost exceeding \$600,000 per year, every year, for life. In 2014, sales of eculizumab climbed 44% to \$2.234 billion.

### To Continue or Discontinue Treatment

The duration of treatment with eculizumab poses a challenging dilemma for patients, clinicians, and health care providers. Eculizumab is the only effective treatment for a life-threatening condition, and the manufacturer, Alexion, recommends

lifelong therapy of its product that has no competitors. Our patient was treated with 47 fixed-dose infusions of eculizumab at 2-week intervals from May 31, 2014, to February 18, 2016, at a cost of \$737,957.80. The commercial cost outside the VA would be about 1.8 times this amount (\$1.3 million). This extraordinary cost is the basic ethical issue. Without competition there is little to negotiate.

Need the treatment be lifelong? The AEs of eculizumab are not trivial, and some clinicians felt evidence for indefinite use in this patient was not compelling. Our patient's initial critical and unstable condition had completely resolved after 2 months of eculizumab. The initial unknown precipitating event triggering the patient's aHUS probably had resolved. His genetic testing did not disclose any HUS-related mutation. The patient's serum was sent to Cincinnati Children's Hospital (CCH) Clinical Laboratory Service to determine his eculizumab level and complement inhibition. His complement inhibition, as measured by CH50 activity, was adequately suppressed at 6% on eculizumab (target of < 10%) in spite of a free serum eculizumab level (81 mg/mL) that was somewhat below the therapeutic range of > 100 mg/mL.

Arguments for lifelong eculizumab therapy are based in part on the theoretical development of anti-eculizumab antibodies that could render reinstitution of eculizumab ineffective.<sup>22</sup> Monitoring patients for relapse of their aHUS involves following markers of disease activity (levels of creatinine, LDH, haptoglobin, platelet counts, and Hb in urine). A report of 10 adult patients with aHUS who were treated effectively with eculizumab supports a trial of discontinuation.<sup>23</sup> Seven of the 10 patients did not re-

lapse following discontinuation of eculizumab. Three of 10 patients experienced a relapse when monitored for a cumulative 95 months, but all 3 had immediate and complete recovery after resuming therapy. All 3 patients who experienced relapse carried a complement factor H mutation. Their relapses occurred within 6 weeks from the last dose and were detected simply by performing home urine dipstick monitoring for haptoglobin 3 times per week. The 3 patients who relapsed promptly responded to eculizumab reinstitution with return of their labs to baseline.

Monitoring of complement function in patients with aHUS can guide clinically appropriate dosing intervals without changing disease activity markers.<sup>24</sup> The half-life of eculizumab is about 11 days, and dosing intervals may be safely extended beyond 2 weeks in select patients.<sup>25</sup> The target minimum inhibitory serum eculizumab level necessary to inhibit complement-mediated hemolysis is 50 µg/mL and 35 mg/mL for aHUS and PNH, respectively. In a small pharmacokinetic pilot study, Gatault and colleagues noted that trough levels during eculizumab maintenance by enzyme-linked immunosorbent assay (ELISA) of 44 mg/mL to 59 mg/mL inhibited the complement cascade.<sup>26</sup> We suggested that weight-based dosing aiming at a trough > 50 mg/mL (rather than fixed dosing at a fixed interval) would be a better maintenance strategy.

In select patients, a trial of gradual discontinuation by lengthening the dosing interval of eculizumab seems a reasonable and safe alternative to indefinite continuation of the drug. After a patient's successful recovery, the initial and unknown trigger of aHUS may no longer play a role. Improvement in the patient's

medical condition may permit the restoration of the patient's defenses to once again function normally. Eculizumab seemed to retain its efficacy in the small number of patients who relapsed. Those who relapsed had positive genetic markers.

Further arguments favoring trial discontinuation in patients without known genetic predisposition are that continuation is not without risk, particularly of meningococcal infection, necessity for infusion every 2 weeks for life, little is known regarding long-term risk of the drug, and a lot is known of its extreme cost. Suppression of C5 inhibitory effect can lead to increased susceptibility to infections, whereas increased C5 activity may lead to a continued autoimmune attack on native cells.

As proposed by others, we suggest that this decision be made on a case by case basis, tailoring treatment based on an individual's genetics and medical history.<sup>27</sup> Although the European Medicines Agency has approved lifelong therapy for aHUS, this may be appropriate only for patients who have aHUS complement mutations associated with poor outcomes.<sup>27</sup> This approach may not be warranted, however, in a patient, such as the one presented with no genetic mutations, or in those with mutations of uncertain clinical consequence. In such cases, given that 90% of adults who have a relapse experience within the first year after an aHUS episode, a reasonable alternative may be a trial discontinuation.<sup>27,28</sup> After 1 year of eculizumab therapy, a trial of discontinuation with urine dipstick monitoring for Hb (Hemastix) 3 times a week for relapse may avoid the unnecessary expense and risk for infection posed by lifelong therapy, and eculizumab

may be effectively restarted in case of relapse.

We propose that in these cases it would be reasonable to perform a trial of discontinuation after 1 year of therapy with urine dipstick monitoring for relapse, as lifelong therapy may pose unnecessary expense and risk for infection. In fact, given the financial burden of prolonged therapy on society, we believe it is unethical to continue treatment in a patient with unknown risk for relapse without a trial of discontinuation, as evidence has shown good response to re-initiation of therapy in the event of relapse.<sup>28</sup> Agencies that have negotiated or attempted to regulate the cost of eculizumab have been met with public media campaigns featuring afflicted children at risk of death without eculizumab. The public relations company behind these efforts received support from Alexion.<sup>29-31</sup>

## CONCLUSION

Given the formidable cost and the international monopoly status of eculizumab for a life-threatening condition, prospective discontinuation trials supported by the manufacturer would seem warranted in select cases. Delineating which patients will have a chronic relapsing course and those who will not should be one of these clinical trials. For now, one can only wonder: What's worse than having a rare disease like aHUS? Perhaps the cost of treatment for a potentially indefinite period of time—now that's a "bitter pill."<sup>32</sup> ●

## Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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