Market Research Paper

Market Research on Therapies Treating Anemia due to Chronic Kidney Disease in the United States

Introduction

The chronic kidney disease (CKD) population in the United States, particularly those on dialysis, has realized significant improvements in the treatment of anemia since the introduction of erythropoesis stimulating agents (ESAs), and more specifically, Epogen™ (epoetin-alfa) in 1989. Since 1991, increasing use of Epogen in this population has resulted in mean monthly hemoglobin (Hb) levels increasing from 9.6 g/dL to 11.9 g/dL in 2005, reduced transfusions and improved quality of life for patients. In that same time the mean weekly dose of Epogen has increased from roughly 6,000 to more than 18,000 units[1]. Due to U.S. patent protection, Amgen Incorporated, the manufacturer of Epoetin-alfa, continues to be the sole producer of ESAs in the U.S. market resulting in total revenues of more than $5 billion for all indications[2]. Medicare alone paid out more than $1.8 billion in 2004 outpatient costs for the use of ESAs in the ESRD population, accounting for 10% of total ESRD Program. In the past two years however, there have been a number of firms progressing through various stages of product development with the goal of bringing an improved therapy and competition to market.

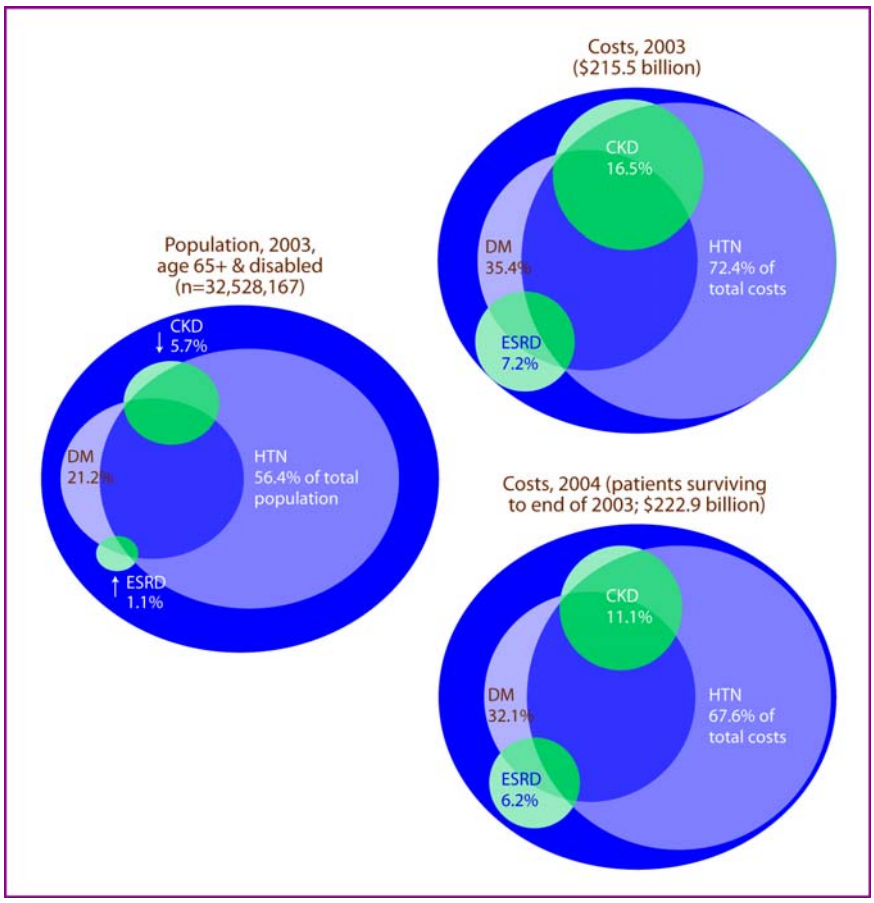
The desire for competition in this market has come to the forefront in recent months, as Congress is now taking notice of the substantial costs to Medicare under the current payment system, which many suggest encourages the over-utilization of Epogen by providers, and its reliance on a single supplier for anemia treatment. Furthermore, recent clinical trial results have highlighted a heightened risk of adverse events in CKD patients being treated with ESAs toward Hb levels beyond the clinically recommended range of 11-12 g/dL. These issues and the

increasing likelihood of competitors entering the market, suggest significant changes are brewing. The history, current state, and potential future of the CKD-Anemia market in the United States will be presented through discussion of the anticipated impact of earlier disease recognition and the possible entry of new therapies on the horizon.

Background

The CKD population in the United States has until recently been under-acknowledged in the general medical community. Though a small subset of these patients live to the final disease state, end-stage renal disease (ESRD), and have been fully covered by Medicare since creation of the ESRD program in 1972, those with CKD are severely under-recognized until their disease state is severe enough that symptoms begin to reveal the condition. In recent years, more attention has been brought on CKD, the care of those diagnosed with it and earlier detection of it. This has been accomplished through inclusion in the Healthy People 2010 objectives, the efforts of the National Kidney Foundation (NKF), research publication and annual reporting on the care of these patients by numerous investigators and the United State Renal Data System (USRDS), created in 1996 to maintain the ESRD registry database for the Center for Medicare and Medicaid Services (CMS) and the National Institute of Diabetes, and Digestive & Kidney Diseases (NIDDK). Though much is known of the care received in the ESRD community, the CKD population not on dialysis remains comparatively less explored with respect to anemia therapy. However, with U.S. population estimates for those with evidence of reduced kidney function in upwards of 20 million[3], increasing rates in obesity and diabetes, and recent reports on the "multiplier effect" of CKD on the cost of care (Figure 1), the government is taking note of the current and potential impact this population has and could have on the Medicare system, as the U.S. population ages.

Distribution of Medicare patient counts & costs for CKD, HTN, diabetes, & ESRD
USRDS 2006 ADR
Figure 1



The Disease

Chronic kidney disease is a progressive and typically irreversible medical condition in which the body's kidneys experience a decline in their ability to filter excess nutrients and toxins from the bloodstream. Symptoms are typically silent until the disease has progressed to a state of near-failure. The loss of kidney function is often referred to in terms of the "amount of filtrate formed in the kidneys each minute,"[4] called the glomerular filtration rate (GFR), measured in ml/min. Since this measurement necessitates an involved diagnostic procedure, GFR is typically estimated (eGFR) based on a formula using serum creatinine levels in the blood, age, gender, and race[5]. A normal eGFR is roughly 100 ml/min. In 2005, new ICD-9 codes were created using the

NKF's staging definition, based on eGFR, to identify the patient's stage of CKD, or level of residual kidney function at the time of diagnosis (Table 1).

Stage of CKD	Description	GFR (mL/min/1.73 m2)
Stage 1	Kidney damage with normal or Higher GFR	≥90
Stage 2	Kidney damage with mild Decrease in GFR	60-89
Stage 3	Kidney damage with moderate Decrease in GFR	30-59
Stage 4	Kidney damage with severe Decrease in GFR	15-29
Stage 5	Kidney failure	<15

Table 1. Stages of Chronic Kidney Disease, K/DOQI, National Kidney Foundation

As noted above, U.S. estimates are as high as 20 million for patients with evidence of kidney damage[6], see Table 2. The findings further suggest there are approximately 8 million Americans with moderate to severe kidney disease (Stage 3-4).

Table 2. Trends in prevalence of CKD by survey year and estimated number in 2000, Coresh, *et al*

CKD		Prevalence (%)			
Stage	Description	1988–1994[b]	1999–2000[b]	Prevalence Ratio (95% CI)[c]	No. in U.S. in 2000[d], Thousands (95% CI)
1	GFR ≥90 and persistent albuminuria[e]	2.2	2.8	1.26 (1.00–1.59)	5600 (4000–7200)
2	GFR 60–89 and persistent albuminuria[e]	2.2	2.8	1.27 (1.00–1.61)	5700 (4200–7200)
3	GFR 30–59	4.2	3.7	0.88 (0.67–1.10)	7400 (6000–8900)
4	GFR 15–29	0.19	0.13[f]	0.68 (0.07–1.44)	300 (24–500)
Total	Stages 1–4	8.8	9.4	1.07 (0.93–1.22)	19,000 (16,300–21,600)

The recognized CKD population is much smaller, however, due to the low awareness of CKD in the first place, Coresh *et al*. Likely, patients only become aware of CKD when symptoms begin to reveal themselves and they are motivated to see a doctor. The vast majority of recognized CKD patients suffer from multiple comorbidities, most commonly diabetes

mellitus (DM) and hypertension (HTN) – also evident in Figure 1, but often they suffer from anemia, a condition resulting from an abnormally low number of red blood cells (RBCs) in the bloodstream, reducing its capacity to transport oxygen throughout the body.

The World Health Organization defines anemia as a hemoglobin (Hb) level <13 g/dL in males and <12 g/dL in females. In U.S. ESRD patients however, the National Kidney Foundation (NKF) published a set of guidelines from their Kidney Disease Outcome Quality Initiative (K/DOQI); recommending treatment to a target Hb range of 11-12 g/dL for anemic patients on dialysis. Some reasons for this are described in another section. Patients who have been diagnosed with anemia due to CKD may be treated with erythropoesis stimulating agents (ESAs), which are designed to trigger the production of erythropoietin which, in turn, results in the production of RBCs. Still, utilization of ESAs in the CKD population is low. As evidence, the population initiating dialysis in 2005 did so with a mean overall Hb of 10.3 g/dL. Of those patients, only one-third received any ESAs prior to initiation[7]. Yet, within one month of initiating dialysis as an ESRD patient, more than three-quarters have been given their first dose of an ESA, and more than 90% begin therapy within their first year. Some possible reasons for the low utilization of ESAs in the CKD population may relate to the delayed recognition of the disease, as well as how and by whom ESA therapy is delivered.

Delivery of Care

This therapy to date is typically prescribed by nephrologists and often administered in the dialysis center. It is given by injection, either intravenously or subcutaneously, has specific storage needs, and is subject to a detailed payment system. Primary care practitioners generally refer CKD patients to nephrologists for care and are less involved in the specialized care these patients receive. Often CKD patients do not see or delay seeing a nephrologist until the disease

becomes quite severe. The two ESAs currently on the market in the U.S. are Epoetin-alfa (EPO) and Darbepoetin-alfa (DPO). Similar in make-up to EPO, DPO is a longer acting agent. EPO is administered frequently, often during dialysis sessions, three times weekly. DPO is typically administered once-weekly in the dialysis population. Reviewing other therapies in development, it appears the trend in new therapies may be toward those with a sustained release.

The Players

EPO and DPO were both developed under a 50-50 joint venture between Amgen and Kirin Brewing Company called Kirin-Amgen Inc (KA). EPO was approved in 1989, though the primary patents were not awarded until 1998, meaning Amgen's U.S. patents protecting EPO expire in 2013. DPO was approved in 2001, and is under U.S. patent protection until 2014. KA provided Amgen with an exclusive license to manufacture these agents in the United States. Amgen retained an exclusive license to market EPO to the CKD population on dialysis as Epogen™, while the license to market to all other indicated populations (including CKD not on dialysis) in the U.S. was sold to Ortho Pharmaceutical Corporation, a subsidiary of Johnson & Johnson, who markets the agent under the brand Procrit™. The license to market DPO (Aranesp™) in the U.S., for all indications was provided to Amgen. At this time there are no direct competitors to Amgen in the U.S. dialysis market, and in the U.S. CKD market they are the sole manufacturer. Additional firms are in various stages of research and development of agents that may one day compete with Amgen's products.

F. Hoffmann-La Roche (Roche), the U.S. subsidiary of Roche Holdings AG, is currently in Phase III trials seeking FDA approval for its anemia therapy. CERA, an acronym for continuous erythropoietin receptor activator, branded Mircera, is a long-acting therapy with a monthly dosing interval. In 2006, Roche filed marketing applications in the U.S. to sell CERA to the

CKD population both on and not on dialysis, making it the first potential competitor in Amgen's stronghold. In November 2005, Amgen filed a lawsuit for patent infringement, arguing that Mircera violates six EPO patents protecting Epogen and Aranesp. Recent documents filed by Roche indicate that Mircera is a pegylated erythropoietin-alfa, meaning it has the same biochemical make-up as Epogen, but has been altered by attaching a polyethylene glycol (PEG) group to the protein chain. Many analysts think this substantiates Amgen's case against Roche. It seems to be generally expected that Mircera will ultimately be approved by the FDA sometime during 2007, and depending on how long the case is drawn out, Mircera may get the opportunity to enter the U.S. market before a decision is made. Amgen, in anticipation of U.S. market competition, has been seeking exclusive contracts for supplying anemia therapy to large dialysis organizations (LDOs). They have succeeded with one organization thus far.

If Mircera does enter the U.S. market, Congress, CMS, and Medicare may get its wish: market competition in anemia therapy for the CKD market, particularly for those on dialysis where Medicare covers all services under the ESRD Program. It remains to be seen if competition will drive down the cost of treatment for Medicare.

Payment

In the CKD population, not on dialysis, Procrit and Aranesp use is reimbursed on the Part B side at 6% above the average sale price (ASP+6). Reimbursement for Epogen, in the dialysis population, has seen a variety of payment systems tested. As mentioned, in 90% of those on dialysis, EPO is typically administered through an IV during dialysis. Dialysis and ancillary services or products used during sessions are paid for at a bundled, "composite rate." EPO came to market after establishment of the composite rate, and is to this day reimbursed separately. The initial payment system (circa 1989) for EPO in the dialysis setting was set at a flat rate of $40

multiplied by the number of administrations in the month with a $30 supplement for administrations over 10,000 units[8]. In 1991, CMS changed to paying for EPO at a rate of $11 per 1,000 units, and in 1994 to $10 per 1,000 units. Recall from the introduction that from 1991 to 2004 the mean weekly dose tripled from 6,000 to 18,000 units. The effective change in the payment system was to give providers a green light to use EPO, resulting in increasing utilization and costs. By 1997, CMS had seen total costs increase to a breaking point, resulting in the announcement of the Hematocrit management audit (HMA) policy which sought to deny any payment for EPO given to patients with a 3-month rolling average hematocrit above 36.5 (roughly equivalent to a hemoglobin >12.2). Ultimately, the policy never went into effect because the impact of the announcement alone resulted in a significant drop in population hemoglobin levels, prompting CMS to forego the policy change. Since that time, CMS has attempted to take more palatable steps in reducing the over-utilization of EPO. Most recently, CMS has decided to modify payment from the "per 1000 unit" rate to match the way it pays for similar agents in CKD, ASP+6. In addition, CMS has implemented a revision to the HMA termed the Claims Monitoring Policy, effective April 1, 2006, which requires providers to reduce EPO a patient's EPO dose by at least 25% if they reach a Hb>13 g/dL, else CMS will reduce payment by 25% in accordance with the suggested dose reduction. Though this policy appears reasonable for controlling increasing costs for EPO, Congress did not think this went far enough.

Politics

In December 2006, the House Ways and Means Committee held a special hearing to discuss Medicare reimbursement for and the safety of ESAs, in particular Epogen. Representatives heard testimony from field investigators and held a hard line with CMS, citing recent clinical trial findings that Hb levels above 13 g/dL were potentially harmful in CKD

patients[9], and saying that the payment reduction policy focused on a threshold of 13 g/dL was negligent to the beneficiaries and served only to boost Amgen's monopolistic profits. They requested a full report from CMS investigating alternative methods for handling the payment of EPO, suggesting a demonstration project to show the impact of including ESAs in a new bundled composite rate, and promoting competition in the market.

Current Research and Development

The impact of this heightened interest has resulted in efforts in the scientific community and the industry to investigate the recommended target hemoglobin range in CKD. Upon release of the clinical trial finding in November 2006, the FDA released an "alert" reminding the community that Epogen had been approved with a recommended hemoglobin range of 11-12 g/dL. Primary research questions that now stand out are:

- How many patients exceed recommended Hb ranges?
- Is there a difference in those who transiently exceed versus persist above the target range?
- To what extent do patients' hemoglobin levels vary and what range of Hb variability is acceptable, safe, etc?
- Do stable levels result in better outcomes?

Given the questions and concerns that exist, the market seems ripe for new players with novel improvements. Some potential improvements suggested by those developing new therapies are:

- Sustained release
- New delivery mechanisms, e.g. oral
- Lower cost therapies
- New biochemical compositions, e.g. non-recombinant

The sustained release of longer-acting agents is of particular interest given the scrutiny of variable hemoglobin levels in the research community. Many of the firms developing new ESAs suggest that a sustained release will help to stabilize hemoglobin levels, and potentially reduce

hospitalization and mortality by reducing hemoglobin excursions beyond the target range, both on the high and low ends.

Summary

Though Roche's Mircera is farthest along in development, its future in the U.S. market is uncertain. Other firms with promising agents are FibroGen, which is developing a pill form therapy prompting the release of erythropoietin into the body in a manner similar to when we are exposed to high altitudes, Affymax, GlycoFi and DNAPrint Genomics all developing compounds structurally different from EPO. Generics of Epogen are on the horizon, but still some time away. The entry of additional players into this market will likely be welcomed by many, save for Amgen. Market competition in the ESRD arena may provide some cost reduction benefits to Medicare, but is realistically years away. However, given the estimated current and forecasted size of the CKD population, the most potentially lucrative market may not be in ESRD, but in opening the non-dialysis CKD population to increased utilization via increased referrals to nephrologists or by developing a therapy that primary care may be willing to prescribe.

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[1] USRDS 2006 ADR
[2] Amgen Inc. 2005 Form 10-K
[3] Coresh J, Byrd-Holt D, Astor BC, Briggs JP, Eggers PW, Lacher DA, Hostetter TH: Chronic kidney disease awareness, prevalence, and trends among US adults, 1999 to 2000. J Am Soc Nephrol 16: 180–188, 2005
[4] Tortora GJ, Principles of Anatomy and Physiology, copyright 2006.
[5] MDRD Study
[6] Coresh J, Byrd-Holt D, Astor BC, Briggs JP, Eggers PW, Lacher DA, Hostetter TH: Chronic kidney disease awareness, prevalence, and trends among US adults, 1999 to 2000. J Am Soc Nephrol 16: 180–188, 2005
[7] USRDS 2006 ADR
[8] Trends in Use, Cost, and Outcomes of Human Recombinant Erythropoietin, 1989-98 Joel W. Greer, Ph.D., Roger A. Milam, M.S., and Paul W. Eggers, Ph.D., Health Care Financing Review, Spring 1999
[9] Singh, A. K., Szczech, L., Tang, K. L., Barnhart, H., Sapp, S., Wolfson, M., Reddan, D., the CHOIR Investigators, (2006). Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease. NEJM 355: 2085-2098