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REFERENCE
Aliaksei Hintau has captured a spectacular image of an Indian Peafowl (*Pavo cristatus*) in his *Beautiful Peacock* photograph. A member of the pheasant family, the Indian Peafowl is one of the most recognizable birds on earth. The male peafowl is called a peacock, and the female is a peahen. This large, brightly colored bird is native to South Asia, but many feral populations exist throughout the world. The ancient Phoenicians introduced peafowl to the pharaohs of Egypt, and the species eventually made its way to Europe among the spoils of Alexander of Macedon's returning army. “From the time of Cicero until the Renaissance, no truly sumptuous European feast was held without a dish of peacock, often adorned with the bird’s feathered head and fan of tail feathers,” according to the Khandro.net Web site.

The Indian peacock is predominantly blue with a train of 100 to 150 iridescent feathers. Each one has a colorful ocellus (eye-spot). During courtship, these elongated feathers are raised and spread into a fan-like display. The peahen lacks the train, and has a greenish lower neck and dull, brown plumage. Peafowl spend most of the day on the ground pecking for food, but as evening falls, they fly up and roost in trees. In the spring (and when disturbed), the male can produce a loud, screeching call. Peacocks are sometimes kept on estates not only as decorative birds, but as reliable “watchdogs.”

As stated in the “Causes of Color” section of the WebExhibits Web site (webexhibits.org), “Behind the stunningly beautiful plumage of a peacock lies a complex structure that changes color with the angle of incident light. … Each feather consists of thousands of flat branches. When light shines on the feather, we see thousands of glimmering colored spots, each caused by minuscule bowl-shaped indentations. Stronger magnification reveals microscopic lamellae (thin plate-like layers) at the bottom of the indentations. As with butterfly wings, the regular pattern of the lamellae leads to [light-wave] interference phenomena and iridescent colors.”

The peacock has been the national bird of India since 1963. Throughout history, it has symbolized royalty, prosperity, beauty, grace, love, compassion, and peace. Because of the ancient belief that peacock flesh does not decay after death, the peacock is also considered to be a symbol of immortality. As such, peacock imagery can be found in early Christian paintings and mosaics. A notable example is the peacock in Fra Filippo Lippi’s *Adoration of the Magi* painting, circa 1450. In Greek mythology, the peacock was the favorite bird of the goddess, Hera. According to one particular myth, she took the eyes from the head of her hundred-eyed guard, Argus, and placed them on the peacock’s feathers. In the Buddhist tradition, the peacock’s remarkable ability to eat poisonous snakes without harm can be understood as a symbol of the conversion of evil to good. And the 2 peacocks found on each side of the Persian “Tree of Life” decorative motif signify the “psychic duality of man,” similar to the Gemini twins in Western astrology.

Peacocks have also played an important role in Native American Indian culture. Their feathers are often used in healing rituals and religious ceremonies, as well as adornments on headdresses and jewelry.

Artist Patty Szymkowicz’s “Magpie’s Nest” blog has a wonderful poem that Gene Griffin wrote about the peacock, aptly titled “The Peacock.”

“There he goes with his head up high,  
Proudly thinking, ’No creature is so beautiful as I.’  
He struts about with an arrogant air,  
Satisfied with his beauty so fair.

The peacock thinks himself to be without flaw,  
Thinks that all who see him should be in awe,  
His Creator has given him a plumage rare,  
Causing all that see him to stop and stare.

The peacock has a flaw not plain to him,  
A flaw to his eyes very dim.  
He arrogantly prances about with very ugly feet,  
Proud of his beauty, but deceived—like so many we meet.

He’s not altogether what he thinks he is,  
To see himself as he is would be great bliss.  
But he struts about with blinded eye,  
Thinking, ’No creature is so beautiful as I.’

The peacock teaches a lesson true,  
That there are flaws in me and you.  
That we are not so mighty and so high,  
That we should see ourselves with the humble eye.”

Sheila Macho  
Cover Editor

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http://bitze.wordpress.com/2008/07/14/peacock-fans.
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- Subject Reviews
- Formulary Management
- Contemporary Subjects
- Brief Communications
- Commentary/Editorials
- Letters

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Addition of Generic Medication Vouchers to a Pharmacist Academic Detailing Program: Effects on the Generic Dispensing Ratio in a Physician-Hospital Organization

Vinay Bhargava, PharmD; Mark E. Greg, PharmD; and Mark C. Shields, MD, MBA

ABSTRACT

BACKGROUND: Generic dispensing ratio (GDR) is an important measure of efficiency in pharmacy benefit management. A few studies have examined the effects of academic detailing or generic drug samples on GDR. On July 1, 2007, a physician-hospital organization (PHO) with a pay-for-performance incentive for generic utilization initiated a pilot generic medication voucher program that augmented its existing pharmacist-led academic detailing efforts. No published studies have examined the role of generic medication vouchers in promoting generic drug utilization.

OBJECTIVE: To determine if supplementing an existing academic detailing initiative in a PHO with a generic medication voucher program would be more effective in increasing the GDR compared with academic detailing alone.

METHODS: The intervention took place over the 9-month period from July 1, 2007, through March 31, 2008. Vouchers provided patients with the first fill of a 30-day supply of a generic drug at no cost to the patient for 8 specific generic medications obtained through a national community pharmacy chain. The study was conducted in a PHO composed of 7 hospitals and approximately 2,900 physicians (900 primary care providers [PCPs] and 2,000 specialists). Of the approximately 300 PCP practices, 21 practices with at least 2 physicians each were selected on the basis of high prescription volume (more than 500 pharmacy claims for the practice over a 12-month pre-baseline period) and low GDR (practice GDR less than 55% in the 12-month pre-baseline period). These 21 practices were then randomized to a control group of academic detailing alone or the intervention group that received academic detailing plus generic medication vouchers. One of 10 intervention groups declined to participate, and 2 of 11 control groups dropped out of the PHO. GDR was calculated monthly for all pharmacy claims including the 8 voucher medications. GDR was defined as the ratio of the total number of paid generic pharmacy claims divided by the total number of paid pharmacy claims for 108 prescriber identification numbers (Drug Enforcement Administration [DEA] or National Provider Identifier [NPI]) for 9 intervention groups [n = 53 PCPs] and 9 control groups [n = 55 PCPs]. For both intervention and control arms, the GDR for each month from July 2007 (start of 2007 Q3, intervention start date) through September 2008 (end of 2008 Q3, 6 months after intervention end date) was compared with the same month in the previous year. A descriptive analysis compared a 9-month baseline period from 2006 Q3 through 2007 Q1 with a 9-month voucher period from 2007 Q3 to 2008 Q1. A panel data regression analysis assessed GDR for 18 practices over 27 months (12 months pre-intervention and 15 months post-intervention).

RESULTS: A total of 656 vouchers were redeemed over the 9-month voucher period from July 1, 2007, through March 31, 2008, for an average of about 12 vouchers per participating physician; approximately one-third of the redeemed vouchers were for generic simvastatin. The GDR increase for all drugs, including the 8 voucher drugs, was 7.4 points for the 9 PCP group practices with access to generic medication vouchers, from 53.4% in the 9-month baseline period to 60.8% in the 9-month voucher period, compared with a 6.2 point increase for the control group from 55.9% during baseline to 62.1% during the voucher period. The panel data regression model estimated that the medication voucher program was associated with a 1.77-point increase in overall GDR compared with academic detailing alone (P = 0.047).

CONCLUSION: Compared with academic detailing alone, a generic medication voucher program providing a 30-day supply of 8 specific medications in addition to academic detailing in PCP groups with low GDR and high prescribing volume in an outpatient setting was associated with a small but statistically significant increase in adjusted overall GDR.

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What is already known about this subject

- Increasing the generic dispensing ratio (GDR) is associated with reduction in drug costs. For example, Express Scripts, a pharmacy benefits management company, estimated that every 1 percentage point increase in GDR is associated with an approximate 1 percentage point reduction in overall drug expenditures.
- Scott et al. (2006) found that a generic drug sampling program using automated generic dispensing machines (kiosks) in physician offices was associated with a higher GDR (55.3%) in the first year of the intervention for kiosk users compared with physicians who did not use the kiosks (54.1%), but the 1.2 percentage point difference in GDR was not statistically significant and declined to a 0.8 percentage-point difference in the second year.
- O’Malley et al. (2006) examined 4 interventions intended to increase GDR (member mailings, advertising campaigns, free generic drug samples to physicians, and physician financial incentives) compared with a benefit design change that doubled copayments for brand name drugs. None of the 4 interventions had a discernable effect on GDR, but doubling copayments for brand drugs was associated with a large positive effect on GDR.

What this study adds

- A generic voucher program providing a 30-day supply of medication to the patient with no copayment in 9 primary care physicians (PCP) medical practices in addition to academic detailing was associated with an increase in GDR that was 1.77 percentage points greater than the GDR increase in PCP medical practices that received academic detailing only (P = 0.047).
- This is the first study to evaluate the effect of a generic voucher program on GDR.
The last several years have seen an explosion in the availability of generic versions of branded blockbuster medications. One may refer to it as the “golden age” of generics. In the recent past, widely prescribed brand medications such as Ambien, Flonase, Fosamax, Imitrex, Norvasc, Protonix, Risperdal, Toprol XL, Zithromax and Zocor have all become available as generics. Major brands will continue to lose patent protection into the foreseeable future.

The advantages of utilizing generic drugs, when medically appropriate, are numerous. In addition to substantially lower cost, generic drugs offer the same clinical profile as their brand-name counterparts. For example, in a systematic review and meta-analysis for studies published through August 2008, Kesselheim et al. (2008) found no evidence of superiority of brand drugs compared with generic drugs in 9 subclasses of cardiovascular medications.1 For health plan members, copayment cost savings from generic drugs average $15 to $30 per 30-day prescription or $180 to $360 annual savings per maintenance drug in 2009.2 From the health plan perspective, it has been estimated that each 1 percentage point increase in the generic dispensing ratio (GDR) results in a 1% reduction in overall pharmacy benefit expenditure.3

Despite these advantages, however, significant obstacles remain in the promotion of generic medications. Since generic drugs directly compete with therapeutically similar branded offerings, the pharmaceutical manufacturers of branded medicines utilize their resources to promote the use of single-source brands. The use of samples, detailing by professional sales representatives, and direct-to-consumer advertising (DTCA) are 3 key tactics employed by the pharmaceutical industry.1,5

Most promotional spending by pharmaceutical companies is targeted directly at physicians through sampling (57% of total promotional expenditures) or detailing (26%).6 Although studies are lacking on the impact of detailing on prescribing behavior, the effect of drug samples on prescribing patterns has been studied. For example, in a prospective randomized trial, internal medicine resident physicians randomized to access to drug samples were less likely than control physicians to choose unadvertised drugs (64.9% vs. 73.4% of prescribing decisions, respectively) or to choose over-the-counter (OTC) drugs (25.2% vs. 38.8% of prescribing decisions, respectively).7

In addition to samples, pharmaceutical companies have more than quadrupled their spending on DTCA over the last decade. Whereas drug manufacturers spent $985 million on DTCA in 1996, it accounted for more than $4.2 billion in 2005.4 According to research conducted by the Kaiser Family Foundation, on average, each additional dollar spent on DTCA in 2005 yielded $4.20 in additional pharmaceutical sales in that year.5

In an effort to combat the brand messaging being deployed by the pharmaceutical industry, many insurers and pharmacy benefits management companies (PBMs) have implemented various programs to take advantage of the favorable generic marketplace. Many of these strategies have centered on patients in the form of benefit design incentives. Some of these tactics include (a) lower copayments for generics than for brands, (b) financial penalties for using a brand drug when a generic drug is available, and (c) step-therapy edits that require the use of a generic drug prior to initiating therapy with a branded product.

At the physician level, Scott et al. (2007) conducted a study at a health plan that assessed the impact of an office-based generic drug sampling system on GDR.8 The health plan used an automated generic dispensing machine (kiosk) in physician offices to dispense 21 distinct generic drugs. In the first year of this program, the average overall GDR for physicians participating in the sampling program was 1.2 percentage points higher than for physicians who did not participate in the program. However, this difference was not statistically significant, and the difference declined to 0.8 percentage points in the second year of the intervention. O’Malley et al. (2006), using a quasi-experimental study design, evaluated the effect of 4 different interventions (member mailings, advertising campaigns, free generic drug samples to physicians, and physician financial incentives) on changes in GDR.9 The study was performed at Blue Cross Blue Shield of Michigan utilizing multiple comparison groups of insured individuals who closely matched enrollees exposed to the interventions. Results showed that none of these 4 interventions had a positive effect on GDR. For example, for retail pharmacy sales with a baseline GDR of 45%, there was a -6.03 percentage-point change in GDR with the mailing intervention, -0.15 change with advertising, -0.02 change with generic sampling, and -0.40 change with physician incentive. The only intervention that did show a positive effect on GDR was a doubling of copayments for brand name drugs: the GDR increased by +9.55 percentage points.9

Advocate Physician Partners (APP), a physician-hospital organization (PHO), is the care management and managed care contracting joint venture between Advocate Health Care and select physicians on the medical staff of Advocate hospitals. The physician network includes more than 900 primary care physicians (PCPs) and 2,000 specialists. APP is associated with 7 hospitals in the Chicagoland area. As part of its clinical integration program, APP has GDR as one of its pay-for-performance (P4P) measures.

APP initiated an academic detailing program for its physicians in the second quarter of 2006. Academic detailing involves the use of clinical consultants, typically pharmacists, who meet face-to-face with providers to offer them unbiased, evidence-based clinical information about the medications that they frequently prescribe.10 In late 2006, APP made a decision to pilot a generic medication voucher program. APP saw several benefits to offering its physicians a voucher program instead of a generic sampling initiative. First, a voucher program would allow for a longer duration of use for the medications (i.e., a 30-day supply) compared with samples, which are typically
given out for 5-10 days of use. Because Illinois pharmacy laws have explicit labeling requirements for samples exceeding a 72-hour supply, providing a 30-day supply of samples would have been onerous for the organization.11 Second, a voucher program would bypass the need for shelf space to store samples. Third, whereas in a sampling program a physician office needs to track or monitor each dispensed sample, this tracking would be unnecessary with a voucher initiative. Lastly, APP wanted to evaluate the impact of a voucher program from a research perspective, since there have been no scientific studies of vouchers for generic medications.

The goal of this study was to assess the impact on GDR for PCP sites that received both academic detailing and generic medication vouchers versus physician practice sites that received academic detailing alone. The project was approved by the Advocate Institutional Review Board (IRB).

### Methods

#### Subject Selection

The PHO receives pharmacy claims data quarterly from 6 contracting insurers. Prescription claims data were used to calculate prescriber-level GDRs, where prescribers were uniquely defined by either their Drug Enforcement Administration (DEA) number or National Provider Identifier (NPI). At the group practice level, the pharmacy director sorted prescription utilization data both by claims volume and GDR. Practice sites with relatively high volumes (more than 500 prescription claims for the practice over a 1-year pre-baseline period from 2005 Q4 through 2006 Q3) and low GDRs (practice GDR less than 55% over the 1-year pre-baseline period) were chosen for randomization. Twenty-one practice sites were eligible for the pilot program based on these criteria. The practices that met the criteria were generally the larger practices (on average 3 or more physicians per practice) typically located in affluent suburban areas.

In December 2006, these 21 group practices were randomized using a random number generator (available at http://pangloss.com/seidel/rnumber.cgi) for inclusion in either the control group (academic detailing only) or the intervention group (academic detailing plus access to generic medication vouchers). After randomization, 10 group practices were included in the intervention arm, and 11 group practices were part of the control group. One intervention group practice declined participation because it had recently moved to an electronic medical record (EMR) system and did not want to initiate a paper-based program. Thus, the GDR for that group is not presented here, and it was not included in the final analysis. Two control group practices dropped out of the PHO for business reasons after randomization had occurred but prior to the start of the study. As no data were available on these 2 groups after 2006 Q4, these practices were also excluded from the final analysis. The final sample included physicians in 9 PCP intervention and 9 PCP control practices. The pilot trial (i.e., the period during which generic vouchers were redeemed) took place over 9 months between July 1, 2007, and March 31, 2008. The data presented in this study were derived from the pharmacy claims for dates of service from July 1, 2006, through September 30, 2008 (i.e., 12 pre-intervention months from 2006 Q3 through 2007 Q2 and 15 post-intervention months from 2007 Q3 through 2008 Q3).

#### Intervention Procedures

Program medicines were selected from the top 25 medications based on prescription volume for the entire PHO in the 1-year pre-baseline period from 2005 Q4 through 2006 Q3. High-volume medications in the areas of hypertension, type 2 diabetes, depression, and hyperlipidemia were selected. These 4 disease states were chosen because these are 4 common chronic conditions where a number of generic alternatives exist. Table 1 lists the medications selected for the voucher program, including their dosages and the maximum allowed quantity.

APP contracted a PBM with a large retail pharmacy presence, Walgreens Health Initiatives, to produce the vouchers, perform the claims processing, and provide reporting on voucher use. Weekly conference calls were conducted with the PBM in the months prior to the program launch and for several weeks following launch. The study PBM was the exclusive administrator for the free generic medications pilot program.

### TABLE 1: Generic Voucher Medication List

<table>
<thead>
<tr>
<th>Drug Therapy Indication</th>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Voucher Doses (mg)</th>
<th>Quantity Covered</th>
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<tbody>
<tr>
<td>Depression</td>
<td>citalopram</td>
<td>Celexa</td>
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<tr>
<td></td>
<td>sertraline</td>
<td>Zoloft</td>
<td>25 50</td>
<td>30</td>
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<td>Diabetes</td>
<td>metformin</td>
<td>Glucophage</td>
<td>500</td>
<td>60</td>
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<tr>
<td></td>
<td>metformin ER</td>
<td>Glucophage XR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>simvastatin</td>
<td>Zocor</td>
<td>510 20 40</td>
<td>30</td>
</tr>
<tr>
<td>Hypertension</td>
<td>atenolol</td>
<td>Tenormin</td>
<td>525 50</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Hydrodiuril</td>
<td></td>
<td>25 50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lisinopril</td>
<td>Prinivil/</td>
<td>2.5 5 10 20</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>HCTZ</td>
<td>Zestoretic</td>
<td>10 / 12.5 20 / 25</td>
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</table>

ER = extended release; HCTZ = hydrochlorothiazide; mg = milligrams; XR = extended release.
APP employs a pharmacy director who oversees all pharmacy programs for the organization and a clinical pharmacist whose primary responsibility is to provide support to APP physicians related to pharmacy P4P measures. The pharmacy director and clinical pharmacist scheduled meetings with each of the intervention group practices to introduce the program. At each practice, all of the physicians and key clinical staff were invited to attend these meetings. The PHO director and PHO medical director were also invited and provided support. Program overview folders were prepared for the site visit. Each folder contained (a) a 1-page program overview summary, (b) a color mock-up of the medication voucher, (c) a 3-page question and answer summary, (d) a list of all Walgreens pharmacies in Illinois, (e) type 2 diabetes treatment guideline, (f) congestive heart failure treatment guideline, (g) statin-based lipid-lowering guideline, and (h) generic antidepressant use summary. Whereas the intervention groups received all of this material, the control groups, as part of the existing academic detailing program, received only items e-h.

Each voucher was 8½" by 11" and contained a unique voucher number to allow pharmacy claim submission and tracking. This unique number was used to validate the eligibility of the prescription within the program. For this reason, each voucher was to be used for only 1 medication. Physicians could provide their patients with multiple vouchers if 2 or more medications were necessary for the patient. Vouchers were printed on tear-off pads containing 100 vouchers each. Each physician and office manager were given a pad of 100 vouchers.

The pharmacy director and clinical pharmacist then followed up with the offices biweekly to assess the need for additional vouchers, answer questions, and obtain program feedback. The study PBM provided a secure Internet-based reporting portal to track processed vouchers. The clinical pharmacist monitored the report each business day. APP received a monthly invoice for processed vouchers from the study PBM.

Group practices in both the control and intervention arms received academic detailing from the clinical pharmacist throughout the course of the study. Academic detailing involved the following: (a) regular meetings with physicians, key office contacts, and the office manager; (b) pharmacy reports on physician/practice performance related to pharmaceutical utilization; and (c) clinical recommendations rooted in evidence-based medicine provided by the pharmacist to assist the physician and practice in improving performance. Although participation was voluntary, offices were strongly encouraged by APP leadership to participate. An additional incentive for physicians was the inclusion of the voucher program claims data in their P4P calculations. Some physicians indicated that patients were not interested in the vouchers because numerous pharmacies in the area offered low-cost (discount) 30-day and 90-day generic medication fills. The extent of use of these community pharmacy discount generic drug programs could not be determined because there were no claims data for this drug use.

Outcome Measures
For each month, the GDR was calculated for all drugs (i.e., all drug classes, not just the study drugs) by dividing the total number of paid generic pharmacy claims by the total number of all paid pharmacy claims (generic and brand) dispensed. The GDR was calculated for each of 108 prescribers (identified by prescriber DEA or NPI number) for the 53 PCPs in the 9 intervention groups and 55 PCPs in the 9 control groups. Every quarter, the PHO provided the 6 health plans and PBMs that processed PHO pharmacy claims with the prescriber identification numbers for all PHO physicians. The plans/PBMs generated pharmacy claims reports for these pre-specified prescriber identification numbers only. Thus, only pharmacy claims with DEA/NPI numbers for PHO physicians were reported to the PHO. Pharmacy claims for all study PCPs were included in data analysis. GDRs for each practice were aggregated to the practice level, with both numerator (generic claims count) and denominator (total claims count) summed across all physicians in the practice.

Statistical Analysis
To assess the baseline demographic characteristics of the physicians in the intervention and control arms, Pearson chi-square tests and 2-sample t-tests were used. The physicians in the 2 groups were compared in terms of enrollment size, years in practice, gender, and practice specialty. In a descriptive analysis of study outcomes, a 9-month baseline period from 2006 Q3 through 2007 Q1 was compared with a 9-month voucher period from 2007 Q3 to 2008 Q1. Additionally, the GDR for each month from July 2007 through September 2008 was compared with the same month in the previous year (e.g., July 2007 vs. July 2006).

Panel-data regression methods were used to analyze the effect of the voucher program on GDR. The data were a panel of GDR measurements for 1 = 18 practices, over T = 27 months, for a total of 486 observations. The practices were divided into 2 groups: control and intervention, with 9 practices in each group.

Regression Model. GDRit denotes the GDR measure for practice i in month t, (1 ≤ i ≤ 18, 1 ≤ t ≤ T = 27) A difference-in-difference regression model on practice-month GDR measurements was used:

\[ GDR_{it} = a + \beta \cdot \text{(voucher)} + \gamma \cdot \text{(time)} + \delta \cdot \text{(voucher)} \cdot \text{(time)} + \epsilon_{it}, \]

where \( a \) is a constant that estimates the unconditional mean GDR for pre-intervention control practices; \( \beta \) estimates the difference in GDR between the intervention and control group; \( \gamma \) estimates the trend effect of time on GDR; and \( \delta \) estimates the effect that the voucher program had on GDR when controlling for these other effects. That is, \( \delta \) uses the control group observations along with the pre-intervention observations on the intervention group to disentangle the specific effect of the voucher program.

The data are not random, independent, and identically
distributed. For example, the observations on GDR come from practices of different sizes; some practices account for more than 10% of the total claims, while others account for less than 1%. Thus, in order to get consistent results and meaningful standard errors, as outlined in Wooldridge (2001), this type of stratification is corrected by using the following weighted version of the model:

\[ w_{GDR_i} = a \cdot w_i + \beta \cdot w_i \cdot \text{voucher} + \gamma \cdot w_i \cdot \text{time}_i + \epsilon_i \cdot w_i + w_i \cdot \epsilon_i \]

where each weight, \( w_i \), is given by

\[ w_i = \sqrt{\frac{\text{claims of practice } i}{\text{total claims}}} \]

and \( I = 18 \). This weighting scheme makes the data suitable for regression analysis.

## Results

### Randomization of Practices

The 2 PCP groups were statistically similar by the characteristics of average enrollment size, years in medical practice for the PCPs, physician gender, and practice specialty (Table 2).

The baseline average GDR at the time of randomization for both the intervention and control groups was 49.0%, based on prescription claims data during the pre-baseline period from 2005 Q4 through 2006 Q3.

### Generic Dispensing Ratio

After the pilot phase ended on March 31, 2008, data collection regarding GDR continued for an additional 6 months until September 30, 2008. Prior to program implementation, the monthly aggregated GDR for the control group was higher than that of the intervention group (Figure 1, Table 3). This difference, however, narrowed during the course of the post-implementation phase, and finally, in August 2008, the GDR for the intervention group exceeded that of the control group.

Figure 2 illustrates the changes in GDR from baseline, with baseline for each month defined as 1 year prior to that month (e.g., baseline for January 2008 was January 2007) for the intervention and control groups. Generally, during the course of the 15 months, the intervention group demonstrated a greater change in GDR from baseline compared with the control group. Comparing the 9-month baseline period (from 2006 Q3 through 2007 Q1) with the 9-month voucher period (from 2007 Q3 through 2008 Q1), the GDR increases for all drugs, including the 8 voucher drugs, were 7.4 percentage points for the intervention group (from 53.4% to 60.8%) and 6.2 percentage points for the control group (from 55.9% to 62.1%).

In the panel regression analysis, the estimated effect of the voucher program on GDR (\( \delta \)) was an increase of 1.77 percentage points. The estimate has a t-value of 1.99 (\( P = 0.047 \), Table 4).

### Number of Vouchers Redeemed and Top Medications Used

Thirty vouchers were redeemed during the first month of the program (Table 5). Over the following 8 months, an average of 78 vouchers was redeemed monthly for a total of 656 vouchers redeemed during the 9-month pilot period. Cardiovascular medications simvastatin and lisinopril were the 2 most common drugs in the voucher program (Table 5).

### Discussion

APP recognizes that preferential generic prescribing requires a change in behavior. The intent of the voucher program was to provide another tool to PHO physicians that could potentially affect their prescribing behavior. The voucher initiative was a value-added program that complemented various existing promotional efforts (e.g., academic detailing, P4P) that encourage the use of cost-effective medically appropriate generic medications.

Frequent program reminders in person, phone calls, and emails were required to encourage and maintain program participation. The office manager and nursing staff served as important resources for reinforcing the program with the physicians. Participation in the voucher program afforded an opportunity for the clinical pharmacists to develop relationships with the physicians and practices. In turn, these relationships allowed the communication of other generic medication-related information including benefit plan design changes favoring generic medications, 1-page summaries of new brand-name medications, and announcements of newly approved generic medications. Several of the practices indicated that they liked the program and wanted it to continue beyond the pilot period. In addition, some of the physician offices not involved in the voucher program expressed their interest in participating.

Feedback provided by physicians and office staff indicated that patients were satisfied with the program. This was noted particularly for the simvastatin vouchers, since this medication...
was not usually included in the low-cost 30- or 90-day generic drug discount programs offered by the large community pharmacy chains such as Walmart and Target.

In terms of the change in monthly GDR when compared with baseline, intervention group practices generally outperformed control group practices. Although the control group initially had a higher GDR than the intervention arm, the difference narrowed during the course of the study, and eventually the GDR for the intervention group slightly exceeded the GDR for the control group. Finally, the regression analysis demonstrated that the intervention (i.e., vouchers for generic medications) had a small but statistically significant impact on GDR; it was estimated that the generic medication voucher program increased the GDR by 1.77 percentage points.

The authors anticipated a learning curve for physicians and office staff pertaining to the consistent use of vouchers. Whereas most physicians are intimately familiar with the use of drug samples for branded pharmaceuticals, the voucher program for generic medications is a relatively untested concept. Also, the impact of the voucher program is not seen immediately because when the voucher is redeemed, that generic prescription counts as only 1 fill; it takes multiple refills of that generic prescription over several months before there is an observable impact on the GDR. Regardless, for any organization looking to implement a similar program, the results from this study demonstrate the need for a long-term commitment.

This pilot program demonstrated that a generic medication voucher program could be an effective tool for influencing prescribing behavior and result in an increase in the use of generics. This effect is potentially important for managed care organizations in light of estimates that each percentage point increase in the generic GDR leads to a 1 percentage point reduction in pharmaceutical expenditure. Applying this estimate to our finding that the differential effect was 1.77 percentage points in GDR, this generic voucher program could produce drug cost savings of approximately $0.71 per member.
Addition of Generic Medication Vouchers to a Pharmacist Academic Detailing Program: Effects on the Generic Dispensing Ratio in a Physician-Hospital Organization

**TABLE 3**  Generic Dispensing Ratios by Calendar Quarter

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<td>Post-Program Implementation (%)</td>
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*Generic dispensing ratio was calculated as total generic pharmacy claims divided by total pharmacy claims for 108 prescriber identification numbers on pharmacy claims, 53 PCPs in 9 physician practice groups (intervention), and 55 PCPs in 9 physician practice groups (control), aggregated to the practice level.

PCP = primary care provider.

per month (PMPM) in a pharmacy benefit plan with a $40.00 PMPM cost, or savings of $8.50 per member per year.

Based on the results of the pilot and interest in the program from other physicians within the organization, APP continued offering the generic voucher program to its physicians. Starting in 2008 3Q, APP expanded the program to other specialties such as cardiology, pediatrics, ophthalmology, and obstetrics and gynecology. Generic medication offerings were also increased substantially at that time and in 2010 include nearly 100 different medications but in a copayment-subsidy method rather than complete generic copayment waiver.

**Limitations**

First, the PCP practice groups for both the intervention and control arms were chosen based on their high prescription claims volume and low GDRs (less than 55%) in a 12-month pre-baseline period from 2005 Q4 through 2006 Q3 that overlapped the 12-month “baseline” period for the panel regression analysis (2006 Q3 through 2007 Q2). Although the average GDR for both the intervention and control groups was 49% in the pre-baseline period, the average GDR in the last quarter of the baseline period (2007 Q2) was 55.6% for the 9 medical practices in the intervention group versus 58.2% for the 9 medical practices in the control group. Therefore, unmeasured differences between the groups may have accounted for some of the variation in prescribing behavior and GDR, possibly biasing the results in favor of the intervention. Second, the pilot test was limited to low-GDR practices to maximize the program’s potential benefit to the PHO. The medical practices that met the inclusion criteria tended to be larger (3 or more physicians per practice) and more often located in affluent areas. Thus, study results may not be generalizable to all
Addition of Generic Medication Vouchers to a Pharmacist Academic Detailing Program: Effects on the Generic Dispensing Ratio in a Physician-Hospital Organization

**FIGURE 2** Monthly Percentage Point Changes in Generic Dispensing Ratio Compared with Baseline\(^a\)

![Graph showing monthly percentage point changes in generic dispensing ratio](image)

\(^a\)Baseline is defined as the same month during the previous year. The voucher intervention started July 1, 2007. Generic dispensing ratio was calculated as total generic pharmacy claims divided by total pharmacy claims for 108 prescriber identification numbers on pharmacy claims, 53 PCPs in 9 physician practice groups (intervention), and 55 PCPs in 9 physician practice groups (control), aggregated to the practice level.

PCP = primary care provider.

---

**TABLE 4** Weighted Difference-in-Difference Regression of Generic Dispensing Ratio Level on Time and Intervention\(^a\)

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>T-Statistic</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha)</td>
<td>0.5641</td>
<td>0.0045</td>
<td>126.16</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>(\beta)</td>
<td>-0.025</td>
<td>0.0059</td>
<td>-4.23</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>(\gamma)</td>
<td>0.0704</td>
<td>0.0068</td>
<td>10.37</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>(\delta)</td>
<td>0.0177</td>
<td>0.0089</td>
<td>1.99</td>
<td>0.0471</td>
</tr>
</tbody>
</table>

Coefficient Estimate Standard Error T-Statistic P Value

\(w_{GDR_i} = \alpha w_i + \beta w_i(voucher) + \gamma w_i(time) + \delta w_i(voucher)(time) + w_ie_i\)

\(^a\)The regression equation is multiplied by weights to adjust for the stratified sample. The weights are given by

\[w_i = \sqrt{\frac{\text{claims of practice } i}{\text{total claims}}}\]

and \(i = 18\) (count of practices).

The data are a panel of 18 practices measured monthly from July 2006 to September 2008. The intervention began in July of 2007.

GDR = generic dispensing ratio.

---

**TABLE 5** Number of Redeemed Vouchers by Generic Medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number of Vouchers Processed (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>206</td>
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<tr>
<td>Lisinopril</td>
<td>106</td>
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<tr>
<td>Sertraline</td>
<td>86</td>
</tr>
<tr>
<td>Citalopram</td>
<td>69</td>
</tr>
<tr>
<td>Lisinopril/HCTZ</td>
<td>65</td>
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<tr>
<td>HCTZ</td>
<td>35</td>
</tr>
<tr>
<td>Metformin ER</td>
<td>34</td>
</tr>
<tr>
<td>Metformin</td>
<td>33</td>
</tr>
<tr>
<td>Atenolol</td>
<td>22</td>
</tr>
<tr>
<td>Total vouchers redeemed</td>
<td>656</td>
</tr>
</tbody>
</table>

\(^a\)Number of vouchers redeemed between July 6, 2007, and March 31, 2008. ER = extended release, HCTZ = hydrochlorothiazide.
prescribers and physician practices.

Third, the study is somewhat limited in sample size. While panel data studies often deal with small samples, the fact remains that such small samples hinder parametric analysis. More data would be useful in evaluating the statistical model. Fourth, because this PHO provides care to several health plans, pharmacy claims for the prescribers in the control and intervention reports were extracted based on a list of DEA numbers with a crosswalk to NPI numbers rather than by member ID number. Therefore, some pharmacy claims, generally in the range of 2%-3% for the several sources of pharmacy claims, have either missing or unmatched DEA/NPI numbers, and there may have been some undetected systematic bias in the number of pharmacy claims that could not be matched to a valid prescriber. Fifth, there is the important issue of the unmeasured effect of community pharmacy generic discount programs (e.g., $4 for 30-day supply or $10 for 90-day supply) offered by pharmacy chains such as Target and Walmart. However, we have assessed pharmacy claims data for this PHO and could not discern a drop in PMPM utilization that might be associated with “lost” generic claims.

Sixth, the pharmacists who provided academic detailing were not blinded to the intervention (i.e., the pharmacists were aware of which practices were receiving academic detailing only and which practices were receiving academic detailing and vouchers). Seventh, because we did not measure the cost of the intervention or whether its effects persisted beyond the brief study period (e.g., whether patients continued to use generic medication), it is not possible to draw conclusions about the intervention’s cost effectiveness. Finally, we could not investigate the possible effects of member cost share differences for generic versus brand drugs because of the number of different pharmacy benefit designs among several health plans.

Conclusion

The combination of a generic medication voucher program for 8 specific drugs plus academic detailing resulted in a small but statistically significant increase in GDR of 1.77 percentage points compared with academic detailing alone.

DISCLOSURES

There was no external funding for this intervention in this physician-hospital organization. Bhargava and Shields designed the study. Greg had primary responsibility for data collection with the assistance of Bhargava and Shields. All 3 authors analyzed and interpreted the data. Bhargava had primary responsibility for writing and revising the manuscript with the assistance of Greg and Shields.

ACKNOWLEDGEMENTS

Mark E. Hendricks, a PhD candidate at the University of Chicago Booth School of Business, assisted with the statistical analysis.

REFERENCES


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Development and Delivery of a Quality Improvement Program to Reduce Antipsychotic Polytherapy

Jessica L. Gören, PharmD; Stuart E. Beck, MD; Barry J. Mills, MD, PhD; Derri L. Shtasel, MD, MPH; and Robert L. Dufresne, PhD

ABSTRACT

BACKGROUND: Although antipsychotic polytherapy is considered appropriate in limited circumstances (e.g., during a brief "cross-titration" period when switching medications), its increasing prevalence indicates use beyond this limited scope. Despite absence of support in the medical literature and higher costs, antipsychotic polytherapy is common in the treatment of schizophrenia and related disorders. The highest utilization of antipsychotic polytherapy occurs on psychiatric inpatient units, and in 2008, the Joint Commission released the first set of 7 hospital-based inpatient psychiatric services (HBIPS) core measures, 2 of which assess antipsychotic polytherapy at time of discharge.

OBJECTIVE: To describe the effect on antipsychotic polytherapy at time of discharge of a 2-part quality improvement program composed of educational seminars and prescriber-specific feedback provided to 11 psychiatrists in 4 acute inpatient psychiatric units in 2 hospitals.

METHODS: In a regional academic health care system, we determined the prevalence of antipsychotic monotherapy and polytherapy at time of discharge for all patients discharged on standing antipsychotic medications during 3 periods: (a) a 3-month baseline period (August 2006 through October 2006); (b) in July 2007, after delivery of 4 educational luncheon seminars to 11 psychiatrists from November 2006 through June 2007; and (c) in June 2008, following the provision of monthly prescriber-specific audit feedback from August 2007 through June 2008. To prepare nurses for the change and address possible safety concerns, an educational module was delivered to the psychiatric nursing staff at “best practice” day lectures held in the first quarter of 2007. General themes in the educational presentations included literature-based reviews of (a) safety and efficacy of antipsychotic polytherapy, (b) medical risks of antipsychotic medications, (c) specific versus nonspecific effects of these medications, and (d) effectiveness of first- versus second-generation antipsychotic medications. The prescriber-specific audit feedback was provided in paper form and masked the identity of the other prescribers. The chief of service reviewed audit feedback individually with each psychiatrist on a quarterly basis. The audit feedback was delivered to the psychiatric nursing staff at “best practice” day lectures in group settings were associated with a decrease in the rate of prescribing 2 or more antipsychotics at discharge from acute psychiatric inpatient units. Addition of monthly audit feedback provided to psychiatrists was associated with further decreases.

CONCLUSION: Educational modules presented to psychiatrists and nurses in group settings were associated with a decrease in the rate of prescribing 2 or more antipsychotics at discharge from acute psychiatric inpatient units. Addition of monthly audit feedback provided to psychiatrists was associated with further decreases.

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What is already known about this subject

- Because of high cost and lack of evidence of efficacy or safety, antipsychotic polytherapy, the prescribing of 2 or more antipsychotics, is discouraged in treatment guidelines except under limited circumstances (e.g., cross-titration when switching medications or failure/ineligibility for clozapine treatment). Nonetheless, antipsychotic polytherapy is highly prevalent in psychiatric inpatient units, with rates of 30%-40% in studies of acutely hospitalized patients.
- The Joint Commission's first set of hospital-based inpatient psychiatric services (HBIPS) core measures (2008) included a) decreasing antipsychotic polytherapy at time of discharge and b) documentation of appropriate justification for antipsychotic polytherapy, with appropriate justification defined as a history of 3 or more failed antipsychotic monotherapy trials, cross-titrating antipsychotic medications with the ultimate goal of antipsychotic monotherapy, or clozapine augmentation.
- The results of algorithms for decreasing psychotropic polytherapy and antipsychotic polytherapy have been mixed. Thompson et al. (2007) found that the likelihood of receiving polytherapy was decreased after implementing a system of chart reminders, education, and cognitive behavioral techniques but reported that the improvements were of limited benefit given the labor-intensive nature of the intervention.
A ntipsychotic monotherapy with first- and second-generation antipsychotics has demonstrated efficacy in the treatment of schizophrenia and other psychotic disorders. However, 20%-35% of patients fail to respond to or have incomplete response to antipsychotic monotherapy. For such treatment-resistant patients, clozapine is the only treatment proven effective. However, clozapine has some particularly dangerous side effects and requires regular monitoring of white blood cell count, limiting its use. As a consequence of this problem, clinicians and patients struggle to find an effective medication regimen. One particularly prevalent medication regimen is concomitant prescription of 2 or more standing antipsychotics (antipsychotic polytherapy).

Antipsychotic polytherapy has not been consistently proven effective or safe for patients with no or partial response to antipsychotic monotherapy. In the majority of randomized controlled efficacy trials, antipsychotic polytherapy did not significantly differ from monotherapy on primary outcome measures. Of the randomized controlled efficacy trials that found differences between groups on primary outcome measures, 2 studies reported antipsychotic polytherapy superior, and 1 reported antipsychotic monotherapy more effective. Effects on secondary outcome measures were mixed, but benefits gained with polytherapy were often, although not always, small. Results of analyses of side effects with polytherapy were mixed. Adherence is decreased with antipsychotic polytherapy, and the additional medication costs associated with antipsychotic polytherapy do not appear to be offset by cost savings in other areas of treatment.

Despite these mixed data, the use of antipsychotic polytherapy is common. Within the California Medicaid population in 2004, an estimated 13.7% of outpatients with schizophrenia who were treated with antipsychotics received multiple second-generation antipsychotics. Rates are even higher during psychiatric inpatient stays, with antipsychotic polytherapy prescribed in up to 40% of psychiatric inpatients. However, no antipsychotic is approved for adjunctive use with other antipsychotic agents, and such practice is discouraged in treatment guidelines.

Not all antipsychotic polytherapy is unjustified. For example, treatment guidelines suggest that cross-titration of antipsychotics is preferable to abrupt discontinuation of a medication when switching from one drug to another. In addition, treatment guidelines suggest antipsychotic polytherapy for patients who are treatment resistant and have failed or are ineligible for a clozapine trial. The guidelines caution that such use is not evidence-based, should be monitored closely, and discontinued if ineffective.

One of the most commonly cited justifications for antipsychotic polytherapy is treatment resistance. However, data suggest that antipsychotic polytherapy is not being reserved for treatment-resistant populations. Lee and Walker (2008) reported that in patients continuously enrolled in the California Medicaid program for at least 3 months, 3.7% of new users of second-generation antipsychotics received antipsychotic polytherapy as their initial antipsychotic treatment.

Schumacher et al. (2003) found that 79 of 85 patients (93%) on antipsychotic polytherapy did not have an adequate trial of monotherapy (4-9 weeks of optimal antipsychotic monotherapy dose). Even if we presumed that all patients on antipsychotic polytherapy were truly treatment resistant, Schumacher et al. found that 97.6% of patients did not receive a trial of clozapine, the only antipsychotic proven effective for treatment-resistant schizophrenia.

High prevalence and lack of evidence about safety and efficacy have produced concerns about antipsychotic polytherapy. Heeding these concerns, the Joint Commission in October 2008 released the first set of hospital-based inpatient psychiatric services (HBIPS) core measures, including 2 measures of antipsychotic polytherapy at discharge (Figure 1). Patients discharged without antipsychotic medications represent a different population than those discharged with antipsychotic medications and are not included in the antipsychotic polytherapy core measure.

In anticipation of the release of the Joint Commission’s antipsychotic polytherapy core measure, the study authors designed a quality improvement project to address antipsychotic polytherapy. In alignment with the Joint Commission’s core measure, the study’s primary outcome was use of antipsychotic polytherapy at discharge. Since the project began during development of the HBIPS core measure, initial data collection was based on early drafts of the measure, which did not include a measure of appropriate justification of antipsychotic polytherapy. Therefore, data on justification of antipsychotic polytherapy were not collected during the earlier portion of our intervention. Once the core measure criteria expanded to include appropriate justification of antipsychotic polytherapy, we began to collect these data.

What this study adds

- This quality improvement program can serve as a potential model for other inpatient facilities trying to meet the Joint Commission’s antipsychotic polytherapy HBIPS core measure.
- At baseline, 5.9% of patients discharged from an acute inpatient psychiatric stay on antipsychotic medication received discharge prescriptions for 3 or more antipsychotics. After the provision of education to psychiatrists and nurses, that rate declined to 2.5%. The rate further declined to 0.5% following the delivery of feedback from 11 monthly audits to psychiatrists.
- Of 389 patients discharged on antipsychotics at baseline, 132 (33.9%) were prescribed 2 or more antipsychotics. After completion of the educational and audit feedback components of the program, 12.2% (18 out of 147 patients) were prescribed 2 or more antipsychotics at discharge (P<0.001).
Development and Delivery of a Quality Improvement Program to Reduce Antipsychotic Polytherapy

Methods

All data were gathered as part of a quality improvement project. As such, our local institutional review board deemed publication of research using de-identified patient and psychiatrist data exempt from institutional review board approval. To ensure confidentiality during the project, all data analyses were conducted and reported for internal use with de-identified patient data.

Setting

At the time of the quality improvement project, Cambridge Health Alliance (CHA), a regional academic health care system, consisted of 3 inpatient hospitals, more than 20 outpatient clinics, a Medicaid health maintenance organization (HMO), and the Cambridge Public Health Department. As a safety net hospital system, CHA serves a racially and ethnically diverse population. Approximately 50% of CHA patients are uninsured or enrolled in Medicaid or Commonwealth Care, the state health insurance program.

During implementation of the quality improvement program, CHA had 4 acute inpatient adult psychiatric units housed within 2 hospitals (2 units at each hospital). Each adult inpatient psychiatric unit cares for approximately 40 patients daily. One hospital follows an academic model, with residents, students, and interns involved in patient care. The other hospital follows a community model without trainee involvement. There were no prescribing guidelines for the use of antipsychotic medications prior to initiation of the quality improvement program.

Educational Component

Reports of educational efforts to improve physician adherence with evidence-based medicine within and outside of psychiatry have been mixed. However, an educational program was considered by the study authors to be crucial to this quality improvement program for several reasons, including the need to (a) open a dialogue regarding goals and concerns with the quality improvement program, (b) address the evidence base supporting the quality improvement program, (c) obtain clinician “buy-in” for the program, and (d) allow nurses and psychiatrists access to the same information regarding the purpose and methods of the quality improvement program. A pharmacist who is board certified in psychiatric pharmacy practice worked as part of the interdisciplinary team to develop and deliver the education.

Educational modules were developed using a discipline-specific approach. Specific learning objectives are presented in Table 1. The primary educational goal was to ensure realistic expectations of what an antipsychotic could do and in what time frame. The secondary educational goal was to initiate discussion of the risks of antipsychotic medications, especially with antipsychotic polytherapy. Discussions centered on risks and benefits of antipsychotic monotherapy and polytherapy, relative risks and benefits of first- and second-generation

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**FIGURE 1** The Joint Commission’s Hospital-Based Inpatient Psychiatric Service Core Measures on Antipsychotic Polypharmacy

Patients Discharged on Multiple Antipsychotic Medications

**Denominator Statement:** Psychiatric inpatient discharges

**Included Populations:**
- Patients with ICD-9-CM Principal or Other Diagnosis Codes for Mental Disorders as defined in Appendix A, Table 10.1 discharged on one or more routinely scheduled antipsychotic medications (refer to Appendix B, Table 10.0- Antipsychotic Medications)

**Excluded Populations:**
- Patients who expired
- Patients with an unplanned departure resulting in discharge due to elopement
- Patients with an unplanned departure resulting in discharge due to failing to return from leave

Patients Discharged on Multiple Antipsychotic Medications with Appropriate Justification

**Denominator Statement:** Psychiatric inpatients discharged on two or more routinely scheduled antipsychotic medications

**Included Populations:** Not applicable

**Excluded Populations:**
- Patients who expired
- Patients with an unplanned departure resulting in discharge due to elopement
- Patients with an unplanned departure resulting in discharge due to failing to return from leave
- Patients with a length of stay ≤3 days

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antipsychotics, and use of antipsychotics for acute agitation versus primary psychosis.

All 11 inpatient psychiatrists met as a group 4 times during the 9-month intervention period. The initial meetings were in November and December 2006. The remaining 2 seminars were conducted quarterly during the first and second quarters of 2007. The meeting site was varied in order to decrease travel burden on any one group of psychiatrists. Core information was presented during lunch by the psychiatric pharmacist, chief of adult psychiatry, and local psychiatry directors from each hospital. An interactive seminar format was used to present information and allow psychiatrists to provide input and express their concerns about antipsychotic polytherapy in the clinical setting. To engage psychiatrists in discussion, the seminars included discussions of recent patients who were particularly complex and challenging.

Nursing staff were included for 2 reasons: (a) to prepare nursing staff for possible changes in prescribing practices, and (b) psychiatrists’ prescribing can be influenced by nursing input, specifically fears about violence on the unit. Given the goal of preparing nursing staff for possible prescribing changes, similar educational content was provided to nurses and psychiatrists. Education for nursing staff was conducted during 2007 Q1 through a series of lectures delivered by the psychiatric pharmacist during mandatory nursing “best practice” days. The format was a 45-minute lecture with a 15-minute question and answer period. A single lecture was delivered 7 times to allow maximal nursing participation. Supplemental written materials were provided. The 10% of psychiatric nurses unable to attend the lecture due to vacation or sick time received a printed copy of the lecture and contact information for the psychiatric pharmacist.

Audit Feedback
Because of the extensive literature on audit feedback as a method of quality improvement, the educational component was combined with prescribing feedback to improve the likelihood of success. Psychiatrists were provided with monthly “dashboard” (visual presentation of prescribing data) reports of their antipsychotic prescribing from August 2007 to June 2008 (Figure 2). They were also provided with de-identified peer data for comparison. Data presented in the monthly dashboard included the number of patients treated, number of patients treated with antipsychotics, number of patients treated with monotherapy or polytherapy, patient diagnoses, and specific antipsychotic combinations used. Psychiatrists met individually with the chief of service quarterly to review their antipsychotic prescribing dashboard, discuss concerns, and offer suggestions for improvements to the antipsychotic polytherapy project.

Outcome Measures
In alignment with the Joint Commission HBIPS-5 core measure, the primary outcome measure was the number of patients discharged on 2 or more standing antipsychotic medications divided by the number of patients discharged on at least 1 antipsychotic. Given the potential for increased risks and paucity of data on use of 3 or more antipsychotics, we believed this practice could never be justifiable. Therefore, the secondary outcome measure was prescription of 3 or more antipsychotics at discharge. Information on patients discharged on no antipsychotic was not reviewed because such patients represent a different population with disorders not responsive to antipsychotic treatment.

Sample and Data Collection Process
All patients on regularly scheduled antipsychotic medication for any indication at time of discharge from the 4 acute adult inpatient units were included. Baseline data were collected prior to any discussion of antipsychotic polytherapy usage (August through October 2006). Data following the educational component and the monthly audit component were collected in July 2007 and June 2008, respectively. Appropriate justification data were collected from November 2007 until the conclusion of the program in June 2008. Collection of these data coincided with inclusion of appropriate justification of antipsychotic polytherapy criteria into drafts of the HBIPS core measure.

Data were collected from the Meditech Health Care Information System, the electronic database used in CHA’s hospital system. Data collected included number of patients treated, standing antipsychotic medications at the time of discharge, and diagnoses. All cases of antipsychotic polytherapy were confirmed by a chart review conducted by the chief of adult psychiatry or chief of psychiatric quality improvement. Justification of antipsychotic polytherapy was confirmed through chart review by the chief of adult psychiatry.

Data Analysis
A comparison of the use of antipsychotic polytherapy in the 2 hospital settings prior to education was performed using a Pearson’s chi-square test of independence. As there were no significant differences between usage in these settings, data

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**TABLE 1** Educational Learning Objectives

- Describe medical risks of antipsychotic medications
- Identify specific versus nonspecific effects of antipsychotic medications (e.g., sedation vs. psychosis)
- Compare and contrast effectiveness and safety of first- and second-generation antipsychotics
- Describe data regarding the safety and efficacy of antipsychotic polytherapy
### FIGURE 2  Sample Audit Feedback: Antipsychotic Prescribing “Dashboard”

<table>
<thead>
<tr>
<th>Prescriber X</th>
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<th>8/07</th>
<th>9/07</th>
<th>10/07</th>
<th>11/07</th>
<th>12/07</th>
<th>1/08</th>
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<td>12</td>
</tr>
<tr>
<td># Patients on antipsychotics</td>
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<td>14</td>
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<td>% Patients on antipsychotics</td>
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**Patient Category**

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<th>Psychosis</th>
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*Numbers shown in the “dashboard” are hypothetical and presented for purposes of illustration only.
Adjust = adjustment disorder; anx = anxiety disorder; ARIP = aripiprazole; BPD = bipolar disorder; CLOZ = clozapine; cog = cognitive disorder; CPZ = chlorpromazine; eat = eating disorder; FLU (D) = fluphenazine (decanoate); HPD-D = haloperidol (decanoate); MDD = major depressive disorder; Mono = monotherapy; OZPA = olanzapine; PER = perphenazine; QTP = quetiapine; RPR (C) = risperidone (consta); SA = substance abuse; ZIP = ziprasidone.*
were combined across settings. Fisher’s Exact tests were performed on the primary outcome measure, receipt of 2 or more antipsychotics at discharge. These tests compared (a) July 2007 (the month following completion of the education) with August through October 2006 (the baseline period) and (b) June 2008 (the month following the completion of the monthly provider-specific feedback) with July 2007. A Pearson chi-square test of independence and a Cochran-Armitage test assessed the significance and trend of the relationship between the intervention and antipsychotic polytherapy, using a 2 X 3 table of the antipsychotic polytherapy measure (i.e., 1 vs. 2 or more antipsychotics at discharge over the 3 time periods—baseline, then education alone, then education plus monthly feedback). The strength of the association between the prescription of 1, 2, or 3 antipsychotics and increasing intervention (i.e., the 3 time periods) was assessed using a Goodman-Kruskal gamma test. Because no cells had less than 5 expected cases, continuity correction was not required for the Pearson chi-square tests. The a priori P value for statistical significance was 0.05. All statistical analyses were performed with Systat 12.0 (Systat Software Inc., Chicago, IL).

### Results

There were 389 patients prescribed at least 1 antipsychotic at discharge during the baseline period. Bipolar disorder was the most common diagnosis (37.0%) followed by schizophrenia/schizoaffective disorder/schizophreniform disorder (32.9%), major depression (28.0%), other mood disorder with psychosis (2.1%), and other (3.1%). Patients could be diagnosed with more than 1 primary psychiatric disorder; hence, the total of reported diagnoses exceeds 100%. During the baseline period, 109 (28.0%) of patients were treated with 2 antipsychotics, and 23 (5.9%) were treated with 3 antipsychotics at discharge, for an overall antipsychotic polytherapy rate of 33.9% (Table 2). Patient case mix and average length of stay did not differ between baseline and active intervention time periods (data not shown).

The frequency of antipsychotic polytherapy decreased significantly after the educational and audit feedback components of the intervention (Pearson chi-square = 28.81, df = 2, P < 0.001; Figure 3). In July 2007, after the educational modules had been delivered, of 202 patients prescribed antipsychotics at discharge, 44 (21.8%) were prescribed 2 or more antipsychotics. This rate represented an absolute reduction of 12.1% compared with baseline (Fisher’s Exact test, P = 0.002). Following the audit intervention, there was a further reduction to an antipsychotic polytherapy rate of 12.2% (18 of 147 patients), representing an absolute reduction of 9.6% (Fisher’s Exact test, P = 0.023). The Cochran-Armitage test for trend showed a significant (Pearson chi-square = 28.69, df = 1, P < 0.001) linear decrease in the proportion of patients who were treated with 2 or more antipsychotic drugs over the 3 time periods (i.e., using the progressive education to audit strategy).

In July 2007, 5 patients (2.5%) had 3 or more antipsychotics prescribed at discharge; that number declined to 0 in June 2008. Combinations involving clozapine accounted for less than 1% of antipsychotic polytherapy at all time points. When antipsychotic usage was classified as the frequency of patients receiving 1, 2, or 3 or more antipsychotic medications, the incremental intervention (i.e., 3 time periods) was associated with decreased combination use (Goodman-Kruskal gamma = 0.39, P < 0.001).

Justification of antipsychotic polytherapy data were collected from November 2007 until conclusion of the quality improvement project. Rates of appropriate justification ranged from 21% to 100%.

### Discussion

Our findings of decreased antipsychotic polytherapy during a quality improvement program are consistent with those of other reports in the literature. Similar to our report, successful interventions typically include multifaceted approaches. The present study is the first, to our knowledge, to find an association between the combination of discipline-specific group education for nursing and psychiatry staff with audit feedback and reduced rates of antipsychotic polytherapy.

Other reports address interventions to decrease antipsychotic polytherapy with different quality improvement programs. Mason et al. (1978) first reported more than 30 years ago on attempts to reduce antipsychotic polytherapy in state psychiatric hospitals. The authors reported that peer review, small group educational sessions, audit feedback, and written educational materials on basic principles of antipsychotic prescribing led to a rate of antipsychotic polytherapy of 152 of 802 (19.0%) at follow-up compared with 357 of 1,190 (30.0%) at baseline.
In another study, Chong et al. (2006) developed and implemented an evidence-based treatment algorithm for patients accepted into an early psychosis intervention program. Introduction of the algorithm was associated with decreased antipsychotic polytherapy. However, the algorithm was for “first break” psychosis and may not be applicable to patients who have been ill for many years.

In the previous research most similar to the present study, Thompson et al. (2008) reported a decrease in antipsychotic polytherapy in a randomized controlled trial involving 19 psychiatric units that included a 3-part intervention of academic detailing, chart-based reminders, and an educational workbook documenting alternatives to polytherapy, including cognitive behavioral techniques. Cognitive challenges to polypharmacy prescribing were identified from the rationales used by clinicians to justify polypharmacy, and alternatives to polypharmacy were reviewed in workbooks provided to nurses and physicians. Initial rates of polytherapy were 71 of 204 (34.8%) and 130 of 270 (48.1%) patients on the control and intervention units, respectively. Upon completion of the interventions, polytherapy was prescribed in 92 of 220 (41.8%) and 104 of 260 (40.0%) patients on the control and intervention units, respectively. However, given the modest gains and labor-intensive efforts, the authors recommended caution when interpreting their results. In contrast, the process described in the present study was less labor intensive. We did not rely on staff commitment of personal time for the educational program, providing the modules during normal working shifts. This feature may have improved the palatability of educational programs to psychiatric physicians and nursing staff. This difference may partially account for the present study’s finding of an absolute 22% decrease in rates of antipsychotic polytherapy.

The present study’s authors noted a decrease in the most egregious form of antipsychotic polytherapy (3 or more antipsychotics) after the introduction of educational programming only. Therefore, group education may be useful in decreasing the most egregious form of antipsychotic polytherapy. Study results, which represent academic and community hospitals, demonstrate that focused educational group sessions have the potential for broad application.

**Limitations**

First, the health care system in which the present study was conducted is a public health safety net hospital system. Additionally, 33% of sample patients were diagnosed with schizophrenia, schizoaffective disorder, or schizophreniform disorder, and 55% were diagnosed with bipolar disorder or major depression. As such, our population may not necessarily reflect other patient populations, including those in other facilities or with a different diagnostic profile. Second, this study reflects only a limited number of staff psychiatrists (n = 11). It is possible that other psychiatrists may be more resistant to prescribing change. However, the study investigators noted improvements in antipsychotic prescribing patterns in all 11 psychiatrists.
Third, all units involved in the study were within 1 health care system. This factor may limit the generalizability of our findings. However, the study did demonstrate that group educational modules can be conducted despite practice sites being in more than 1 city or town. Although all educational meetings in the present study were conducted in person, use of teleconferencing could decrease the time commitment of psychiatry staff or allow inclusion of remote sites.

Fourth, because the psychiatrists who were the subject of the intervention were aware of the objective of the quality improvement initiative, they may have changed their prescribing behavior as a result of being observed and not as a direct result of either the educational or audit feedback interventions. However, the Hawthorne effect has been viewed as an acceptable and useful aspect of quality improvement initiatives.37

Fifth, we did not measure whether patients in any time period also had observations in other periods. To the extent that this problem occurred, it would have violated the assumptions of the statistical tests used, which assume independent samples. However, persistence of educational effects into the audit feedback period for both new and repeat cases was an intended outcome of the program.

# Conclusion

Standardized group educational presentations were associated with decreases in concomitant use of 2 or more antipsychotics prescribed at discharge from an acute psychiatric inpatient stay. The addition of audit feedback was associated with an additional decrease in the concomitant use of 2 or more antipsychotics.

**DISCLOSURES**

There was no external funding for this quality improvement project or this research. Goren has served on advisory boards and speakers bureaus for Astra Zeneca and Eli Lilly and Company and has provided expert testimony for Morrison Mahoney, LLP, on the topics of drug pharmacokinetics, drug monitoring, and drug toxicity. Dufresne has served on an advisory board and speakers board for Eli Lilly and Company and Janssen Pharmaceutica. Mills has served on speakers boards for Janssen Pharmaceutica. The other authors reported no financial or other conflicts of interest related to the subject of this manuscript.

Beck, Goren, Mills, and Shtasel were responsible for concept and design. Shtasel had primary responsibility for data collection with the assistance of Goren. Dufresne, Goren, and Shtasel had primary responsibility for interpreting the data. Goren had primary responsibility for writing and revising the manuscript. Dufresne assisted with the revisions.

**REFERENCES**


Development and Delivery of a Quality Improvement Program to Reduce Antipsychotic Polytherapy


Formulary Review of 2 New Biologic Agents: Tocilizumab for Rheumatoid Arthritis and Ustekinumab for Plaque Psoriasis

Jeremy A. Schafer, PharmD; Nicole K. Kjesbo, PharmD, BCPS; and Patrick P. Gleason, PharmD, BCPS, FCCP

ABSTRACT

BACKGROUND: Two autoimmune biologics were recently approved by the FDA: ustekinumab in September 2009 for the treatment of moderate to severe plaque psoriasis in adults who are candidates for phototherapy or systemic therapy and tocilizumab in January 2010 for adult patients with moderate to severe rheumatoid arthritis (RA) who have not responded adequately to 1 or more tumor necrosis factor (TNF) antagonist therapies. Both agents use new mechanisms of action and add to the growing group of autoimmune biologics.

OBJECTIVE: To critically review the phase 3 trials for ustekinumab and tocilizumab and provide managed care considerations in the context of the 9 other biologic agents on the market in the United States that are used to treat moderate to severe RA or psoriasis.

METHODS: A MEDLINE review was performed for articles published and available through January 2010 using keywords “ustekinumab” and “tocilizumab” with an emphasis on phase 3 trials. The literature search was limited to articles in English, clinical trials, randomized controlled trials, and research conducted in humans. Search results for ustekinumab included 8 articles of which 4 were excluded for not being psoriasis or psoriatic arthritis trials. Search results for tocilizumab included 16 articles of which 8 were excluded for not being RA trials or using biomarkers as primary endpoints. Additional information was obtained from the FDA website.

RESULTS: Three phase 3 trials are available for ustekinumab. Ustekinumab demonstrated superior efficacy to placebo in 2 trials for the treatment of psoriasis. In a 12-week trial, ustekinumab 45 milligrams (mg) and 90 mg demonstrated significantly higher rates of 75% improvement in the psoriasis area and severity index (PASI 75) (67.5% and 73.8%, respectively) compared with etanercept (56.8%) in the first phase 3 comparative psoriasis trial between autoimmune biologics (P < 0.05 for both comparisons). In a phase 3 trial of RA patients who had failed prior TNF antagonist therapy, a 20% improvement in signs or symptoms according to the American College of Rheumatology criteria (ACR 20) at week 24 was achieved by significantly more study participants in the tocilizumab 8 mg per kilogram (kg) (50.0%) and 4 mg per kg (30.4%) groups than the placebo group (10.1%, P < 0.001 for both tocilizumab groups compared with placebo). Safety data for ustekinumab are limited to use for less than 2 years, and the prescribing information contains warnings regarding infection and malignancy. Tocilizumab is associated with neutropenia, thrombocytopenia, and elevations in lipids and liver function tests. Tocilizumab has unique adverse events when compared with other autoimmune biologics and requires laboratory testing and careful monitoring.

CONCLUSIONS: Ustekinumab and tocilizumab are new additions to the treatment of autoinflammatory disease. The majority of safety data for both agents are from trials lasting 3 to 6 months. Published long-term safety data for tocilizumab are limited to less than 143 patients treated longer than 5 years, and safety data for ustekinumab are scant beyond 2 years of use; therefore, clinicians should exercise caution prior to widespread adoption. The comparative efficacy and safety trial of etanercept and ustekinumab brings important clinical information to decision makers. Tocilizumab is indicated after failure or intolerance to a TNF antagonist and has unique safety concerns. Managed care plans will consider the experience and long-term data of these agents along with efficacy data and cost when establishing management programs such as prior authorization or step therapy.

What is already known about this subject

- Biologics are an important component in the management of moderate to severe rheumatoid arthritis (RA) and psoriasis.
- Tumor necrosis factor (TNF) antagonists have been found to be effective in multiple autoinflammatory diseases including RA, psoriasis, Crohn’s disease, and ulcerative colitis. However, patients may not experience adequate response with a TNF antagonist or lose the therapeutic response. New agents with different mechanisms of action are needed.

What this study adds

- Ustekinumab demonstrated superior efficacy to etanercept in a phase 3 psoriasis trial. The FDA-approved indication for tocilizumab is supported by clinical data demonstrating efficacy in RA patients who had failed 1 or more TNF antagonists.
- Long-term safety data are limited for ustekinumab and tocilizumab. Both agents increase the risk of infection, and tocilizumab has adverse effects on neutrophils, platelets, lipids, and liver enzymes.
- How ustekinumab and tocilizumab will be used in clinical practice is unclear at this time. More data and experience are needed. Cost continues to be an issue with autoimmune biologics, with increases in population-level expenditures due to the combination of higher utilization and price inflation.
- Ustekinumab has higher drug cost at initiation of therapy because 2 doses are administered in the first 30 days at weeks 0 and 4, a current (2010) average wholesale price (AWP) of $11,912, and $5,596 every 12 weeks thereafter, yielding an annual drug cost of approximately $33,576 in the first year for 6 doses and $22,384 annually thereafter for 4 doses per year. The cost of tocilizumab depends on body weight, with dosing every 4 weeks at either 4 mg or 8 mg per kg. The initial dose is 4 mg per kg. Annual tocilizumab drug cost in a 70 kg person ranges from $13,368 at 4 mg per kg to $26,748 at 8 mg per kg at 12 doses per year.
Rheumatoid arthritis (RA) is an autoimmune, chronic, multisystem, inflammatory joint disease characterized by synovitis, pain, and fatigue. RA affects an estimated 1.3 million American adults aged 18 years or older, or 0.6% of the population of the United States. The costs of RA to society and individuals are considerable. The estimated annual cost of RA in the United States is between $26 and $32.4 billion. An analysis of studies on the cost of RA estimated the annual mean direct cost of RA per patient to be $5,425 with annual indirect costs of $9,744 (1998 dollars). RA patients with concomitant cardiovascular disease or depression have even higher costs, more medication use, and more hospitalizations compared with patients with RA only. Patients with RA progressively accumulate disability leading to unemployment and increasing health care utilization.

Psoriasis is a common chronic autoimmune condition that is characterized by red, scaly, and indurated skin lesions. These lesions more commonly occur on the scalp, elbows, umbilicus, gluteal cleft, genital areas, and knees. Symptoms usually include itching, burning, and soreness of the lesions as well as joint pains or true arthritis. The exact cause of psoriasis is unknown. Psoriasis affects between 1% and 3% of the U.S. population, an estimated 4.5-7.5 million Americans. Of these persons, approximately one-third suffer from moderate to severe disease that can not be controlled by topical therapies. Total direct and indirect health care costs of psoriasis are calculated at $11.25 billion annually in the United States. Loss of work accounts for 40% of the cost burden.

Biologics are therapeutic agents derived from human or animal sources or manufactured using recombinant deoxyribonucleic acid (DNA) technology. Biologics may be proteins, monoclonal antibodies, recombinant receptors, or complex sugars. Biologics are used in a variety of disease states including autoimmune disease. The introduction of the autoimmune biologics has had a significant impact on the management of autoinflammatory diseases. Guidelines have predominantly placed biologic treatments as second line behind conventional therapy for RA and psoriasis. The American College of Rheumatology 2008 guidelines recommend methotrexate as first-line therapy to be followed by a tumor necrosis factor (TNF) antagonist if the response to methotrexate is inadequate. Similar recommendations can be found in other guidance including the National Institute for Health and Clinical Excellence (NICE) technology appraisal no. 130 (October 2007). American Academy of Dermatology guidelines recommend topical therapies for patients with limited disease. Biologics are an option along with ultraviolet light A or B/psoralen (UVB/PVUA) or other systemic therapies (acretin, methotrexate) for psoriasis patients with extensive disease or those with local disease who fail topical therapy.

There is a significant amount of clinical data on the use of biologics in autoinflammatory diseases, but questions remain on management of treatment failures and comparative efficacy. A United Kingdom (UK) database study found, in a registry of 6,739 patients with RA, that a total of 856 patients (12.7%) switched to a second TNF due to lack of efficacy or intolerance. Patients who switched due to lack of efficacy (n = 503) were more likely to fail a second TNF (hazard ratio [HR] = 2.7, 95% confidence interval [CI] = 2.1-3.4). Additional studies have found that patients switching from 1 TNF antagonist to another have a progressively smaller chance of treatment success with each switch. Choice of autoimmune biologic is limited by the lack of comparative data between different agents. A 2007 report sponsored by the Agency for Healthcare Research and Quality stated that there is an urgent need for comparative data for the autoimmune biologics.

Ustekinumab, approved by the U.S. Food and Drug Administration (FDA) in September 2009, and tocilizumab, approved in January 2010, are autoimmune biologics indicated for the treatment of psoriasis and RA, respectively (Table 1). Both agents have distinct mechanisms of action that differ from those of previously available autoimmune biologics. Tocilizumab has demonstrated efficacy in patients failing at least 1 TNF antagonist, and the product label specifies use in “adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF therapies.” Ustekinumab has been compared with etanercept in the first phase 3, double-blind, trial to compare autoimmune biologics. Ustekinumab is approved for use in “the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.”

The purpose of this review is to provide a summary of the clinical data for ustekinumab and tocilizumab with an emphasis on the phase 3 clinical trials. Issues with the autoimmune biologics are discussed in a managed care context, and insight is provided for formulary decision makers on management options.

Methods

A MEDLINE review was performed for articles published and available through January 2010, using keywords “ustekinumab” and “tocilizumab” with an emphasis on published, randomized, controlled trials (Figure 1). The literature search was limited to articles in English, clinical trials, randomized controlled trials, and research conducted in humans. Articles that were review articles, meta-analyses, or not clinical trials were excluded. Articles for disease states other than RA and psoriasis were also excluded. Search results for ustekinumab included 8 articles of which 4 were excluded for not being psoriasis or psoriatic arthritis trials. Search results for tocilizumab included 16 articles of which 8 were excluded for not being RA trials or using biomarkers as primary endpoints. Additional information was obtained from the FDA website.
Results

Pharmacology

Ustekinumab. Interleukin (IL) IL-12 and IL-23 are involved in innate and adaptive immune response and have been implicated in the pathogenesis of psoriasis. IL-12 stimulates T-helper (TH1) cell immune responses leading to the secretion of interferon and T cell recruitment. IL-23 induces IL-17, regulates T memory cells, and activates macrophages to maintain chronic autoimmune inflammation. Ustekinumab is a fully human immunoglobulin (Ig)G1 antibody that binds to the p40 subunit of IL-12 and IL-23 (Figure 2). The binding prevents interaction with the IL-12Rβ1 receptor, neutralizing IL-12 and IL-23 mediated cell immune responses.

Tocilizumab. IL-6 acts as a stimulator of B and T cell functions, including promoting the differentiation of B cells into antibody producing plasma cells. When bound to the soluble IL-6 receptor, has been shown to activate chemokine production and up regulate expression of adhesion molecules, leading to recruitment of leukocytes at inflammatory sites. These actions have implicated IL-6 as an important component of inflammatory diseases including RA. High levels of IL-6 have been found in the serum and joints of RA patients. Additionally, IL-6 has been shown to induce proliferation of osteoclasts, which may be a component of the bone degradation seen in RA. Tocilizumab is a humanized, monoclonal antibody that can bind to both membranous and soluble IL-6 receptors (Figure 2). The blockade prevents the interaction of IL-6 and IL-6 receptor, interrupting the actions of IL-6 that contribute to the disease processes in RA.

Efficacy

PHOENIX 1: Ustekinumab in psoriasis patients eligible for systemic treatment. The efficacy of ustekinumab in the treatment of patients with moderate to severe psoriasis was assessed in the “PHOENIX 1” study, a phase 3, double-blind, placebo-controlled, randomized trial (Table 2). Patients eligible for enrollment were at least 18 years of age, had a diagnosis of psoriasis for at least 6 months with at least 10% of the body surface affected, and were candidates for systemic or phototherapy. Exclusion criteria included nonplaque forms of psoriasis, history or symptoms of active tuberculosis, a recent serious systemic or local infection, malignancy, treatment with any agent that specifically targeted IL-12 or IL-23, treatment with a biological or investigational agent received in previous 3 months, treatment with conventional systemic psoriasis therapy or phototherapy received within the previous 4 weeks, or a topical psoriasis treatment received within the previous 2 weeks.

The trial had 3 phases: a placebo-controlled phase between weeks 0-12, a placebo cross-over and active treatment phase from weeks 12-40, and a randomized withdrawal phase between weeks 40-76. Patients were randomized to subcutaneous injections of ustekinumab 45 milligrams (mg; n = 255; mean age 44.8 years, 68.6% male), 90 mg (n = 256; mean age 46.2 years, 67.6% male), or placebo (n = 255; mean age 44.8 years, 71.8% male) at weeks 0, 4, and every 12 weeks thereafter. The primary endpoint was achievement of a 75% improvement in the psoriasis area and severity index (PASI 75) at week 12. Secondary endpoints included the proportion of patients achieving a clear or minimal physician’s global assessment (PGA) score at week 12, and the time to loss of PASI 75 during the withdrawal phase.

<table>
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<td>IV infusion</td>
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<td>✘</td>
<td>✘</td>
<td>✘</td>
<td>✘</td>
<td>✘</td>
<td>✘</td>
</tr>
</tbody>
</table>

aIndications approved by the U.S. Food and Drug Administration as of May 2010.

bAfter failure or intolerance to a TNF antagonist.
The study enrolled 766 patients. Baseline demographic and clinical characteristics were similar between treatment groups. Patients had an average 20-year history of psoriasis, and approximately two-thirds of patients in each group were men. Mean involved body surface area (BSA) at baseline was between 25.2% and 27.7% for all groups. A total of 55.3%, 55.1%, and 55.7% in the ustekinumab 45 mg, 90 mg, and placebo groups, respectively, had tried psoralen plus ultraviolet A (PUVA), methotrexate, acitretin, or cyclosporine in the past. A total of 52.5%, 50.8%, and 50.2% in the 45 mg, 90 mg, and placebo groups, respectively, had tried an autoimmune biologic—etanercept, alefacept, efalizumab, infliximab, or adalimumab—prior to study initiation.

A PASI 75 score was achieved by 67.1%, 66.4%, and 3.1% of patients in the ustekinumab 45 mg, 90 mg, and placebo groups, respectively ($P < 0.001$ for both strengths compared with placebo) at week 12. A PGA score of clear or minimal was achieved by 60.4%, 61.7%, and 3.9% of patients treated with ustekinumab 45 mg, 90 mg, and placebo, respectively ($P < 0.001$ for both strengths compared with placebo), at week 12. Week 28 results demonstrated durable results for ustekinumab with 71.2% and 78.6% of patients treated with 45 mg or 90 mg achieving or maintaining a PASI 75 score. Patients moving from placebo to ustekinumab 45 mg or 90 mg had PASI 75 response rates of 65.9% and 84.9%, respectively, at week 28. The median time to loss of PASI 75 in patients withdrawn from therapy was 15 weeks. Patients sustained on ustekinumab during the withdrawal phase did not lose response.

PHOENIX 2: Ustekinumab in psoriasis patients eligible for systemic treatment. “PHOENIX 2” compared ustekinumab with placebo for the treatment of moderate to severe psoriasis in a study design similar to PHOENIX 1 (Table 2). Patients were at least 18 years of age, had a diagnosis of psoriasis for at

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**TABLE 2** Primary Endpoint Results from Phase 3 Trials of Ustekinumab

<table>
<thead>
<tr>
<th>Drug</th>
<th>PASI 75 Response at Week 12 (%)</th>
<th>$P$ Value Compared with Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PHOENIX 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ustekinumab 45 mg</td>
<td>67.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ustekinumab 90 mg</td>
<td>66.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.1</td>
<td>—</td>
</tr>
<tr>
<td><strong>PHOENIX 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ustekinumab 45 mg</td>
<td>66.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ustekinumab 90 mg</td>
<td>75.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.7</td>
<td>—</td>
</tr>
<tr>
<td><strong>ACCEPT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ustekinumab 45 mg</td>
<td>67.5</td>
<td>0.012</td>
</tr>
<tr>
<td>Ustekinumab 90 mg</td>
<td>73.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Etanercept 50 mg</td>
<td>56.8</td>
<td>—</td>
</tr>
</tbody>
</table>

$mg = \text{milligram}; \text{PASI} 75 = 75\% \text{improvement in the psoriasis area and severity index.}$

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**FIGURE 1** Flowchart of Literature Selection

- **Limits:** English, “human,” “clinical trial,” or “randomized controlled trial”
- **21 articles excluded for not being in English or about humans**
- **36 articles excluded for not being clinical trials or RCTs**
- **8 articles remain**

- **77 articles excluded for not being in English or about humans**
- **124 articles excluded for not being clinical trials or RCTs**
- **16 articles remain**

RA = rheumatoid arthritis; RCT = randomized controlled trial.
least 6 months with at least 10% of the body surface affected, and were candidates for systemic or phototherapy. Exclusion criteria were similar to criteria used in PHOENIX 1.

The trial had 3 phases: a placebo-controlled phase between weeks 0-12, a placebo cross-over and active treatment phase from weeks 12 to 28, and a randomized dose-intensification phase from weeks 28-52. Patients were randomly assigned to subcutaneous ustekinumab 45 mg (n = 409; mean age 45.1 years, 69.2% male), 90 mg (n = 411; mean age 46.6 years, 66.7% male), or placebo (n = 410; mean age 47.0 years, 69.0% male) at weeks 0, 4, and every 12 weeks thereafter. At week 12, patients treated with placebo were re-randomized to either ustekinumab 45 mg or 90 mg every 12 weeks. At week 28, patients achieving a partial response (improvement of at least PASI 50 but less than PASI 75) were re-randomized to ustekinumab dosed every 8 or 12 weeks. The primary endpoint was achievement of a PASI 75 score at week 12. Secondary endpoints included the proportion of patients achieving a clear or minimal PGA score at week 12, and the proportion of patients achieving a PASI 75 score between weeks 40 and 52 during the dose-intensification phase.

The study enrolled 1,230 patients of whom approximately two-thirds in each group were men. Groups were balanced with regard to demographic and baseline characteristics. Average disease duration of psoriasis was approximately 20 years. Involved BSA at baseline was 25.9%, 27.1%, and 26.1% in the ustekinumab 45 mg, 90 mg, and placebo groups, respectively. A total of 54.5%, 54.5%, and 58.8% in the 45 mg, 90 mg, and placebo groups, respectively, had tried PUVA, methotrexate, acitretin, or cyclosporine prior to study initiation. A total of 38.4%, 36.5%, and 38.8% in the 45 mg, 90 mg, and placebo groups, respectively, had tried an autoimmune biologic—etanercept, alefacept, efalizumab, infliximab, or adalimumab—prior to study initiation.
A PASI 75 score was achieved by 66.7%, 75.7%, and 3.7% of patients in the ustekinumab 45 mg, 90 mg, and placebo groups, respectively, at week 12 (P < 0.001 for both ustekinumab regimens compared with placebo). A PGA score of cleared or minimal was achieved by 68%, 73.5%, and 4.9% of patients in the ustekinumab 45 mg, 90 mg, and placebo groups, respectively, at week 12 (P < 0.001 for both ustekinumab regimens compared with placebo). At week 28, the proportions of patients who were partial responders in the ustekinumab 45 mg and 90 mg groups were 22.7% and 15.8%, respectively. Increasing the dosing frequency to every 8 weeks did not increase the number of visits with a PASI 75 response (1.75 visits in 8-week group vs. 1.56 visits in 12-week group, P = 0.468).

Analysis of secondary endpoints in the PHOENIX-2 trial determined the effect of ustekinumab on anxiety and depression scores in patients with psoriasis.27 The analysis used the Hospital Anxiety and Depression Scale (HADS) to assess patients’ mental health in the study. A score of 8 or greater on the HADS scale indicated presence of depression or anxiety, respectively. Baseline, a HADS-Anxiety score of 8 or greater was reported in 38.2%, 41.0%, and 41.6% of patients in the ustekinumab 45 mg, 90 mg, and placebo groups, respectively. A HADS-Depression score of 8 or greater at baseline was reported in 24.7%, 31.1%, and 24.2% of patients in the ustekinumab 45 mg, 90 mg, and placebo groups, respectively. At week 12, the proportion of patients reporting a HADS-Anxiety score of 8 or greater was 25.7%, 27.1%, and 43.0% in the ustekinumab 45 mg, 90 mg, and placebo groups, respectively (P < 0.001 for both ustekinumab groups compared with placebo). At week 12, the proportion of patients reporting a HADS-Depression score of 8 or greater was 12.8%, 12.5%, and 34.4% in the ustekinumab 45 mg, 90 mg, and placebo groups, respectively (P < 0.001 for both ustekinumab groups compared with placebo).27

ACCEPT: Comparative trial of ustekinumab and etanercept. The efficacy of ustekinumab in the treatment of moderate to severe plaque psoriasis was compared with etanercept in a phase 3, investigator-blinded, randomized trial.28 Patients who were at least 18 years of age with a diagnosis of plaque psoriasis for at least 6 months with at least 10% of BSA affected, were candidates for phototherapy or systemic therapy, and had failed to respond to (or were intolerant of) cyclosporine, methotrexate, or PUVA, were eligible to enroll. No previous treatment with ustekinumab or etanercept was allowed. Other exclusion criteria included nonplaque or drug-induced forms of psoriasis, a recent serious infection or a history of chronic or recurrent infectious disease, or a known malignant condition. Before enrollment, patients could not have received conventional systemic therapy or phototherapy within 4 weeks before enrollment; topical psoriasis agents within 2 weeks; investigational drugs within 4 weeks or 5 half-lives, whichever was longer; or biologic agents within 3 months or 5 half-lives, whichever was longer.

Patients were randomized to receive either subcutaneous ustekinumab 45 mg (n = 209) or 90 mg (n = 347) at weeks 0 and 4 or subcutaneous etanercept 50 mg (n = 347) twice weekly through week 12. The primary endpoint was the proportion of patients who achieved a PASI 75 at week 12. The secondary endpoints were the proportion of patients achieving a PGA score of cleared or minimal at week 12 and the proportion of patients achieving a PASI 90 score at week 12. Patients in the etanercept group who did not demonstrate a PASI 75 score at week 12 received ustekinumab 90 mg at weeks 16 and 20. Patients not achieving a PASI 75 score in the ustekinumab group at week 12 got an additional dose of ustekinumab.

The study enrolled 903 patients. Baseline demographic and disease characteristics were similar among treatment groups. Patients were an average age of 45 years and had an average duration of psoriasis of 18.8 years, with a mean involved BSA of 25%. A total of 61.7%, 52.4%, and 57.3% in the ustekinumab 45 mg and 90 mg and etanercept groups, respectively, had tried PUVA, methotrexate, acetretin, or cyclosporine prior to study initiation. A total of 12.8%, 10.4%, and 11.8% in the ustekinumab 45 mg and 90 mg and etanercept groups, respectively, had tried an autoimmune biologic—alefacept, efalizumab, infliximab, or adalimumab—prior to study initiation.

At week 12, a total of 67.5% of patients treated with ustekinumab 45 mg and 73.8% treated with 90 mg achieved a PASI 75 score compared with 56.8% of patients treated with etanercept (P = 0.012 for ustekinumab 45 mg vs. etanercept and P < 0.001 for ustekinumab 90 mg vs. etanercept). A PGA score of cleared or minimal was achieved by 65.1% of patients treated with ustekinumab 45 mg and 70.6% for 90 mg compared with 49.0% of patients treated with etanercept at week 12 (P < 0.001 for both ustekinumab groups vs. placebo). A total of 48.9% of patients not achieving a response in the etanercept group achieved a PASI 75 score when treated with ustekinumab 90 mg, and 23.4% had 90% improvement.

RADIATE: Tocilizumab in RA patients with prior TNF failure. The efficacy of tocilizumab in the treatment of patients with moderate to severe RA with prior TNF failure was assessed in a 24-week, double-blind, randomized, placebo-controlled trial (Table 3).28 Patients eligible for enrollment were aged 18 years or older and had moderate to severe RA and failed to respond or were intolerant to previous treatment with 1 or more TNF antagonists in the previous year. Patients had active RA for 6 months or more and discontinued all prior therapies (except methotrexate) prior to study initiation. Infliximab or adalimumab had to be discontinued 8 weeks prior and etanercept 2
weeks prior to the start of the study. Exclusion criteria included prior treatment with cell-depleting agents (e.g., azathioprine), uncontrolled medical conditions, history of malignancy, other inflammatory diseases or recurrent infection, abnormal liver function, leukopenia, neutropenia, or thrombocytopenia.

Patients were randomized to tocilizumab 8 mg per kilogram (kg), tocilizumab 4 mg per kg, or placebo infusion every 4 weeks. Infusions were administered over 1 hour. All patients were treated with a stable dose of methotrexate (10-25 mg weekly) and folicale. Stable oral corticosteroids (prednisone 10 mg or less or equivalent) and nonsteroidal anti-inflammatory drugs (NSAIDs) were permitted, but other disease-modifying antirheumatic drugs (DMARDs) were not allowed. The primary endpoint was the proportion of patients achieving an American College of Rheumatology criteria 20% improvement in signs or symptoms of RA (ACR 20) at week 24. Secondary endpoints included the proportion of patients achieving an ACR 50 or ACR 70, and patients achieving disease remission defined as a disease activity score of 28 joints (DAS 28) less than 2.6.

The study enrolled 499 patients. Baseline characteristics were similar between groups. Average disease duration prior to the study was 12.6, 11.0, and 11.4 years in the tocilizumab 8 mg per kg, 4 mg per kg, and placebo groups, respectively. A total of 50%, 47%, and 42% of patients in the tocilizumab 8 mg per kg, 4 mg per kg, and placebo groups, respectively, had tried 1 prior TNF agent. Two prior TNFs had been tried in 32%, 41%, and 42%, respectively, and 3 or more TNFs had been tried in 18%, 12%, and 14%, respectively. Approximately 95% of patients discontinued prior TNF therapy due to inadequate efficacy. An ACR 20 at week 24 was achieved by significantly more study participants in the tocilizumab 8 mg per kg (50.0%) and 4 mg per kg (30.4%) groups than the placebo group (10.1%, P<0.001 for both tocilizumab groups compared with placebo). An ACR 50 was achieved by 28.8% and 16.8% of patients in the tocilizumab 8 mg per kg and 4 mg per kg groups, respectively, compared with 3.8% in the placebo group (P<0.001 for both tocilizumab groups compared with placebo). An ACR 70 was achieved by 12.4% and 5.0% of patients in the tocilizumab 8 mg per kg and 4 mg per kg groups, respectively, compared with 1.3% for the placebo group. The ACR 70 response was significant compared with placebo for the tocilizumab 8 mg per kg group (P<0.001) but not the 4 mg per kg group (P=0.1). Disease remission was reported at week 24 in 30.1%, 7.6%, and 1.6% of patients in the tocilizumab 8 mg per kg, 4 mg per kg, and placebo groups, respectively (P=0.001 for 8 mg per kg compared with placebo and P=0.053 for 4 mg per kg compared with placebo).

**OPTION: Tocilizumab in RA patients with prior methotrexate failure.** The OPTION trial was a 24-week, phase 3 double-blind, randomized, placebo-controlled trial (Table 3).29 Patients eligible for enrollment were adults with moderate to severe RA of at least 6 months duration and an inadequate response to methotrexate. Patients had to be treated with methotrexate for at least 12 weeks prior to the study with a stable dose of 10 mg to 25 mg weekly for at least 8 weeks. Patients were excluded if they had other autoimmune disorders, currently active or recurrent infections, or had an inflammatory joint disease other than RA.

Patients were randomized to either tocilizumab 8 mg per

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**Formulary Review of 2 New Biologic Agents: Tocilizumab for Rheumatoid Arthritis and Ustekinumab for Plaque Psoriasis**

**TABLE 3 Primary Endpoint Results from Phase 3 Trials of Tocilizumab**

<table>
<thead>
<tr>
<th>Drug</th>
<th>ACR 20 Response at Week 24 (%)</th>
<th>P Value Compared with Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab 4 mg per kg+MTX (n=163)</td>
<td>30.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tocilizumab 8 mg per kg+MTX (n=175)</td>
<td>50.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo+MTX (n=160)</td>
<td>10.1</td>
<td>—</td>
</tr>
</tbody>
</table>

**OPTION**

<table>
<thead>
<tr>
<th>Drug</th>
<th>ACR 20 Response at Week 24 (%)</th>
<th>P Value Compared with Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab 4 mg per kg+MTX (n=214)</td>
<td>48.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tocilizumab 8 mg per kg+MTX (n=205)</td>
<td>59.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo+MTX (n=204)</td>
<td>26.0</td>
<td>—</td>
</tr>
</tbody>
</table>

**TOWARD**

<table>
<thead>
<tr>
<th>Drug</th>
<th>ACR 20 Response at Week 24 (%)</th>
<th>P Value Compared with Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab 8 mg per kg+DMARD (n=802)</td>
<td>60.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo+DMARD (n=414)</td>
<td>24.5</td>
<td>—</td>
</tr>
</tbody>
</table>

**SAMURAI**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean TSS Change at Weeks 28 and 52</th>
<th>P Value Compared with Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab 8 mg per kg (n=157)</td>
<td>1.9 (95% CI=1.2-2.6) at week 28</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>2.3 (95% CI=1.5-3.2) at week 52</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Placebo (n=145)</td>
<td>4.5 (95% CI=3.1-6.0) at week 28</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>6.1 (95% CI=4.2-8.0) at week 52</td>
<td>—</td>
</tr>
</tbody>
</table>

**AMBITION**

<table>
<thead>
<tr>
<th>Drug</th>
<th>ACR 20 Response at Week 24 (%)</th>
<th>P Value Compared with MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab 8 mg per kg (n=265)</td>
<td>69.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MTX (n=259)</td>
<td>52.5</td>
<td>—</td>
</tr>
</tbody>
</table>

ACR 20 = American College of Rheumatology criteria 20% improvement in signs or symptoms of rheumatoid arthritis.

CI = confidence interval; DMARD = disease-modifying antirheumatic drug; kg = kilogram; mg = milligram; MTX = methotrexate; TSS = total Sharp score.
kg, 4 mg per kg, or placebo infusion once every 4 weeks as a 1-hour infusion for 24 weeks. All patients continued their baseline stable methotrexate regimen (10-25 mg weekly). Oral corticosteroids (prednisone 10 mg or less or equivalent) and NSAIDs were permitted if the patient had received a stable dose for at least 6 weeks prior to the study. DMARDs (other than methotrexate) or biologics were discontinued prior to the beginning of the study. The primary endpoint was achievement of an ACR 20 score at week 24. Secondary endpoints included achievement of an ACR 50 score or ACR 70 score and achievement of disease remission (DAS 28 < 2.6).

The study enrolled 622 patients with a mean age of 51 years (71% female). Mean disease duration was 7.5 years. Concomitant use of corticosteroids or NSAIDs was similar between groups. Mean methotrexate dose was 14.5, 14.7, and 14.8 mg weekly in the tocilizumab 8 mg per kg, 4 mg per kg, and placebo groups, respectively. An ACR 20 score at week 24 was achieved by 59%, 48%, and 26% in the tocilizumab 8 mg per kg, 4 mg per kg, and placebo groups, respectively (P < 0.001 for both tocilizumab groups compared with placebo). An ACR 50 score at week 24 was achieved by 44%, 31%, and 11% in the tocilizumab 8 mg per kg, 4 mg per kg, and placebo groups, respectively (P < 0.001 for both tocilizumab groups compared with placebo). An ACR 70 score at week 24 was achieved by 22%, 12%, and 2% of patients in the tocilizumab 8 mg per kg, 4 mg per kg, and placebo groups, respectively (P < 0.001 for both groups compared with placebo). Disease remission was reached by 27%, 13%, and 0.8% of patients in the tocilizumab 8 mg per kg, 4 mg per kg, and placebo groups, respectively (P < 0.05 for both groups compared with placebo).

Treatment in RA patients, comparison of methotrexate only, methotrexate plus tocilizumab, and tocilizumab only. A European trial reported by Maini et al. (2006) enrolled 350 RA patients for a 24-week, double-blind, placebo-controlled, randomized trial. Patients with active RA despite previous treatment with methotrexate and on a stable dose for at least 4 weeks prior to randomization were enrolled. Patients were randomized to 1 of 7 groups: tocilizumab 2 mg per kg, 4 mg per kg, or 8 mg per kg plus placebo capsule; tocilizumab 2 mg per kg, 4 mg per kg, or 8 mg per kg plus methotrexate; or placebo infusion plus methotrexate. The primary endpoint was an ACR 20 score at week 16. Secondary endpoints included ACR 50 and ACR 70 scores at week 16.

An ACR 20 score at week 16 was achieved by 31%, 61%, and 63% of patients in the tocilizumab 2 mg per kg, 4 mg per kg, and 8 mg per kg monotherapy groups, respectively, compared with 41% for methotrexate monotherapy (P < 0.05 for 4 mg per kg and 8 mg per kg compared with methotrexate, P > 0.05 [exact P value not reported] for 2 mg per kg compared with methotrexate). An ACR 20 score at week 16 was achieved by 64%, 63%, and 74% of patients in the tocilizumab 2 mg per kg, 4 mg per kg, and 8 mg per kg + methotrexate group compared with 41% in the methotrexate monotherapy group (P < 0.05 for all comparisons to methotrexate monotherapy). An ACR 50 score was achieved by 53% of patients in the tocilizumab 8 mg per kg + methotrexate group compared with 29% in the methotrexate monotherapy group (P < 0.05). An ACR 70 was achieved by 37% of patients in the tocilizumab 8 mg per kg + methotrexate group compared with 16% in the methotrexate monotherapy group (P < 0.05). Rates of achievement of ACR 50 and ACR 70 scores did not differ for any of the other tocilizumab groups compared with methotrexate monotherapy.

TOWARD: Treatment in RA patients in combination with DMARDs (except TNFs). The TOWARD trial was a 24-week, phase 3, double-blind, randomized, placebo-controlled trial (Table 3). Patients eligible for enrollment were aged 18 years or older and had moderate to severe RA for at least 6 months and were currently being treated with a conventional DMARD at a stable dose for 8 weeks or more prior to study entry. Permitted conventional DMARDs included methotrexate, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide. Exclusion criteria included previous treatment and failure with a TNF antagonist or prior treatment with a cell-depleting agent.

Patients were randomized 2:1 to either tocilizumab 8 mg per kg or placebo once every 4 weeks. Tocilizumab and placebo infusions were administered over 1 hour. All patients continued their conventional DMARD therapy at a stable dose. Oral corticosteroids (<10 mg prednisone or equivalent) and NSAIDs were permitted if the patient had received a stable dose for at least 6 weeks prior to the study. The primary endpoint was achievement of an ACR 20 score at week 24. Secondary endpoints included achievement of an ACR 50 score or ACR 70 score and achievement of disease remission (DAS 28 < 2.6).

The study enrolled 1,220 patients with a mean age of 53.5 years (82.5% female). Mean disease duration was 9.8 years. One DMARD was used in 77% and 75% in the tocilizumab 8 mg per kg and placebo groups, respectively. Two or more DMARDs were used by 22% and 24% in patients in the tocilizumab 8 mg per kg and placebo groups, respectively. The most commonly used DMARD was methotrexate (mean dose 15 mg weekly) in 75.8% and 73.9% of patients in the tocilizumab 8 mg per kg and placebo groups, respectively. An ACR 20 score at week 24 was achieved by 60.8% and 24.5% in the tocilizumab 8 mg per kg and placebo groups, respectively (P < 0.001). An ACR 50 score at week 24 was achieved by 37.6% and 9.0% in the tocilizumab 2 mg per kg, 4 mg per kg, or placebo groups, respectively (P < 0.001). An ACR 70 score at week 24 was achieved by 27%, 13%, and 0.8% of patients in the tocilizumab 8 mg per kg, 4 mg per kg, and placebo groups, respectively (P < 0.05).
SAMURAI: Tocilizumab compared with DMARD in joint damage progression. The efficacy of tocilizumab in the inhibition of progression of structural joint damage in RA was assessed in a 52-week, open-label, x-ray reader blinded, controlled trial.32 Adult patients aged 20 years or older with active RA and a disease duration between 6 months and 5 years were enrolled. All patients had an inadequate efficacy response to at least 1 DMARD or immunosuppressant. Exclusion criteria included medical history of a serious allergic reaction, significant underlying disease process other than RA, or active infection.

Patients were randomized to receive either tocilizumab 8 mg per kg monotherapy once every 4 weeks or conventional DMARD. DMARDs or immunosuppressants were discontinued in the tocilizumab group at the beginning of the study. Patients in the DMARD group were treated with a DMARD (except TNFs) or immunosuppressant at the discretion of the treating physician. Oral corticosteroids (prednisone 10 mg or less or equivalent) were permitted if the patient had received a stable dose for at least 2 weeks prior to the study. Oral NSAIDs were allowed during the trial. The primary endpoint was the change in the mean modified total Sharp score (TSS) at weeks 28 and 52.

The study enrolled 306 patients (mean age 53 years) with a mean duration of disease of 2.3 years. Demographic and baseline characteristics did not differ between groups. A total of 37%, 30%, and 22% of patients in the DMARD group received methotrexate in combination with DMARDs, methotrexate monotherapy, and DMARDs other than methotrexate, respectively. At baseline, the mean (standard deviation) TSS was 30.6 (42.0) and 28.3 (43.9) in the tocilizumab and DMARD groups, respectively. Mean change in the TSS at week 28 was 1.9 (95% CI = 1.2-2.6) and 4.5 (95% CI = 3.1-6.0) in the tocilizumab and DMARD groups, respectively (P < 0.05). Mean change in the TSS at week 52 was 2.3 (95% CI = 1.5-3.2) and 6.1 (95% CI = 4.2-8.0) in the tocilizumab and DMARD groups, respectively (P < 0.01). These data demonstrate that tocilizumab significantly inhibited the progression of structural joint damage compared with conventional DMARD therapy.

AMBITION: Tocilizumab monotherapy compared with methotrexate monotherapy. The AMBITION trial was a 24-week, phase 3, double-blind, randomized, placebo-controlled trial.33 Patients eligible for enrollment were aged 18 years or older and had moderate to severe RA for at least 3 months. Exclusion criteria included treatment with methotrexate in the 6 months prior to trial initiation or any discontinuation of prior methotrexate and/or TNF antagonist due to intolerance or lack of efficacy.

Patients were randomized 1:1:1 to either tocilizumab 8 mg per kg every 4 weeks, methotrexate 7.5 mg initially with titration to 20 mg weekly by week 8, or placebo for 8 weeks and then tocilizumab 8 mg per kg every 4 weeks. Tocilizumab and placebo infusions were administered over 1 hour. Oral corticosteroids (prednisone 10 mg or less or equivalent) and NSAIDs were permitted if the patient had received a stable dose for at least 6 weeks prior to the study. The primary endpoint was achievement of an ACR 20 score at week 24. Secondary endpoints included achievement of an ACR 50 score or ACR 70 score and achievement of disease remission (DAS 28 < 2.6). The primary efficacy analysis was a noninferiority comparison of tocilizumab and methotrexate using the per protocol population. If noninferiority of tocilizumab was met, then superiority was assessed in the intention-to-treat (ITT) group.

The study enrolled 673 patients with a mean age of approximately 50 years (81% female). Mean disease duration was approximately 6.3 years. The majority of patients (approximately 66% in each group) were methotrexate naive. The mean number of previous DMARDs/TNFs was 0.5, and 40% of patients had received prior oral steroids. An ACR 20 at week 24 was achieved by 69.9% and 52.5% in the tocilizumab 8 mg per kg and methotrexate groups, respectively (weighted difference 0.19, 95% CI = 0.34-0.52, P < 0.001). An ACR 50 at week 24 was achieved by 44.1% and 33.5% in the tocilizumab 8 mg per kg and methotrexate groups, respectively (weighted difference 0.12, 95% CI = 0.04-0.20, P = 0.002). An ACR 70 score at week 24 was achieved by 28.0% and 15.1% of patients in the tocilizumab 8 mg per kg and methotrexate groups, respectively (weighted difference 0.14, 95% CI = 0.07-0.22, P < 0.001).

Safety

Ustekinumab. Infection was the most common adverse event in patients treated with ustekinumab in clinical trials (Table 4). Infections were reported in 73.3% and 71.9% of patients in the ustekinumab 45 mg and 90 mg groups, respectively, through 100 weeks in the PHOENIX-2 trial.34 During the double-blind phase of PHOENIX-2 (12 weeks) infections occurred in 21.5%, 22.4%, and 20.0% of patients in the ustekinumab 45 mg, 90 mg, and placebo groups, respectively.34 Nasopharyngitis and upper respiratory tract infection were the most commonly reported events.34 During the double-blind portion of the phase 3 trials, the incidence of infection was similar between ustekinumab and placebo. The incidence of serious infections during the double-blind portion of the phase 3 trials was 0.3% and 0.4% in the ustekinumab and placebo groups, respectively.34

Patients treated with ustekinumab may be at an increased risk for malignancy. Animal models have shown that blockade of the IL-12/23 subunit increases the risk of malignancy.34,35 A total of 30 malignancies were reported in 26 patients treated with ustekinumab over 100 weeks of the PHOENIX-2 trial.34
Twelve patients were diagnosed with solid tumors that included prostate, bladder, pancreatic, breast, colon, and endometrial cancers. An evaluation of ustekinumab and cancer risk is severely limited by the lack of long-term data in large populations. Safety data beyond 2 years are not currently available.

The ACCEPT trial provides data on the comparative safety between ustekinumab and etanercept; however, this trial lasted only 12 weeks. Adverse events of any kind were experienced by 70.0%, 66.0%, and 69.2% of patients in the etanercept, ustekinumab 45 mg, and ustekinumab 90 mg groups, respectively, by week 12 (P values for comparisons were not reported). Discontinuation due to adverse events occurred in 2.3%, 1.9%, and 1.2% of patients in the etanercept, ustekinumab 45 mg, and ustekinumab 90 mg groups, respectively. Injection site reactions, predominantly mild, occurred in 24.8% of patients treated with etanercept compared with etanercept with 4.3% and 3.7% of patients in the ustekinumab 45 mg and 90 mg groups, respectively. Infection rates were similar between groups, occurring in 29.1%, 30.6%, and 29.7% of patients in the etanercept, ustekinumab 45 mg, and ustekinumab 90 mg groups, respectively. No comparative data beyond 12 weeks have been reported.

**Tocilizumab.** Tocilizumab has been shown to increase the risk of neutropenia. In the 24-week RADIATE trial, transient neutropenia (neutrophils <2,000 cells per cubic millimeter [mm\(^3\)]) occurred in 28.0%, 20.3%, and <1.0% of patients in the tocilizumab 8 mg per kg, 4 mg per kg, and placebo groups, respectively (Table 4). Four patients in the tocilizumab 8 mg per kg (n=175) and 1 in the 4 mg per kg (n=163) groups experienced an absolute neutrophil count less than 500 per mm\(^3\) and were withdrawn from the study. The 24-week OPTION trial found higher rates of grade 1 (>1,500 cells per mm\(^3\); 18.8% vs. 4.3% placebo), grade 2 (1,000–1,500 cells per mm\(^3\); 11.6% vs. 0.5% placebo), and grade 3 (500–1,000 cells per mm\(^3\); 3.7% vs. 0.0% placebo) neutropenia in the tocilizumab groups compared with placebo. The long-term extension trial involving 5 years of follow-up (n=143) documented grade 2 neutropenia in 17 (11.9%) patients and grade 3 in 9 (6.3%) patients. No patients discontinued tocilizumab in the long-term extension due to neutropenia. Monitoring of neutrophil counts is recommended every 4–8 weeks, and patients experiencing a neutrophil count less than 500 cells per mm\(^3\) should discontinue tocilizumab. A connection between infections and tocilizumab-associated neutropenia has not been proven in clinical trials; however, the risk of infection in neutropenic patients has been well documented in other disease states (e.g., cancer).

Infection was the most common adverse event associated with tocilizumab in clinical trials. According to an FDA analysis, combination therapy of tocilizumab 8 mg per kg or 4 mg per kg and a DMARD had infection rates of 133 events and 127 events per 100 patient years, respectively, compared with 112 events per 100 patient years in the placebo plus DMARD groups. Serious infections occurred more commonly in the tocilizumab monotherapy cohort (3.6 events per 100 patient years) compared with methotrexate monotherapy (1.5 events per 100 patient years, P values not reported). A 5-year extension trial involving 143 patients treated with tocilizumab monotherapy (median duration of treatment 66.7 months)
Managed Care Considerations

Ustekinumab and tocilizumab are new options in the treatment of autoimmune inflammatory disease with unique mechanisms of action. The clinical trial data for ustekinumab include the first results from a phase 3 comparison to an active autoimmune agent, showing superiority to etanercept for the treatment of psoriasis. Tocilizumab has demonstrated efficacy in patients with an inadequate response to 1 or more TNF antagonists. Comparative efficacy trials and studies in patients with multiple prior failures provide useful data to clinicians and managed care decision makers. However, questions remain regarding (a) how both agents will be used in clinical practice, (b) short- and long-term safety, and (c) the additional value brought to patients and payers.

Long-term safety data are sparse for both ustekinumab and tocilizumab. There are 5-year data available for tocilizumab but only for 143 patients. Safety data beyond 2 years of use of ustekinumab are unknown. Biologics, like many drugs, require years of extensive use before the full adverse event profile is understood. Infliximab was approved in 1998 with few warnings and precautions including hypersensitivity, autoimmunity, infection, and possible malignancy. No boxed warnings were present at approval. The prescribing information approved in 2009 for infliximab now includes warnings for hepatotoxicity, avoidance in patients with heart failure, reactivation of hepatitis B, hematologic toxicity, and neurologic events. Additionally, infliximab has black-box warnings for serious infections. This rate is higher than the 3.6 events calculated by the FDA using 6-month clinical trial data. Combination tocilizumab 8 mg per kg or 4 mg per kg plus DMARD had serious infection rates of 5.3 and 4.4 events per 100 patient years, respectively, compared with 3.9 events per 100 years in the placebo plus DMARD group. The most common serious infections were pneumonia, urinary tract infection, and cellulitis. Fatal infections were rare (0.13 events per 100 patient years across all groups). Patients should be closely monitored for signs and symptoms of infection prior to and during treatment with tocilizumab.

Malignancy is a common concern with biologics for autoimmune disease. An FDA analysis of the 6-month trials of tocilizumab reported 15 malignancies in the tocilizumab group and 8 in the control group. Exposure-adjusted incidence of malignancy was similar in the tocilizumab groups (1.32 events per 100 patient years) and in the placebo plus DMARD group (1.37 events per 100 patient years). However, the risk of malignancy is complicated by the limited long-term data for tocilizumab. A 52-week study reported 3 malignancies in the tocilizumab group (2 breast cancer and 1 colon cancer) compared with no malignancies in the DMARD group. The 5-year extension trial found 4 malignancies (breast, bladder, colon, and intra ductal cancers) in patients treated with tocilizumab for a rate of 0.7 events per 100 patient years.
increased risk of serious infections and for lymphoma and other malignancies in children and adolescents.\(^3\) Tocilizumab and ustekinumab have unique mechanisms of action, and the effects of widespread, long-term use are unknown at this time. Tocilizumab’s effects on neutrophils, platelets, and lipid levels are unique and concerning amongst the autoimmune biologics, and the long-term implications are unknown. The FDA, in a review of ustekinumab, stated that patients had not been followed for a sufficient period of time, and that the risk of malignancy should be communicated to prescribers.\(^3\) Extended studies are needed to better define and understand the safety risks of both drugs.

The ACCEPT trial introduces phase 3, comparative data to the autoimmune biologics for the first time and presents a challenge for health care professionals on defining the place in therapy of ustekinumab.\(^2\) Clinicians and patients may defend ustekinumab as a first-line option due to superior efficacy to etanercept and comparable short-term safety. However, the data are limited to 1 single-blind (investigator) trial in 903 patients.\(^3\) The TNF antagonists have the advantage in years of experience and a well-defined safety and efficacy profile. Clinicians may continue using the established TNF antagonists first, reserving ustekinumab for patients failing these therapies. Regardless, the phase 3 comparative trial data provide valuable information to decision makers trying to evaluate the clinical advantages between autoimmune biologics. For tocilizumab, the RADIATE trial and FDA indication for tocilizumab place this treatment firmly after TNF antagonist failure.\(^17,28\)

Autoimmune biologics address different components of the autoinflammatory disease process and frequently gain FDA indications in multiple conditions. Ustekinumab 63 mg at weeks 0 and 4 was compared with placebo in the treatment of psoriatic arthritis (n = 146). At week 12, an ACR 20 score was achieved by 42% and 14% of patients in the ustekinumab

### TABLE 5 Cost of Autoimmune Biologics Available in 2010

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maintenance Dosing in RA</th>
<th>Cost(^a) in RA</th>
<th>Maintenance Dosing in Psoriasis</th>
<th>Cost(^a) in Psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira)</td>
<td>40 mg every other week</td>
<td>$959.19 per 40 mg injection or $1,918 monthly</td>
<td>40 mg every other week</td>
<td>$959.19 per 40 mg injection or $1,918 monthly</td>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>50 mg weekly</td>
<td>$498.71 per 50 mg injection or $1,995 monthly</td>
<td>50 mg weekly</td>
<td>$498.71 per 50 mg injection or $1,995 monthly</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>3-10 mg per kg every 8 weeks, maximum dose 10 mg per kg every 4 weeks</td>
<td>Cost for a 70 kg person ranges from $2,367 every 8 weeks ($1,184 monthly) to $5,523 every 4 weeks(^b)</td>
<td>5 mg per kg every 8 weeks</td>
<td>Cost for a 70 kg person is $3,156 every 8 weeks ($1,578 monthly)(^b)</td>
</tr>
<tr>
<td>Certolizumab (Cimzia)</td>
<td>200 mg every other week</td>
<td>$1,841 per 200 mg kit (2 injections; 1-month supply)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Alefacept (Amevive)</td>
<td>NA</td>
<td>15 mg weekly for 12 weeks(^c)</td>
<td>$1,190 per 15 mg injection or $4,760 monthly for 3 months</td>
<td></td>
</tr>
<tr>
<td>Anakinra (Kineret)</td>
<td>100 mg daily</td>
<td>$92.24 per 100 mg injection or $2,767 monthly</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Abatacept (Orencia)</td>
<td>500-1,000 mg every 4 weeks</td>
<td>$609.24 per 250 mg vial (cost per month ranges from $1,218 to $2,437)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>2 X 1,000 mg infusions every 24 weeks</td>
<td>$3,404.50 per 500 mg vial or $13,620 per infusion or $2,270 monthly(^d)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Golimumab (Simponi)</td>
<td>50 mg every 4 weeks</td>
<td>$1,982.62 per 50 mg injections monthly</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ustekinumab (Stelara)</td>
<td>NA</td>
<td>45 or 90 mg every 12 weeks(^d)</td>
<td>$5,595.60 per 45 mg or 90 mg injection or $1,865 monthly(^e)</td>
<td></td>
</tr>
<tr>
<td>Tocilizumab (Actemra)</td>
<td>4 or 8 mg per kg every 4 weeks</td>
<td>Cost for a 70 kg person ranges from $1,114 to $2,229 per month(^f)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

\(^a\)For the autoimmune biologics available in the U.S. market as of May 2010. Cost is derived from the AWP in April 2010\(^5\) and the maintenance dosing regimen shown in the table. The monthly cost estimates assume that a 4-week period is 1 month, and actual cost will also vary depending on discounts.

\(^b\)Cost approximation assumes an AWP of $789 per 100 mg vial and wasting of remaining vial after use.

\(^c\)Regimen may be repeated for 1 more 12-week course at least 12 weeks after the initial course.

\(^d\)U.S. Food and Drug Administration dosing is 45 mg for patients up to 100 kg body weight and 90 mg for patients over 100 kg body weight.

\(^e\)Ustekinumab is dosed at weeks 0 and 4 and then every 12 weeks thereafter. AWP cost for first month of therapy (doses 0 and 4 weeks) would be $11,192, no cost in month 2, and $5,596 in month 3 and every 12 weeks thereafter. Annual cost in the first year will be based on 6 doses and will therefore be higher than in subsequent years at approximately 4 doses per year.

\(^f\)The tocilizumab starting dose is 4 mg per kg every 4 weeks, “followed by an increase to 8 mg per kg based on clinical response” according to the product label. Actual cost depends on body weight and will vary from $1,114 at 4 mg per kg or $2,229 at 8 mg per kg for a 70 kg person. Cost is estimated using an AWP of $79.60 per milliliter for the 20 mg per milliliter vial. Actual costs may be higher as vials are only available in 80 mg, 200 mg, and 400 mg strengths and wastage may occur.

AWP = average wholesale price; kg = kilogram; mg = milligram; NA = not applicable; RA = rheumatoid arthritis.
and placebo groups, respectively (P<0.001).39 Tocilizumab was compared with placebo in a double-blind, withdrawal study in juvenile idiopathic arthritis (JIA) (n = 56).40 At the end of the withdrawal period, 80% and 17% of patients treated with tocilizumab 8 mg per kg and placebo, respectively, maintained an ACR 20.40 According to clinicaltrials.gov, ustekinumab is being studied in psoriatic arthritis and Crohn’s disease, and tocilizumab has trials ongoing or recruiting in JIA and RA.41,42

Clinicians and managed care decision makers should be prepared for additional data and expanded uses of both agents.

Biologic autoimmune agents used to treat RA and psoriasis are expensive, ranging from $25,000-$50,000 per year of therapy. According to Prime Therapeutics’ commercial book of business prescription medication trend data on arthritis and skin agents, which encompass the autoimmune biologics, the annual growth rate in per member per month (PMPM) cost for this category was 21.1% from 2007 Q1 through 2009 Q4 (Figure 3).43 Growth was driven by an average annual utilization growth rate of 9.2% and an average annual price inflation rate of 9.0%.43

Available information on the price of ustekinumab and tocilizumab indicate comparable pricing between these therapies and existing autoimmune biologics (Table 5). However, administration fees, monitoring, and dose changes make an overall cost comparison difficult. Ustekinumab has higher cost at the initiation of therapy because doses are administered at weeks 0 and 4, for a combined average wholesale price (AWP) drug cost at the current (2010) price of $11,912 in the first 30 days, or $16,788 at 16 weeks. The first-year ustekinumab AWP cost is $33,576 for 6 doses, but the cost in subsequent years with dosing every 12 weeks or 4 times per year would be approximately $22,384. The cost of tocilizumab depends on body weight and is dosed consistently every 4 weeks. Tocilizumab AWP cost for a 70 kg person is $1,114 at the dose of 4 mg per kg or $2,229 at 8 mg per kg or an annual cost that ranges from $13,368 to $26,748 if dosed 12 times per year. Managed care decision makers are challenged to find a balance in providing access to new autoimmune biologics for those who need them while encouraging the preferred use of proven cost-effective agents with long-term safety records.

Utilization management programs requiring trial and failure of conventional agents prior to the use of autoimmune biologics is one strategy. A conventional DMARD-first strategy is supported by an analysis by Finckh et al. (2009) showing that conventional DMARD treatment in very early RA is cost effective.44 The analysis also found that autoimmune biologics are not cost effective as first-line therapy and should be reserved for patients failing conventional DMARDs.44 Selecting preferred autoimmune biologics that cover the majority of indications and requiring trial and failure prior to other biologics is another option. Price variability between vendors should be minimized by using a limited distribution channel and restricting dispensing of autoimmune biologics to the specified specialty pharmacy. Health plans may also elect to place autoimmune biologics in a specialty tier with additional cost sharing for the member. However, our research reported previously suggests that patient copayments greater than $100 per month for TNF blockers were associated with prescription abandonment.45

Conclusions

Ustekinumab and tocilizumab are the first biologics to inhibit IL-12/23 and IL-6, respectively. The publication of a comparative trial and treatment in patients failing multiple TNF antagonists would better define the value introduced by ustekinumab and tocilizumab. Long-term safety data are needed to understand how different mechanisms of action modify the safety profile compared with the TNF agents. Additional studies will better define the safety risks and establish the place in therapy for these agents. Cost continues to be a problem for the class of biologicals. Managed care decision makers should use all available tools including utilization management programs, benefit design, and restricted distribution networks to provide the most cost-effective pharmacy benefit management for patients and drug plan sponsors.

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There was no external funding for this manuscript. The authors are employees of Prime Therapeutics, a pharmacy benefits management company whose ownership includes health plans. This manuscript was written primarily from information that was prepared for and presented to a pharmacy and therapeutics committee. Schafer was primarily responsible for the concept and design with assistance of the other 2 authors. Schafer collected the data with assistance from Kjesbo, and Schafer interpreted the data with the assistance of the other 2 authors. Schafer wrote the manuscript with the assistance of the other 2 authors, and Schafer and Gleason revised the manuscript.
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Formulary Review of 2 New Biologic Agents: Tocilizumab for Rheumatoid Arthritis and Ustekinumab for Plaque Psoriasis


43. Prime Therapeutics internal data. Data on file. Costs are reported as total paid per member per month including all actual paid costs (ingredient cost, dispensing, and taxes) by the insurance plan and the member.


A n unusually rancorous debate that was recently
described by the president of the American Heart
Association as “a statistical tug-of-war” has raised more
questions than answers about the risks and benefits of statins
in primary prevention.1,2 Spending money to save money
seemed like a reasonable strategy in lowering serum lipids in
primary prevention of adverse cardiovascular outcomes, par-
ticularly when pravastatin and simvastatin became available by
generic name in April and June 2006, respectively, soon there-
after permitting the treatment of several patients for the same
drug cost as treating 1 patient with either brand pravastatin
(Pravachol) or brand simvastatin (Zocor).3 Nevertheless, it has
long been recognized that the small effect sizes associated with
avoidance of adverse cardiovascular outcomes make the use of
statins expensive even in secondary prevention, up to $1.1 mil-
lion in drug cost in 2004 dollars to prevent 1 nonfatal stroke.4
In an assessment of the cost-effectiveness of primary preven-
tion, Pletcher et al. (2009) used Markov modeling to estimate
the economic and clinical effects of bringing all adults in the
United States into compliance with Adult Treatment Panel III
(ATP III) guidelines, finding that 11.1 million adults without
coronary heart disease (CHD) would undergo newly initiated
(9.7 million) or intensified (1.4 million) statin treatment.5 The
net cost, after accounting for medical cost offsets due to avoided
cardiovascular events (20,000 myocardial infarctions [MIs]
and 10,000 cardiovascular deaths annually), would be $3.6
billion per year, or $42,000 per quality-adjusted life year over a
30-year time horizon. Although the current (July 2010) market
price of generic simvastatin is approximately 60% lower than
the $2.11 per tablet assumed in the model’s base-case analysis,6
and discounts off consumer cash price are commonly taken by
health plans,7 Pletcher et al. note that treating all patients with
low-density lipoprotein cholesterol (LDL-C) exceeding 130
milligrams per deciliter (mg per dL) would yield net cost sav-
ings only if statins cost less than $0.10 per pill.5

The investment strategy for the use of statins in primary
prevention dimmed further with publication of a meta-analysis
by Ray et al. in June 2010.8 The combined results of 11 ran-
domized controlled trials (RCTs) involving 65,229 persons
with intermediate to high risk of a cardiovascular outcome but
without cardiovascular disease at baseline showed that statins
were not associated with reduction in the risk of all-cause
mortality over 244,000 person-years of follow-up. There were
1,447 all-cause deaths among 32,606 patients who received
placebo (4.4%) versus 1,346 deaths among 32,623 patients who
received statins (4.1%, risk ratio = 0.91, 95% confidence interval
[CI] = 0.83-1.01). Across the 11 studies, the mortality rate for
placebo ranged from 3.6 to 26.0 per 1,000 person-years versus
a range from 2.4 to 27.2 per 1,000 person-years for statins, and
participant age at baseline accounted for an estimated 66% of
the variation in mortality rates. There was lack of significant
effect on mortality despite evidence of LDL-C reduction; dur-
ing a mean of 3.7 years follow-up, the mean LDL-C levels for
placebo-treated and statin-treated patients were 134 mg per
dl and 94 mg per dl, respectively. The results of this meta-
analysis were bolstered by the absence of evidence of statistical
heterogeneity among the 11 RCTs despite heterogeneity in the
demographic and clinical characteristics of the study samples.
The research by Ray et al. is also compelling because it is the
first meta-analysis to exclude entirely the effect of statins in
patients with known CHD. A previous meta-analysis of 10
RCTs in primary prevention with statins performed by Brugts
et al. (2009) had found modest effects on all-cause mortality
over an average 4.1 years of follow-up (rates of 5.1% and 5.7%
for statin- and placebo-treated patients, respectively, odds
ratio [OR] = 0.88, 95% CI = 0.81-0.96), but that meta-analysis
included 4,445 participants (6.3%) with a prior history of car-
diovascular disease.9

With the circumspect work of Ray et al., we now have
additional confidence in examining the value for money in
primary prevention of cardiovascular events with statins. If
the 0.3% absolute difference in the mortality rate for statin
therapy (4.1%, weighted mean of 10.7 per 1,000 person-years)
versus placebo (4.4%, weighted mean of 11.4 per 1,000 per-
son years) was statistically significant, which it was not, the
effect of statin treatment was an estimated 7 fewer deaths per
10,000 person-years of treatment.8 At current (July 2010) real-
world discounted drug prices,7 preventing 1 all-cause death in
primary prevention would require about $103,000 of generic
simvastatin ($72 per year times 10,000 patient-years to prevent
7 deaths), $137,000 of generic pravastatin, or $2 million of
rosuvastatin (Crestor). Or, one can use the results from Brugts
et al. to calculate the direct rosuvastatin drug cost to prevent
1 all-cause death, approximately $975,000 (number needed to

Editorial

Tough Questions About the Value of Statin Therapy for
Primary Prevention: Did JUPITER Miss the Moon?

Frederic R. Curtiss, PhD, RPh, CEBS, and Kathleen A. Fairman, MA
Tough Questions About the Value of Statin Therapy for Primary Prevention: Did JUPITER Miss the Moon?

Lack of efficacy is not the only concern with statin therapy for primary prevention of cardiovascular events. Earlier this year, Hippisley-Cox and Coupland reported that statin use was associated with increased risk of cataracts, kidney failure, muscle pain, and “moderate or serious” liver dysfunction.10 This observational study involved 2,004,692 patients in 368 general medical practices in England and Wales of whom 225,922 (10.7%) were new users of statins. Statin use was associated with decreased risk of esophageal cancer but with no apparent unintended benefit (decreased risk) for other cancers. The association of statin therapy with muscle pain was examined last year in a narrative review by Joy and Hegele (2009), who reported that the incidence of myopathy is only approximately 1.5%-5.0% in RCTs but occurs in up to 10% of statin users in observational analyses.11 Interesting for the question of risk versus benefit in primary prevention, a June 2010 market surveillance analysis by Cham et al. found that of 354 patient reports of muscle-related adverse effects with statin therapy, 300 were determined by the study investigators to be probably or definitely drug-attributable using the Naranjo adverse drug reaction probability scale.12 Within this group, investigators found that “most” patients “were in categories for which available [RCT] evidence shows no trend to all-cause mortality benefit with statin therapy.”

In addition to the well-recognized risk of statin-induced myopathy, Sattar et al. (2010) found that statin use was associated with a 9% increase in the risk of developing diabetes (OR = 1.09, 95% CI = 1.02-1.17).11 This study applied meta-analysis to 13 RCTs involving 91,140 patients of whom 4.7% (n = 4,278, including 2,226 statin-treated and 2,052 placebo-treated patients) developed diabetes over an average of 4 years of follow-up; the number needed to harm (NNH) was 255 patients on statin therapy for 4 years to produce 1 additional case of diabetes.

JUPITER Misses the Moon?
The results of the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) clinical trial were first published online on November 9, 2008, apparently opening the door to the use of statins in persons without elevated LDL-C but with elevated high-sensitivity C-reactive protein (hs-CRP) levels.14 Hypothesizing that rosuvastatin would demonstrate cardiovascular benefits in patients who “are at high vascular risk because of an enhanced inflammatory response” despite normal LDL-C levels,15 the JUPITER investigators randomized 17,802 “apparently healthy” participants with LDL-C less than 130 mg per dL (median 108 mg per dL) and hs-CRP greater than 2.0 mg per liter (median 4.2 mg per liter) to treatment with rosuvastatin 20 mg daily or placebo. Over a median of 1.9 years of follow-up, the reported rates of the primary study endpoint (combined outcome of “[MI], stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes”) per 100 person-years of follow-up were 0.77 for patients treated with rosuvastatin versus 1.36 for the placebo group (hazard ratio [HR] = 0.56, 95% CI = 0.46-0.69, P < 0.001).14,16 All of the cardiovascular outcomes favored rosuvastatin over placebo, but there was only a small advantage in all-cause mortality; there were 198 all-cause deaths (2.2%) in the rosuvastatin group versus 247 (2.8%) in the placebo group (HR = 0.80, 95% CI = 0.67-0.97, P = 0.02).14

There was also a blemish on rosuvastatin in the JUPITER trial in the finding of a higher incidence of physician-reported diabetes (270 [3.0%] in the rosuvastatin group compared with 216 [2.4%] in the placebo group, P = 0.01)14 despite an a priori hypothesis by study investigators that rosuvastatin might reduce the incidence of diabetes because hs-CRP levels “predict the onset of diabetes.”17 Still, the results of JUPITER suggested an apparent hit-the-moon achievement in improving the targeting of primary prevention efforts, with an author-estimated NNT of just 25 patients to prevent 1 primary endpoint outcome event over a 5-year period based on the available median 1.9 months of follow-up.14 The results also represented a huge market opportunity for rosuvastatin, despite a practical cost analysis that puts the price tag at approximately $178,000 in rosuvastatin drug cost to prevent 1 major event (i.e., 25 patients treated for 5 years at current real-world rosuvastatin drug cost in mid-2010).17

Criticism of the JUPITER trial results began immediately. Within days of online publication of the JUPITER trial results, 2 BMJ editorialists pointed to weaknesses related particularly to generalizability and clinical relevance.17 The clinical relevance was described by Donner-Banzhoff and Sonnichsen as doubtful because, despite the large relative risk reduction, the absolute reduction in risk of the primary endpoint was only 0.59 events per 100 person-years. They also argued that participants were not truly at low risk of cardiovascular disease by traditional standards because, despite normal LDL-C levels and absence of cardiovascular disease, more than one-half had a Framingham risk score exceeding 10%, and 41.4% had metabolic syndrome. The inclusion of patients with metabolic syndrome and high Framingham risk scores in the JUPITER sample was likely intentional because of previous research showing that, as the JUPITER trial authors observed in their study protocol description, hs-CRP “adds prognostic information on risk at all levels of LDL-C, at all levels of the Framingham Risk Score, and at all
levels of the metabolic syndrome.” Still, Donner-Banzhoff and Sönничsen raised the important point that to obtain a true test of the effect of hs-CRP screening in routine care would require comparing hs-CRP plus conventional risk factors versus conventional risk factors alone as predictors of treatment benefit, something that JUPITER did not do.17

Criticisms of the trial’s external validity are particularly important because a key ostensible purpose of JUPITER was to bolster the appropriate use of statins for primary prevention in routine care. Observing in 2003 that “almost half of all cardiovascular events occur among apparently healthy men and women who have normal or even low levels of [LDL-C],” the JUPITER study chairman advocated for “better screening methods … to detect high-risk individuals for whom the [NNT] is small enough to make prophylactic statin therapy cost-effective.”15 Yet, consistent with the criticisms of the BMJ editorialists, the external validity of JUPITER’s findings was undermined by 2 factors. First, a 4-week placebo run-in period, during which patients had to take more than 80% of all study tablets to continue with the protocol,14 meant that the JUPITER trial participants were probably more compliant than most patients in routine clinical practice. Second, the list of JUPITER trial exclusion criteria was lengthy and contained many common conditions and treatments including current use of post-menopausal hormone-replacement therapy; past or current use of lipid-lowering therapy; diabetes; liver disease; uncontrolled hypertension (defined as systolic blood pressure exceeding 190 millimeters mercury [mm Hg] or diastolic blood pressure exceeding 100 mm Hg); cancer (except for basal-cell or squamous-cell skin carcinoma) within 5 years before enrollment; uncontrolled hypothyroidism; “recent history of alcohol or drug abuse or another medical condition that might compromise safety or the successful completion of the study;” and inflammatory conditions including severe arthritis, lupus, or inflammatory bowel disease.14 Of 26,286 potential study participants who met the primary entry criteria of LDL-C less than 130 mg per dL and hs-CRP of at least 2.0 mg per liter, 3,948 (15.0%) withdrew consent; 957 (3.6%) were excluded for diabetes; 1,202 (4.6%) were excluded for other conditions, predominantly hypothyroidism and liver disease; and 856 (3.3%) were excluded for “other” conditions that were not detailed.18 Of the 19,323 potential participants remaining, 1,521 (7.9%) were excluded for “poor compliance,” leaving 17,802 participants, 67.7% of the initial clinically eligible pool, available for randomization.18

More Criticism Heaped on JUPITER

Among the criticisms raised by Donner-Banzhoff and Sönничsen in 2008 was lack of plausibility of the JUPITER study findings in light of previous work. The evidence that was already known at the time included the results from the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial in patients with mild to severe systolic heart failure. Over a median follow-up period of 32.8 months, 10 months longer than JUPITER, rosuvastatin in the CORONA trial significantly lowered both LDL-C and hs-CRP by relative amounts similar to those observed in the JUPITER trial.19,20 However, rosuvastatin in the CORONA trial performed no better than placebo on the primary composite outcome (death from cardiovascular causes, nonfatal MI, or nonfatal stroke).19 There was also no difference between rosuvastatin and placebo on 3 of 4 pre-specified secondary endpoint outcomes, including death from any cardiovascular cause, all-cause death, or any coronary event; however, there were fewer cardiovascular hospitalizations in the rosuvastatin-treated group.19 Later, Kauf et al. applied a Bayesian analysis of CORONA and JUPITER trial results to find small rosuvastatin treatment effects including an absolute difference of only 0.23% for the combined endpoint of cardiovascular death, MI or stroke (i.e., the CORONA primary endpoint outcome, a subset of the JUPITER primary endpoint outcome), thereby increasing the NNT for the CORONA endpoint outcome from 119 to 434.20

By June 2010, criticism of JUPITER grew into what one press account described as “an avalanche”2 with the publication of 4 articles on the topic of primary prevention with statins in the June 28, 2010, issue of the Archives of Internal Medicine. These articles included the meta-analysis by Ray et al.,2 technical critiques of JUPITER’s methods and findings, and an accompanying editorial.2,8,20,21 Much of the criticism focused on the decision of the JUPITER Independent Data and Safety Monitoring Board (IDSBMB) to terminate the trial after a median follow-up of 1.9 years, raising the possibility that the benefits observed for rosuvastatin treatment represented early effects that would have diminished over time because of regression to the mean, had the entire planned (3- to 4-year) follow-up been completed.

The critique by de Lorgeril et al., including a reanalysis of the JUPITER data, is notable both because it has been the subject of intense media attention1,2 and because a key component of the reanalysis appears to have been based on an erroneous premise. Specifically, de Lorgeril et al. argued that because “an ‘unequivocal reduction in cardiovascular mortality’ was announced in March 2008 as the main justification for the premature trial termination, the absence of cardiovascular mortality data in the published article is striking.”21 On that basis, de Lorgeril et al. reanalyzed the JUPITER data to calculate a cardiovascular mortality rate (fatal stroke plus fatal MI), producing an estimate of 12 cardiovascular deaths in each study group, concluding that “such a lack of effect on cardiovascular mortality associated with a strong effect on nonfatal complications strongly suggests a bias in the data set and should have led to the continuation of the trial rather than to its premature...
Putting aside the ongoing debate over whether the analysis by de Lorgeril et al. was accurate, a question that cannot be resolved here, there appears to be no evidence that anyone connected with the JUPITER trial justified termination of the trial based mainly (or at all) on a specific finding of reduction in cardiovascular mortality. Instead, as indicated on JUPITER’s clinicaltrials.gov web page, the trial was stopped because of “unequivocal evidence of a reduction in cardiovascular morbidity and mortality,” (emphasis added). Although not sufficiently specific for a clinical trial web page, this language was consistent with the trial’s primary endpoint outcome, which encompassed both fatal and nonfatal cardiovascular events. The same language was used in press reports in March 2008 when the decision to terminate the trial was announced.

The study report indicated further that in making its decision, the IDSMB took into account “the size and precision of the observed treatment benefit, as well as effects on the rates of death and other secondary end points being monitored and on major subgroups.” Additional clarification was added by the JUPITER study chairman in 2009, when he reported that the trial was halted early because of “a 44% reduction in the trial primary end point of all vascular events (P<0.00001), a 54% reduction in myocardial infarction (P=0.0002), a 48% reduction in stroke (P=0.002), a 46% reduction in need for arterial revascularization (P<0.001), and a 20% reduction in all cause mortality (P=0.02).”

A more on-point critique was made by Kaul et al. (2010), who observed that important questions about the value of hs-CRP as a potential causal factor for cardiovascular events remain unresolved. Noting that a 2009 report from the U.S. Preventive Services Task Force did not endorse hs-CRP as a cardiovascular risk factor because “evidence that changes in CRP level lead to primary prevention of CHD events is inconclusive,” Kaul et al. made 2 main criticisms of the JUPITER trial analysis.

First, Kaul et al. presented results from an analysis of data provided to the U.S. Food and Drug Administration (FDA) Endocrinologic and Metabolic Drugs Advisory Committee in December 2009. These data, Kaul et al. argued, suggest that “[hs-CRP] appears to be an insufficient predictor of risk and treatment response in JUPITER.” This data included findings that (a) the cardiovascular event rates in the placebo group were approximately equal for subgroups of different hs-CRP levels, suggesting “flat” dose-response for hs-CRP; (b) treatment group patients with lower hs-CRP levels experienced greater treatment benefits; and (c) significant treatment benefit was observed for patients who “met the age and elevated [hs-CRP] level criteria plus at least 1 additional risk factor” but not for patients who met the “age and elevated [hs-CRP] level criteria alone.” However, as Kaul et al. pointed out, some of these analyses were post hoc, and analyses of treatment response by baseline LDL-C level and hs-CRP level were underpowered.

Second, Kaul et al. argued that the decision to put an early halt to any trial, including the JUPITER trial, creates important “perils” including “a false-positive result, an overoptimistic result, a less-convincing result, or a missed opportunity to gather essential data on adverse effects.” In supporting this point, Kaul et al. referred to a systematic review and meta-regression analysis by Bassler et al. (2010), which compared 91 truncated RCTs with 424 matching nontruncated RCTs. For truncated RCTs compared with nontruncated RCTs, the pooled ratio of relative risks was 0.71 (95% CI=0.65-0.77). For example, applying this ratio to a nontruncated trial showing a relative risk of 0.80 or a 20% risk reduction, a truncated trial would show a relative risk of 0.57 (0.80 X 0.71) or a 43% risk reduction. Kaul et al. also pointed to the results of the Optimized Phase 3 Tiacagin in Multicenter International Sepsis Trial (OPTIMIST) and the Candesartan in Heart failure — Assessment of Reduction in Mortality and Morbidity in Heart failure (CHARM) trial, both of which showed significant benefits for study drugs compared with placebo at early assessments (P=0.006 and 0.0006, respectively). Both trials continued “and the apparent early benefit of the intervention disappeared on final evaluation.”

For clinicians, Kaul et al. concluded that JUPITER’s results do not warrant stratifying treatment decisions by hs-CRP level; that the risk reductions estimated in JUPITER are likely “overexuberant” and should not be expected in clinical practice; and that statins should be used only “judiciously” for primary prevention when patients do not modify lifestyle risk factors including diet, exercise and weight loss. Still, despite the controversy about how JUPITER’s findings should be applied in routine practice, rosuvastatin was the only branded statin to increase its U.S. market share despite generic competition for the 2 sequential years ending in 2009; sales of rosuvastatin grew by 29% in 2009 to $4.5 billion.

**Fibrates Take Their Lumps with the Statins**

A meta-analysis of 10 RCTs performed by Saha et al. (2007) found that fibrates join statins in the low return on investment in prevention of adverse cardiovascular outcomes and all-cause mortality. Although fibrates were effective at lowering triglycerides and total cholesterol and increasing high-density lipoprotein cholesterol (HDL-C), nonfatal MI was the only endpoint outcome that was reduced by fibrates. Fibrates did not reduce fatal MI, stroke, or cardiovascular mortality. Noncardiovascular mortality was higher with fibrates, and all-cause mortality appeared to be higher with fibrates versus placebo (but the all-cause comparison was not statistically significant, P=0.08). The exclusion of clofibrate studies resulted in no significant difference in all-cause mortality and noncardiovascular mortality for fibrates compared with placebo.
Primary Prevention with Statins: Cost and Implications for Routine Clinical Practice

Based on the JUPITER trial results, on December 15, 2009, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee recommended approval of rosuvastatin for primary prevention in persons with elevated CRP without reference to LDL-C level, the first statin with this indication. Steven Nissen, MD, chair of cardiovascular medicine at the Cleveland Clinic, was quoted as saying at the time that if the FDA accepts the advisory committee's recommendation, “the number of Americans eligible for statin therapy [would expand] by millions.”29 Other experts noted that FDA approval for this indication would have the unintended consequence of increasing demand for hs-CRP laboratory tests.29 The FDA approved the supplemental indication for rosuvastatin on February 8, 2010.30

The revised label for rosuvastatin includes the indication for “primary prevention of cardiovascular disease in individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥ 50 years old in men and ≥ 60 years old in women” who have CRP of 2 mg per liter or greater and the presence of at least 1 additional cardiovascular disease risk factor (e.g., hypertension, low HDL-C, smoking, or a family history of premature CHD).31

A population-level strategy to treat persons with elevated CRP with primary prevention for cardiovascular disease would be expensive. Relying in part on an analysis by Woloshin et al (2007),32 Shah et al. (2009) assumed a rosuvastatin drug cost of $115 per month and “a conservative strategy” in which patients would be eligible for treatment only if they had 2 or more risk factors, an estimated 10%-20% risk of coronary artery disease over the next 10 years (using Framingham risk scores), and a CRP of more than 3 mg per liter (i.e., a threshold higher than the current FDA-approved indication).33 Under this assumed conservative strategy, Shah et al. estimated that $345,238 in rosuvastatin drug cost would be required to prevent 1 MI, stroke, or death from cardiovascular disease. The population-level rosuvastatin cost in the U.S. would be $2.9 billion per year to treat an additional 2.1 million Americans for 1.9 years.32,33

Under a “broad” strategy of treating all individuals with CRP exceeding 3 mg per liter, the additional treated population would number 25.3 million.32

The cost of hs-CRP testing would also be expensive. The cost of the hs-CRP laboratory test (Current Procedural Terminology [CPT] code 86141)34 is highly variable, typically in the range of $45-$85 but as much as $120, and multiple hs-CRP tests are necessary to determine an average value.34 Assuming testing of only those who meet the other high-risk (“conservative strategy”) criteria specified by Shah et al. and applying a conservative estimate of 2 hs-CRP tests per person tested, $50 per hs-CRP test,35 and 3 persons tested for every person prescribed rosuvastatin for elevated hs-CRP (greater than 3 mg per liter), 6.3 million persons would be tested twice for a total cost of about $630 million.

There are also many unanswered questions about how a test-and-treat strategy would work in routine clinical practice. For example, Woloshin et al. warned about overdiagnosis and estimated that widespread CRP testing would not address the problem of undertreatment of persons at high risk of CHD because most patients who would become eligible for treatment based only on CRP would have the lowest CHD risk.32 And, as Shah et al. pointed out, it is not clear whether practitioners would choose to test patients who have inflammatory disorders, such as severe arthritis, lupus, and inflammatory bowel disease.33 These patients were excluded from the JUPITER trial, and the value of hs-CRP as a predictor of their cardiac risk is questionable, adding uncertainty about the potential value of treatment if providers choose to test and treat them.

Can the Return-on-Investment of Primary Prevention with Statins Be Improved?
The limited evidence currently available suggests that the direct drug cost of rosuvastatin to prevent 1 all-cause death in persons without evident CHD ranges somewhere between approximately $1 million (Brugts et al., NNT = 167, 4 years of treatment) and $2 million (Ray et al., 1 death in 1,429 person-years of treatment), at current (mid-2010) discounted drug cost.7 Since there are no head-to-head trials that would suggest that rosuvastatin is any better than other statins in primary prevention, the statin drug cost to prevent 1 all-cause death can be reduced by about 95% with generic simvastatin or by about 93% with generic pravastatin, to a range of approximately $100,000 to $137,000 per death avoided. This is still a high price to pay, before consideration of the potential clinical and economic impact of adverse effects, which are currently unknown for long-term therapy with statins in primary prevention.36

Despite the potential importance of the notion that we should more accurately target primary prevention to those most likely to benefit from it, there seems to be insufficient evidence to focus on hs-CRP at the present time, let alone “[commit] low-risk subjects without clinical disease to 20 years or more of drug treatment,” as one editorialist observed at the time of JUPITER’s publication.36 In particular, we currently lack experimental comparisons of hs-CRP with traditional risk factors as predictors of benefit from statin treatment. There are also numerous questions about how to apply clinical trial evidence from JUPITER’s highly select sample to routine clinical practice, even putting aside the controversy over JUPITER’s methods and findings. Whether better evidence will “tip the scale” toward a role for hs-CRP in primary prevention remains to be seen. In an era of evidence-based practice, clinicians and patients should await the answer.
Tough Questions About the Value of Statin Therapy for Primary Prevention: Did JUPITER Miss the Moon?

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Tough Questions About the Value of Statin Therapy for Primary Prevention: Did JUPITER Miss the Moon?


Editors’ note to online readers: All JMCP articles contain hyperlinks to the source documents for free-access references. These hyperlinks are embedded in the reference numbers cited in the text as well as in the list of references at the end of each article.
British Petroleum and Pay-for-Performance in Primary Care

The last government employee to inspect the Deepwater Horizon oil rig before it exploded on April 20, 2010, was Eric Neal, an inspector with the U.S. Minerals Management Service (MMS); he was still in training as a drilling inspector. Despite checking well pressures 20 days prior to the catastrophic oil spill, he admitted under testimony on May 11, 2010, that he didn’t collect some of the key data that could have assisted investigators after the fact to determine why safety systems failed.

Notwithstanding the fact that the majority of the actors responsible for the spill work for British Petroleum (BP) and the MMS, many Americans are blaming U.S. President Barack Obama for the fiasco. A CBS news survey published May 14, 2010, showed that 87% of Americans thought President Obama was not doing enough to contain and clean up the spill. Whether one is an Obama fan or not, who can honestly declare that he is significantly responsible for the debacle? He has no personal experience with deep sea oil exploration, did not personally hire and train Eric Neal, nor did he approve of BP taking safety shortcuts. And yet…he has taken criticism from across the political spectrum.

In a similar vein, physicians are sitting in the crosshairs of those aiming to cut medical costs, whether or not reduction in physician pay is warranted. The editorial by Fairman and Curtiss in the June 2010 issue of JMCP provided a welcome and extensive overview of pay-for-performance (P4P) and the lack of evidence supporting retrospective incentive payments based on aggregate outcomes. As a family physician caught in the middle of the P4P debate, I can relate to President Obama in this instance.

At present, more than 20% of all visits to family medicine physicians are from Medicare patients, making them a substantial portion of practice revenue; however, my ability to substantially alter patient outcomes is severely constrained by systemic factors I cannot control. For example, Medicare patients have the choice to self-refer as they see fit. This practice creates skewed care patterns and disjointed medical care. A 2007 analysis of Medicare beneficiaries showed that each patient saw a median of 2 primary care physicians and 5 subspecialists working in 4 different practices per year. Additionally, for 33% of beneficiaries their assigned physician changed from one year to another.

Primary care pillars include first contact with patients, person-focused care (not organ system-focused), continuity over time, comprehensive services, and coordination of all care. As currently configured, Medicare beneficiaries are not receiving the full potential value of primary care. In fact, with so many “-ologists” making independent, organocentric treatment decisions from their highly trained yet stove-piped perspectives, any attempt to make the primary care physician responsible for composite outcomes in Medicare patients with current P4P measurements is simply unjustified. Using the data above, it would be akin to having a food critic rate a meal cooked by 7 different chefs from 4 different kitchens. Even those who blame President Obama for the oil spill would not want to eat such a dish.

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Reaching Out to the Uninsured: Patient-Assistance Program Goes Independent

I volunteer in an indigent clinic where I often see patients struggling with issues that should not exist in contemporary society. I do not believe that Americans should have to choose between buying life-saving medications and putting food on the table. But I witness it each and every time I go to the clinic. Tens of millions of our neighbors have to chose between meeting their needs for medications and meeting their other physiological needs (e.g., food, shelter).1,2

Many patients who were low-income and uninsured or underinsured over the past decade or so found themselves progressively less able to afford medical treatment. Even if they managed to see a doctor and receive a diagnosis, they may have been unable to pay for their prescription medications. People facing this dilemma have no good choices: Should they pay for a prescribed drug and skip the rent this month, hoping to skirt the final eviction notice? Cut their pills in half? Or just skip their medications altogether and take their chances?

Some recent strategies have been developed to assist this population. Support for therapy selection to direct uninsured patients towards the most affordable therapy choice3 and medication therapy management pilot programs for low-income elderly patients4 are 2 recent examples. While encouraging, the scalability of these programs remains a challenge given the size of the population in need.

In 2004, Express Scripts, one of the nation’s largest pharmacy benefits management companies, formed Rx Outreach, a patient-assistance program specifically designed to help people with incomes up to 300% of the federal poverty level (approximately $32,000 annually for an individual and $66,000 annually for a family of 4 in 2009)5 obtain needed medications. In 2010, Express Scripts began the process of spinning off Rx Outreach as a stand-alone charitable organization, completely independent of its parent company.6 As part of the transition to independence, Express Scripts also donated a mail-order pharmacy facility and other assets in St. Louis for process ing prescription drugs for the 500,000 people who have used Rx Outreach services in the past 6 years. We hope that Rx Outreach will stand as a model for other companies concerned about issues of health care access.

Why Become a Not-for-Profit?
The spin-off raises the organization’s potential to a new level, enabling it to reach many more people in need. As an independent not-for-profit organization rather than a publicly held, for-profit corporate entity, Rx Outreach gains increased freedom to act more broadly on behalf of its constituency and further expand access to prescription medications. With not-for-profit status, Rx Outreach can bring public and private resources together, developing working alliances with brand and generic pharmaceutical manufacturers, community health centers, rural clinics, faith-based charities, and health care associations. For example, donations to nonprofits create tax benefits for the donor. Drug manufacturers are not encumbered by “most favored nation” clauses when donating to nonprofit organizations.

Rx Outreach will also be able to customize medication-access programs for free clinics — an important venue for connecting patients with needed medications. We already work closely with hundreds of free clinics across the nation. As many state and local governments find themselves unable to maintain some of their indigent-support programs, Rx Outreach offers help to an otherwise increasingly disenfranchised population.

As a newly formed not-for-profit organization, Rx Outreach continues to draw on its expertise in customer service, drug dispensing, mail-order service, and follow-up care. Motivated by the mission, over 50 experienced employees made the decision to leave Express Scripts and take up the Rx Outreach cause, most of them at a reduced personal income, to help the organization thrive within the narrow budget from modest patient fees and private donations.

How Much Can Be Saved?
Over the past 6 years, Rx Outreach extended a medication lifeline to more than 500,000 people. Moving forward as a not-for-profit charity will enable us to reach many more families across America, potentially numbering in the millions. And, with new flexibility and independence, we should receive greater quantities of donated medications, which in turn will enable us to further lower patient cost.

In 2006, Rx Outreach patients had access to 110 prescription drugs. Today, that number has swelled to more than 400, with additional medications becoming available each year. Over its last year as an Express Scripts subsidiary, Rx Outreach dispensed an adjusted 1.2 million prescriptions and saved $58 million for the approximately 55,000 patients using its services. Most 180-day prescription quantities can be purchased for $20, and many medications are available in a 90-day supply. The drug list includes both brand and generic drugs, covering a nearly comprehensive list for most medical conditions. Specialty drugs remain beyond the current scope of the program.

The Need Continues to Grow
Health care reform will not eliminate the need that low-income Americans have for greater access to prescription drugs. Changes will take years to implement and, in any case, will not eradicate financial hardship. In fact, the nonelderly uninsured population including unauthorized immigrants is projected to exceed 20 million by 2019,7 so the need for safe and affordable drugs continues.

At the same time, disease isn’t taking a holiday. Obesity
rates continue to climb, as does the prevalence of diabetes. High blood pressure and cholesterol continue to pose risk for cardiovascular disease. People still experience pain. These are among the most common medical conditions treated by drugs available through Rx Outreach. However, we’re stepping up our efforts to add a number of other drugs to our list for currently unmet needs — insulin and asthma inhalers, for example.

As a physician, when I survey the state of health care across the country, I see few deficiencies greater than the disparities in access to prescription drugs. Pharmaceutical science has opened amazing new paths for medical therapy, but far too many find those paths blocked due to financial limitations. Our single goal is to remove the blockages and ensure that patients get the medicines they need to improve health outcomes.

With creative thinking, corporations can go a long way toward mitigating the gap in health care resulting from limited financial resources. We’d like to see other companies follow the example of the Rx Outreach program and proactively seek opportunities to expand access to medications through charitable action. Specific information about Rx Outreach, eligibility requirements, and a complete list of available medications are available at: www.rxoutreach.org.

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Need for Coursework in Pharmacy 
Curricula on Managed Care Pharmacy

I read with great interest the article by Pittenger et al. that appeared in the June 2010 issue of JMCP regarding the need for more exposure to managed care in the pharmacy curriculum. I share the authors’ concerns in this respect. When I was invited by the Dean of Midwestern College of Pharmacy-Glendale to assist in the opening of the new college in 1998 and to consider teaching a course in pharmacy administration, I immediately became aware of how little our pharmacy school applicants understand regarding managed health care and prescription benefit management.

Having recently (at that time) retired as Chairman/CEO of PCS Health Systems, I was well aware of the lack of understanding that exists with respect to managing pharmaceutical care. I offered to teach a course in health care administration with an emphasis on what pharmacists need to know to understand the functionality of PBMs, whether they liked them or not. I felt that it was important, as a new college of pharmacy to make certain that our students at least understood this important contemporary aspect of delivering health care. At the time I expected that I would do this for a year or two, and here it is 12 years later and I am still teaching the class. I suspect it is one of very few such courses being taught in our 100+ colleges of pharmacy in the U.S.

The class, while it is an elective, has become very popular with the students, with 60-75 students selecting the course on an annual basis. I find it very rewarding to teach the class and am very pleased that our graduates, most of them at least, have a better understanding of what they will encounter when becoming licensed pharmacists, and how best to serve their patients in a managed health care world.

I am surprised that with Minnesota often being credited as the birthplace of managed care that this important subject was not included in their curriculum many years ago. It is gratifying to note that their faculty recognize this omission and have taken steps to correct it. I would encourage every college of pharmacy in the country to include this most important subject matter in their curriculum.

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Thanks to JMCP Peer Reviewers, 2010 First Half

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