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Medicare reform bill includes medication management services

Pharmacists concerned about reimbursement for Part B-covered drugs

The new Medicare Prescription Drug, Improvement, and Modernization Act, signed into law by President Bush in early December, contains a victory for pharmacists. However, some drug reimbursement changes are also cause for concern.

Pharmacists are cheering the medication therapy management program in the bill. **(For general plan details, see p. 3.)** "For the first time under Medicare, pharmacists can be paid for their services for medication therapy management," says **Kristina E. Lunner**, director of federal government affairs for the American Pharmacists Association (APhA) in Washington, DC.

The bill says that to be part of the benefit, a drug-plan sponsor must have several programs in place, one of which includes medication therapy management. A pharmacist may furnish these services, according to the bill's language. The program should be designed to ensure, with respect to targeted beneficiaries, that covered Part D drugs under the prescription drug plan are appropriately used to optimize therapeutic outcomes through improved medication use, and to reduce the risk of adverse events, including adverse drug interactions.

The targeted beneficiaries are described as individuals who have multiple chronic diseases (such as diabetes, asthma, hypertension, hyperlipidemia, and congestive heart failure), who are taking multiple covered Part D drugs; and who are identified as likely to incur annual costs for covered Part D drugs that exceed a level specified by the Secretary of the Department of Health and Human Services.

The bill suggests that the medication therapy management program promote enhanced enrollee understanding of the appropriate use of medications and the risk of adverse effects; increased enrollee adherence with prescription medication regimens through medication refill reminders, special packaging, and other compliance programs and other appropriate means; and detection of adverse drug events, and patterns of overuse and underuse of prescription drugs.

The bill suggests that the program be developed in cooperation with licensed and practicing pharmacists and physicians. In addition, the drug-plan sponsor should account for resources used, and time required, to implement the medication therapy management program when the sponsor is establishing fees for pharmacists and others providing services under the plan.

"[The language] speaks to the fact that pharmacists could provide the services, but the program is not limited to them," Lunner says. Unfortunately, a one-year assessment of pharmacist services was dropped in the final conference agreement of the bill.

Reimbursement of Part B-covered drug changes

One provision of the bill that does not thrill many pharmacists has to do with changes in the way Part B covered drugs are reimbursed. Instead of the drugs being reimbursed at 95% of the Average Wholesale Price, the legislation shifts the reimbursement to a system based on the average sales price (ASP) of the drugs.

APhA was disappointed in these reforms, Lunner says. "While the scope of the drugs is limited, it will have an impact. It is a concern that [the government] is decreasing the reimbursement but in most cases is not providing a dispensing fee to pay for some of the pharmacist services."

APhA is also not happy that durable medical equipment (DME) reimbursement will go out to a competitive bidding program in the future. "We're concerned that pharmacists, which would be considered small providers of DME, would be less likely to win in a competitively bidding environment," Lunner says. "[This provision] has the potential of having a negative impact in pharmacists' ability to continue to provide those services to patients."

Overall, Lunner sees the Medicare reform bill as imperfect, but it still is a starting place. "We thought it was a good opportunity to set a floor that we can work from." ■

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New treatment guidelines for community-acquired pneumonia available

Therapy should be tailored to specific patients

The Infectious Diseases Society of America (IDSA) has updated its treatment guidelines for community-acquired pneumonia (CAP) in immunocompetent adults, just in time for a season that is expected to have higher-than-normal cases of lung disease.

IDSA, based in Alexandria, VA, has published previous versions of its guidelines in 1998 and 2000. In the most recent update, the committee that was charged with revising the guidelines was troubled by the increasing resistance of bacterial infections to antimicrobial therapy.

"One of our concerns is that if the quinolones keep being misused at the rate that they currently are, this class of drugs may become useless in five to 10 years," says **Lionel A. Mandell**,

Continued on page 4

Medicare prescription drug coverage benefit: General details of plan

Here are details of the recently approved agreement that is designed to give all Medicare beneficiaries access to prescription drug coverage. Most of these details are provided by the U.S. Department of Health and Human Services.

Medicare drug benefit

Beginning in 2006, Medicare beneficiaries will have access to the standard drug benefit described below. The drug benefit will be provided through private prescription drug plans that contract with the Medicare program. To receive the benefit, a beneficiary will have to sign up with a plan offering the drug benefit in his or her area.

Although drug plan sponsors may change some of the specifications, the benefit offered must at least be equal in value to the standard benefit. Standard coverage includes:

- A monthly premium of about $35.
- A deductible of $250.
- Coinsurance of 25% up to an initial coverage limit of $2,250.
- Copays of $2 for generics and preferred multiple source drugs and $5 for all other drugs, or 5% of the price, once an enrollee's out-of-pocket spending reaches a limit of $3,600.

Those beneficiaries with limited savings and low incomes will receive a more generous benefit package. For example, beneficiaries with limited savings and incomes below 135% of the federal poverty line ($12,123 for individuals and $16,362 for couples) will receive:

- A $0 deductible.
- A $0 premium.
- No gap in coverage.
- Copays of $2 for generics and preferred multiple source drugs and $5 for all other drugs, up to the out-of-pocket limit. (NOTE: For full dual eligibles — those eligible for both Medicare and Medicaid — under 100% of poverty, the copayment is reduced to $1 and $3 and for those full dual eligibles who are residents of nursing homes there is no copay.)
- $0 copay for all prescriptions once the out-of-pocket limit is reached.

Beneficiaries with limited savings and incomes below 150% of the federal poverty level ($13,470 for individuals and $18,180 for couples) will receive:

- A sliding scale monthly premium that would be about $35 for beneficiaries with incomes of 150% of the federal poverty level.
- A $50 deductible.
- No gap in coverage.
- Coinsurance of 15% up to the out-of-pocket limit.
- Copays of $2 or $5 once the out-of-pocket limit is reached.

Medicare-endorsed prescription drug discount card

Medicare beneficiaries that do not have drug coverage will be eligible for the Medicare-endorsed Prescription Drug Discount Card, which will begin operation six months after the enactment in December and continue until the full benefit is implemented. The card program is estimated to save beneficiaries between 10% and 25% on most drugs. Those with incomes below 135% of poverty will be given immediate assistance through a Medicare-endorsed prescription drug discount card with $600 annually to apply toward purchasing their medicines.

Critics say the plan won't help seniors

Critics of the plan, however, warn of the "doughnut hole" in the standard coverage. After an individual reaches $2,250 in drug expenses in a year, for instance, the coverage stops and the person has to pay for all of the next $2,850 in drug expenses. Insurance coverage doesn't start again until the drug expenses reach $5,100.

Critics also say that the drug benefit fails to offer incentives to drug companies to lower drug prices. In addition, the drugs covered can vary in each plan. That means seniors must ensure that their plan will pay for the drugs they need. ■

MD, FRCPC, professor of medicine and chief of the division of Infectious Diseases at McMaster University in Hamilton, Ontario, Canada. He is a member of the committee and the lead author of the guidelines.

The committee tried to put quinolones in their proper perspective, he says. "There is a role in macrolides [in this treatment], as well," he says.

Past guidelines included more of an overview of CAP treatment, Mandell says. In contrast, the new ones focus more on new areas of interest, such as updated recommendations and special populations and circumstances such as severe acute respiratory syndrome (SARS) and bioterrorism.

Decide where to treat the patient

One important aspect the committee first considered was the importance of the selection of the initial site of treatment of patients with CAP, whether it be the home or the hospital. (This decision often is made in the emergency department, the entry point for 75% of the 1 million annual pneumonia admissions in the United States, the committee says.) This selection often determines the selection and route of administration of antibiotic agents, intensity of medical observation, and use of medical resources.

The committee follows the suggestion in recent literature that the initial site of treatment decision be selected using a systematic three-step process:

• Step 1 involves assessment of pre-existing conditions that compromise the safety of home care, such as severe hemodynamic instability, active coexisting conditions that require hospitalization, acute hypoxemia or chronic oxygen dependency, and inability to take oral medications.

• Step 2 involves calculation of the Pneumonia PORT Severity Index (PSI), in which patients are stratified into five severity classes by means of a two-step process:

—Patients must meet the following criteria for class I: Age under 50 years, with none of five comorbid conditions (i.e., neoplastic disease, liver disease, congestive heart failure, cerebrovascular disease, and renal disease), normal or only mildly deranged vital signs, and normal mental status.

—Patients not assigned to risk class I are stratified into classes II-V on the basis of points assigned for three demographic variables (age, sex, and nursing home residency), the five comorbid conditions listed above, five physical examination results (pulse, respiratory rate, systolic blood pressure, temperature, and altered mental status), and seven laboratory and/or radiographic results (arterial pH, blood urea nitrogen level, sodium level, glucose level, hematocrit, hypoxemia by O_2 saturation, and pleural effusion on baseline radiograph).

Hospitalization usually is not required for classes I-III. The patient usually will require hospitalization for classes IV and V.

Social factors, such as outpatient support mechanisms and probability of adherence to treatment, are not included in this assessment, the committee says.

• Step 3 involves clinical judgment regarding the overall health of the patient and the suitability for home care. Mitigating factors for step 3 include frail physical condition, severe social or psychiatric problems compromising home care (including a history of substance abuse), and an unstable living situation or homelessness.

Committee suggests new initial empiric therapy

The committee also introduced new diagnostic and management strategies, including suggestions for initial empiric therapy for CAP. For example, the main treatment table in the former guidelines for outpatients primarily recommended macrolides, quinolones, and doxycycline, Mandell says. Now the table is more explanatory and categorizes the treatment recommendation for outpatients by modifying factors, such as someone who is perfectly well otherwise; those with comorbidity, such as chronic obstructive pulmonary disease, diabetes, or cancer; or suspected aspiration. In addition, treatment depends upon whether patients have recently taken antibiotics.

"We didn't have those main categories previously," Mandell says. "[In these guidelines,] we tried to be more careful and detailed in explaining when antibiotics should be used." The guidelines, which were published in the Dec. 1 issue of the journal *Clinical Infectious Diseases* and are available on-line at www.idsociety.org, place these treatment recommendations in an easy-to-read table, and then list the advantages and disadvantages for this empiric antibacterial selection in another table. Pharmacists as well as physicians should become familiar with the treatment tables, Mandell says. **(For an overview of the empiric therapy suggestions, see p. 5.)**

IDSA suggests initial empiric therapy for CAP

In the 2003 recommendations for management of community-acquired pneumonia (CAP) in immunocompetent adults, the Infectious Diseases Society of America (IDSA) in Alexandria, VA, has issued suggestions for initial empiric therapy. Here are some of those suggestions:

• Empiric treatment of suspected bacterial superinfection of influenza should provide activity against *Staphylococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae* with antibiotics such as amoxicillin-clavulanate, cefpodoxime, cefprozil, cefuroxime, or a respiratory fluoroquinolone.

• Fluoroquinolones (gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin) are recommended for initial empiric therapy of selected outpatients with CAP.

Other options (macrolides and doxycycline) generally are preferred for uncomplicated infections in outpatients. Fluoroquinolones (gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin) may be used as monotherapy for patients with CAP who are admitted to a hospital ward. With the exception of gemifloxacin (no intravenous formulation), they may be used as part of a combination for patients with CAP admitted to an ICU.

• A macrolide is recommended as monotherapy for selected outpatients, such as those who were previously well and not recently treated with antibiotics.

A macrolide plus a β-lactam is recommended for initial empiric treatment of outpatients in whom resistance is an issue and for hospitalized patients.

• Telithromycin also may have a role as an alternative to macrolides for treatment of patients with CAP. At this time, however, the U.S. Food and Drug Administration has not yet approved it. ■

Start therapy earlier

Another new recommendation in the guidelines addresses the issue of when antibiotic therapy should be initiated for patients with acute pneumonia. The previous IDSA guidelines recommended initial administration within eight hours after arrival of the patient at the hospital. This was based on a retrospective analysis of Medicare hospitalizations for pneumonia in 1994 and 1995.

A more recent analysis of Medicare hospitalizations, however, demonstrated an association between initiation of antimicrobial therapy within four hours after arrival and improved outcomes. Based on these findings, the committee supports the four-hour initiation of the therapy patients requiring hospitalization for CAP.

In addition, the committee recommends that patients who smoke and who are hospitalized with CAP should have the goal of stopping cigarette use. Besides its association with morbidity and mortality, smoking is associated with a substantial risk of pneumococcal bacteremia and a risk for *Legionella* infection. The committee suggests that patients try to stop smoking while still in the hospital.

Feedback takes both sides

Mandell praises the excellent feedback the committee has received internally from IDSA. He has received some interesting responses, however, as other individuals read the guidelines for the first time. "When they first went on the Internet, one person wrote to us and said they were using quinolones too much. Another person said they were using macrolides too much. We figured that if we were getting it from both sides, we were probably getting it right." ■

Large drug copayment increases lead to decreased utilization

Some patients discontinued therapy altogether

Pharmacists may expect their patients to switch to less expensive drugs when their copayments increase dramatically. A recent study,

however, suggests that some patients may stop taking their important medications altogether.

In an effort to keep down prescription drugs costs, many employers and health plans are choosing to offer their enrollees incentive-based formularies. These formularies offer enrollees financial incentives, such as lower copayments or lot-of-pocket costs, to choose drugs that are preferred by the payer.

The most common type of incentive-based formulary has three tiers. The first tier usually requires the lowest copayment for generic drugs. The second tier has a higher copayment for the brand-name drugs that are preferred by the organization, and the third tier has the highest copayment for brand-name drugs that are not preferred by the organization.

Researchers from Harvard Medical School in Boston and Medco Health Solutions in Franklin Lakes, NJ, wanted to test how patients continue to use their medications when their health plans adopt an incentive-based formulary. To do this, they studied responses from such a switch in 2000 by a large health plan and a national pharmacy benefits manager. The results of the study were published in the Dec. 4 issue of the *New England Journal of Medicine* (*NEJM*).

Increase in copayments decrease utilization

The researchers used claims data to compare the utilization of and spending on drugs in the two employer-sponsored health plans with those in comparison groups of enrollees covered by the same insurers. One plan simultaneously switched from a one-tier (with the same copayment for any drug) to a three-tier formulary and increased all enrollee copayments for medications. The second switched from a two-tier to a three-tier formulary, changing only the copayments for tier-3 drugs. The researchers examined the utilization of angiotensin-converting-enzyme (ACE) inhibitors, proton-pump inhibitors, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins).

Among the enrollees in the first plan who were initially taking tier-3 statins, more enrollees in the intervention group than in the comparison group switched to tier-1 or tier-2 medications (49% vs. 17%). One troubling result, however, is that the enrollees in this plan who had used a tier-3 drug before the policy changes were significantly more likely than enrollees in the comparison group to stop using a drug in the class. In the case of ACE inhibitors and statins, enrollees covered by the first plan were twice as likely as the enrollees in the comparison group to totally discontinue the use of drugs in the given class.

In contrast, the enrollees covered by the employer that implemented more moderate changes were more likely than the comparison enrollees to switch to tier-1 or tier-2 medications but were not likely to stop taking a given class of medications altogether.

The discontinuation of the use of medications such as statins and ACE inhibitors that are needed for the treatment of chronic illnesses raises important questions about potentially harmful effects of formulary changes and the associated changes in copayments, the researchers say.

An editorial accompanying the study in the *NEJM* agrees with this assessment. Although insurers and employers feel that incentive-based formularies can slow the growth of drug expenditures, research has shown that the incentive-based formularies may also "create a particular burden for persons with lower incomes or chronic diseases," says **Cindy Parks Thomas**, PhD, a research scientist at the Schneider Institute for Health Policy, Brandeis University, in Waltham, MA.

The devil is in the details of these plans, the study's researchers say. "As three-tier formularies become increasingly prevalent, we need much greater knowledge about these details in order to reap the advantages in cost savings without causing deleterious consequences for patients." ■

Pediatric rule legislation passes Congress

The U.S. House of Representatives has overwhelmingly approved legislation that will require pharmaceutical companies to test specific

medicines for use in children. Endorsed by the American Academy of Pediatrics (AAP) in Washington, DC, the Pediatric Research Equity Act (S. 650/H.R. 2857) passed the Senate on July 23 by unanimous consent, and was then introduced in the House by Reps. Jim Greenwood (R-PA), Anna Eshoo (D-CA), and Deborah Pryce (R-OH). President Bush is expected to sign the bill.

The Pediatric Rule is a complement to the Best Pharmaceuticals for Children Act, a law that gives financial incentives to pharmaceutical companies that voluntarily decide to test drugs in children. The Pediatric Rule covers medicines not covered by that law.

Last October, a judge struck down the rule, saying Congress hadn't given the Food and Drug Administration (FDA) the authority to require companies to test medications in children. Immediately following the court decision, the AAP asked Congress to act quickly to enact legislation granting the FDA authority and restoring the rule. ▼

Aggressive atorvastatin therapy halts progression of atherosclerosis

Aggressive atorvastatin treatment stopped progression of plaque burden in heart patients in a head-to-head trial that compared moderate with aggressive statin therapy. The trial aimed to lower levels of low-density lipoprotein (LDL) to below 80 mg/dL.

Principal investigator **Steven E. Nissen**, MD, FACC, vice chairman of the Department of Cardiology at the Cleveland (OH) Clinic Foundation, presented these results from the Reversal of Atherosclerosis with Lipitor (REVERSAL) study, on Nov. 12 at the American Heart Association's Scientific Sessions 2003. The information here was reported by Medscape and WebMD.

The study compared two cholesterol-lowering drugs, atorvastatin (Lipitor) and pravastatin (Pravachol), in more than 500 patients with symptomatic coronary artery disease. Lowering LDL cholesterol to an average of 79 mg/dL stopped progression of clogged arteries among patients taking 80 mg atorvastatin, Nissen says. The progression was measured by intravascular ultrasound.

However, taking 40 mg pravastatin did not offer the same slowing effect on heart disease even though some patients were able to achieve the same super-low LDL levels. Heart disease in the pravastatin-treated patients was about 3% worse after 18 months of treatment. Lipitor's manufacturer, Pfizer, sponsored the study. ▼

New indications for valganciclovir HCl tablets

The U.S. Food and Drug Administration and Roche Laboratories are notifying health care professionals of the findings of an active comparator study of valganciclovir HCl tablets (Valcyte) and ganciclovir in heart, liver, kidney, and kidney-pancreas transplant patients at high risk for cytomegalovirus (CMV) disease.

Based on those findings: 1) Valganciclovir HCl is indicated for the prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk; 2) Valganciclovir HCl is not indicated for use in liver transplant patients; and 3) The safety and efficacy of valganciclovir HCl for the prevention of CMV disease in other solid organ transplant patients, such as lung transplant patients, have not been established.

For more information, read the "Dear Healthcare Professional" letter at: www.fda.gov/medwatch/SAFETY/2003/safety03.htm#valcyte. ▼

COMING IN FUTURE MONTHS

- Palonosetron (Aloxi) formulary evaluation
- Hospital increases pharmacist interventions through automation
- Pilot program offer pharmacists for paid medicine reviews
- Study looks at early switches from IV to oral medications
- Multitasking in pharmacy practice

Aventis warns of hepatic injury reports with leflunomide (Arava)

Aventis Pharmaceuticals is warning of reports of hepatic injury with the use of leflunomide (Arava), which is indicated for the treatment of active rheumatoid arthritis.

Rare and serious hepatic injury, including cases with fatal outcomes, has been reported in postmarketing experience worldwide, Aventis says. Most cases occurred within six months of therapy and in a setting of multiple risk factors for hepatotoxicity. Rare postmarketing reports of severe infections, including sepsis, which may be fatal, also were received. Most of the reports were confounded by concomitant immunosuppressant therapy and/or comorbid illness, which, in addition to rheumatoid disease, may predispose patients to infection.

For more information, see www.fda.gov/medwatch/SAFETY/2003/arava_deardoc.pdf. ▼

Seniors most vulnerable to hospital medication errors

More than one-third of hospital medication errors that reach the patient involve seniors, indicating that they continue to be a vulnerable population in U.S. health care facilities. This information comes from the United States Pharmacopeia (USP) in Rockville, MD. The USP recently released its fourth annual national report summarizing the most recent data collected by MEDMARX℠, the anonymous national medication error-reporting database operated by USP.

The MEDMARX data report, "Summary of Information Submitted to MEDMARX in the Year 2002: The Quest for Quality," provides an analysis of 192,477 medication errors as voluntarily reported by 482 hospitals and health care facilities nationwide, including community, government, and teaching institutions. MEDMARX is the nation's largest database of medication errors, containing more than 530,000 released records. By the end of the third quarter of 2004, the number of records in the MEDMARX database will approach 1 million.

The 2002 MEDMARX data report revealed a number of significant findings with regard to the senior population, including:

- A majority (55%) of fatal hospital medication errors reported involved seniors.
- Almost 10% of the medication errors that caused harm to seniors were prescribing errors.
- When harm occurred, wrong route (7%), such as a tube feeding given intravenously, and wrong administration technique (6.5%), such as not diluting concentrated medications, were the second and third most common errors among those ages 65 and older.
- Omission errors (43%), improper dose/quantity errors (18%), and unauthorized drug errors (11%) were the most common types of medication errors among seniors.

The 2002 MEDMARX data report also found that incorrect administration technique continues to be responsible for the largest number of harmful medication errors (6.2%). This occurs when medications are either incorrectly prepared or administered, or both. Examples include not diluting concentrated medications, crushing sustained-released medications, wrong eye application of eye drops, and using incorrect IV tubes for medicine administration. ■

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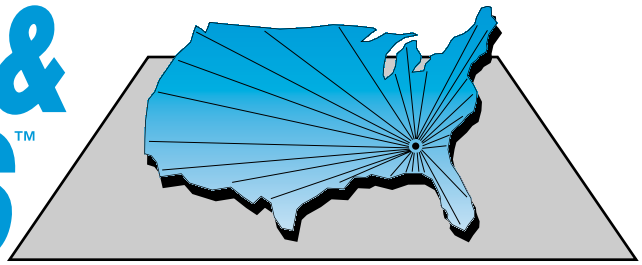

Formulary Evaluation of Omalizumab (Xolair)®

By **David McLellan**, PharmD candidate
Harrison School of Pharmacy, Auburn (AL) University
Written while on clinical rotation at Huntsville (AL) Hospital

Asthma affects nearly 18 million individuals in the United States. Prevention and reduction of asthma exacerbations are important goals of asthma management. Despite improvements in treatment options and an increased understanding of the disease process, many patients continue to have serious exacerbations requiring emergency medical attention. This amounts to approximately 10 million outpatient visits to physician offices and ambulatory clinics, and almost two million visits to hospital emergency rooms annually.

Standard asthma treatment includes inhaled β-agonists, inhaled anticholinergics, and inhaled and systemic steroids. Although these medications are effective in controlling exacerbations of the disease, they are not without side effects. To reduce side effects and patient dependence on asthma treatments, research has moved in the direction of gene therapy to target the disease at its source. Omalizumab (Xolair®) is the first medication of its kind to be approved for treatment of allergic asthma.

Mechanism of action

Omalizumab is a humanized anti-IgE (immunoglobulin E) monoclonal antibody that inhibits the binding of IgE to the high-affinity IgE receptor on mast cells and basophils. This action limits the release of mediators of the allergic response.

Indication

Omalizumab is indicated for adolescents and adults ages 12 years and older with moderate-to-severe, persistent allergic asthma:

- who have had positive skin test or in vitro reactivity to perennial aeroallergens;
- whose signs and symptoms are controlled inadequately by treatment with systemic and inhaled corticosteroids.

Dosing

Omalizumab is dosed in 150 to 375 mg doses and administered as a subcutaneous (SC) injection every two or four weeks **(see Tables 1 and 2)**. Dosage strength and frequency are determined by serum IgE levels (IU/mL taken before treatment initiation) and weight (in kg). Administration is limited to 150 mg per single injection, per injection site.

Dosing adjustments should be made when there are significant changes in body weight. Total serum IgE levels will be elevated during treatment and for up to one year after treatment discontinuation. Measured IgE levels during treatment and within one year following discontinuation should not be used in determining dosing adjustments.

Pharmacokinetics

Omalizumab is absorbed with an average bioavailability of 62% following a single SC injection. The medication exhibits linear kinetics at doses > 0.5 mg/kg, and takes an average of 7-8 days to reach peak serum concentrations. With multiple doses, the area under the serum concentration-time curve from day 0 to day 14 at steady state showed up to a sixfold increase vs. single injection. The volume of distribution in patients was a 78 ± 32 mL/kg.

The liver clears omalizumab in a method similar to IgG elimination. This process involves specific binding and complex formation of the drug with IgE. Omalizumab complexes are eliminated by the liver reticuloendothelial system and endothelial cells. The serum elimination half-life of the drug averaged 26 days with a daily clearance averaging 2.4 ± 1.1 mL/kg/day. Increases in body weight will increase clearance.

Contraindications

Omalizumab should not be administered to

Table 1: Omalizumab dosing every two weeks

Pre-treatment Serum IgE	30-60 weight (kg)	> 60-70 weight (kg)	> 70-90 weight (kg)	> 90-150 weight (kg)
≥ 30-100	Dosed every four weeks			
> 100-200				225
> 200-300		225	225	300
> 300-400	225	225	300	Not recommended
> 400-500	300	300	375	
> 500-600	300	375		
> 600-700	375			

Table 2: Omalizumab dosing every four weeks

Pre-treatment Serum IgE	30-60 weight (kg)	> 60-70 weight (kg)	> 70-90 weight (kg)	> 90-150 weight (kg)
≥ 30-100	150	150	150	300
> 100-200	300	300	300	Refer to two-week dosing schedule
> 200-300	300			
> 300-400				
> 400-500				
> 500-600				

patients who have experienced a severe hypersensitivity reaction to the medication.

Warnings and precautions

Omalizumab is classified as pregnancy category B because animal studies have not illicited fetal toxicities; however, IgG (with which the omalizumab/IgE complexes share elimination pathways) does cross the placenta. The medication should be used in pregnancy only if deemed medically necessary.

Anaphylaxis has occurred within two hours of the first or second dose of omalizumab in three patients without any other identifiable anaphylactic triggers. The patients presented with urticaria and throat and/or tongue edema. Patients who experience reactions such as these should be discontinued from omalizumab therapy.

Malignant neoplasms have occurred in 20 subjects treated with omalizumab. Breast, nonmelanoma skin, prostate, melanoma, and parotid neoplasms were most commonly observed.

Omalizumab is not intended for rescue therapy and should not be used in emergency situations. In patients who are dependent on high-dose steroids, abrupt discontinuation should not be performed. Instead, tapering under the close supervision of a physician is recommended.

Adverse reactions

In placebo-controlled trials, adverse reaction frequency was similar in both the omalizumab-treated and placebo-treated subjects. Some of the adverse reactions reported were: upper respiratory tract infections, viral infections, headache, pharyngitis, back pain, rhinitis, cough, myalgia, urticaria, nausea, dyspepsia, diarrhea, insomnia, and sinusitis.

Drug interactions

To date, no formal, published studies have evaluated omalizumab and potential drug-drug interactions.

Product information

Omalizumab (Xolair) is supplied as a lyophilized, sterile powder in a single-use, 5 mL vial, designed to deliver 150 mg of medication upon reconstitution with 1.4 mL of sterile water for injection. Unreconstituted vials should be stored at controlled temperatures between 2° and 8° C. Because the product contains no preservatives, upon reconstitution it should be used within eight hours if refrigerated or within four hours if stored at room temperature. The reconstituted product also should be protected from direct sunlight.

Cost

The hospital cost for one 5 mL vial of Xolair is $420.88. The suggested average wholesale price is: $541.25 per vial. This price does not include the cost of sterile water or other injection supplies. For the average patient, the monthly cost of Xolair may run from $600 to more than $3,000 dollars a month, including physician visits and supplies.

Evidence of efficacy and safety

Trial 1: Solér M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001;18:254-261.

Objective: To assess the clinical benefit and steroid-sparing effect of treatment with the anti-immunoglobulin-E antibody, omalizumab, in patients with moderate-to-severe allergic asthma.

Study design: In this multicenter, parallel-group, double-blind study, 546 allergic asthmatics that were symptomatic despite inhaled corticosteroids were randomized to receive placebo or omalizumab every two or four weeks subcutaneously for seven months.

Inclusion criteria

- Male or female, 12-75 years of age.
- Asthma diagnosis of one year or more based on the American Thoracic Society criteria.

• Positive skin prick test to a common household allergen.
• Total serum IgE level ≥ 30 and ≤ 700 IU/mL.
• Total body weight ≤ 150 kg.
• Baseline FEV_1 ≥ 40% and ≤ 80% while not on bronchodilator treatment.
• A mean total symptom score of 3 or more for 14 days prior to randomization.
• Treatment with inhaled corticosteroids with a dose of 500-1,200 micrograms of beclomethasone dipropionate daily for three months or more prior to randomization.
• Use of β_2 agonists on an as-needed basis.
• Stable asthma with no significant changes in regular medication and no acute exacerbations for one month or more.

Exclusion criteria

• Regularly taking systemic corticosteroids.

Treatment regimen: Five hundred forty-six subjects were randomized to receive either SC injection of omalizumab or matching placebo after a run-in phase of four to six weeks on beclomethasone dipropionate. During the first 16 weeks of the study, subjects were maintained on the inhaled cortico-steroid therapy while receiving omalizumab or placebo injections (steroid-stable phase). Over the last 12 weeks of the study, the steroid dose was reduced by 25% of baseline dose every two weeks for eight weeks (steroid-reduction phase). During the final four weeks, subjects were maintained on the lowest possible dose of inhaled corticosteroid.

Endpoints: The primary endpoint was the number of asthma exacerbations experienced per patient during the steroid-stable and steroid-reduction phases. The secondary endpoints were the number of patients experiencing asthma exacerbations during either phase, the percent reduction of inhaled corticosteroids, use of rescue inhaler, asthma symptom scores, morning peak expiratory flow, and FEV_1 as percent predicted.

Results: Compared to the placebo group, the omalizumab group showed 58% fewer exacerbations per patient during the stable-steroid phase ($P < 0.001$). During the steroid-reduction phase, there were 52% fewer exacerbations in the omalizumab group vs. the placebo group ($P < 0.001$). Treatment with omalizumab was well-tolerated; the incidence of adverse events was similar in both groups.

Study conclusion: In this study, omalizumab therapy safely improved asthma control in allergic asthmatics that remain symptomatic despite regular treatment regimens, and showed marked reduction in dependence on inhaled corticosteroids.

Study strengths

• Randomized, placebo controlled, double-blind.
• Objective clearly stated.
• Endpoints clearly defined.
• Intent-to-treat analysis performed.
• Baseline demographics evenly matched between treatment and control group.
• Study design reproducible.

Study weaknesses

• Funded by Novartis.
• Did not follow the National Asthma Education and Prevention Program (NAEPP) guidelines for long-term asthma management.

Trial 2: Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment for severe allergic asthma. *J Allergy Clin Immunol* 2001;108: 184-190.

Objective: To evaluate the efficacy and safety of omalizumab in the treatment of inhaled cortico-steroid-dependent asthma.

Study design: In this Phase III, multicenter, parallel-group, double-blind study, 525 inhaled corticosteroid-dependent asthmatics were randomized to receive placebo or omalizumab every two or four weeks subcutaneously for seven months.

Inclusion criteria

• Male or female, 12-75 years of age.
• Asthma diagnosis one year or more.
• Positive skin prick test to a common household allergen.
• Total serum IgE level ≥ 30 and ≤ 700 IU/mL.
• Baseline FEV_1 ≥ 40% and ≤ 80% while not on bronchodilator treatment.
• Treatment with inhaled corticosteroids with a dose of 420-840 micrograms of beclomethasone dipropionate or equivalent daily.
• Provided informed consent.

Exclusion criteria

• Prior exposure or sensitivity to omalizumab.
• Acute upper respiratory tract infection within one month.
• Less than three months of stable immunotherapy.
• Elevated IgE level for reasons other than atopy.
• Regular treatment with β-adrenergic antagonists.
• 750 mg or more omalizumab required per four weeks on the basis of serum IgE and body weight

Treatment regimen: Five hundred twenty-five subjects were randomized to receive either SC injection of omalizumab or matching placebo after a run-in phase of four to six weeks on beclomethasone dipropionate, if they were not already on it. During the first 16 weeks of the study, patients were

maintained on the inhaled corticosteroid while receiving omalizumab or placebo injections (steroid-stable phase). During the last 12 weeks of the study, subjects' steroid dose was reduced by 25% of baseline dose every two weeks for eight weeks (steroid-reduction phase). Subjects were maintained on the lowest possible dose of inhaled corticosteroid in the final four weeks.

Endpoints: The primary and secondary endpoints were the same as those used in Trial 1.

Results: Omalizumab treatment resulted in significantly fewer asthma exacerbations during the steroid-stable phase ($P = 0.006$), and fewer exacerbations during the steroid-reduction phase ($P = 0.003$). Inhaled corticosteroid use was significantly reduced in the omalizumab treatment group vs. placebo ($P < 0.001$), and steroid discontinuation was more likely with omalizumab ($P < 0.001$). Improvements in symptoms and pulmonary function occurred along with a reduction in rescue β-agonist use. Omalizumab was well-tolerated, with an adverse event profile similar to placebo.

Study conclusion: This study showed that addition of omalizumab to standard asthma therapy safely improves asthma control, and showed marked reduction in inhaled corticosteroid and rescue medication use.

Study strengths

- Randomized, placebo-controlled, double-blinded, parallel group.
- Reproducible.
- Objective clearly stated.
- Endpoints clearly defined.
- Intent-to-treat analysis performed.
- Baseline demographics evenly matched between treatment and control groups.

Study weaknesses

- Funded by Novartis.
- Did not follow NAEPP guidelines.

Trial 3: Finn A, Gross G, van Bavel J, et al. Omalizumab improves asthma-related quality of life in patients with severe allergic asthma. *J Allergy Clin Immunol* 2003;111:278-284.

Objective: To evaluate the effects of omalizumab on asthma-related quality of life.

Study summary: The data presented in this article were collected from the previous study (Trial 2) and followed the same criteria from start to finish with the addition of a 24-week double-blind extension phase during which subjects continued on omalizumab or placebo.

Results: The omalizumab and placebo groups were comparable in terms of baseline quality-of-life scores, as determined by the Juniper Asthma Quality of Life Questionnaire (AQLQ). At weeks 16, 28, and 52 (the extension phase), omalizumab-treated subjects demonstrated statistically significant improvements across all AQLQ domains with P values ranging from < 0.05 to < 0.001.

Study conclusion: In patients requiring moderate-to-high inhaled corticosteroid doses for severe allergic asthma, the improvement in disease control added by omalizumab therapy was paralleled by clinically meaningful and statistically significant improvements in asthma-related quality of life.

Additional studies have been performed to show that omalizumab has a positive benefit on asthma control in pediatric subjects. However, the product manufacturer did not seek FDA approval for this indication and does not support its use in this population. Ongoing studies are evaluating omalizumab use for seasonal allergy symptoms. The manufacturer and FDA do not yet support omalizumab's use in this instance and further research is needed to ensure efficacy and safety.

Conclusion

Clinical studies prove that this medication is safe, efficacious, and has a positive benefit on patient quality of life, in populations with moderate-to-severe asthma. Omalizumab is not a substitute for current treatment regimens; the product should be a second-line option for patients whose asthma cannot be controlled by standard treatment regimens.

Because of the expense of the medication and chronic nature of the disease, a yearly financial plan would need to be developed to cover costs of treatment. In addition to the expense of the medication itself, there is increased cost associated with the laboratory work required to obtain initial doses of the drug. Omalizumab should therefore be considered nonformulary. If a patient already receiving omalizumab is hospitalized for a prolonged period of time, the patient should provide his/her home medication when time for administration of the next injection occurs.

Additional resources

- American Lung Association. *Asthma in Adults Fact Sheet,* March 2003. Web site available at: www.lungusa.org/asthma/aduasthmfac99.html. Accessed Sept. 15, 2003.
- Genentech. Xolair® (omalizumab) [product information]. South San Francisco, CA; 2003.
- Milgrom H, Fick RB, Su J, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. *N Engl J Med* 1999;341:1966-1973. ■