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WHEN THE DISTURBANCE OF AFFECT, behavior, and cognition become unmanageable, older persons with acute mental status changes often present in the hospital emergency department and are subsequently admitted to an inpatient psychiatric unit. Without a comprehensive medical evaluation, the risk of morbidity and mortality from undetected medical conditions is increased. By collaborating with managed care organizations (MCOs), a managed behavioral healthcare organization (MBHO) developed and implemented an integrated approach for managing delirium prior to hospital admission.

Delirium, as defined by the American Psychiatric Association, is a disturbance in consciousness and cognition not accounted for by a pre-existing or evolving dementia. Evidence from a history, physical, or laboratory tests attribute the cause of delirium to a general medical condition, substance intoxication or withdrawal, medication, or toxins. Delirium is often undetected or misdiagnosed, or superimposed on existing illnesses, such as dementia. Under-detection is associated with high rates of morbidity, prolonged hospitalization, and increased likelihood of in-hospital death. These risks increase when diagnoses of chronic dementia, depression or psychotic illness hide an underlying causative physical or toxic disorder. In one ED study, 10 percent of persons

A Collaborative Model for Delirium Detection and Early Intervention: A Five-Year Study

Jon D. Beaty, MSW, LCSW, CPHQ, and Christy L. Beaudin, PhD, LCSW, CPHQ

Summary
Older persons with acute mental status changes and behavioral disturbances often present in the hospital emergency department and are subsequently admitted to an inpatient psychiatric unit. Without a comprehensive medical evaluation, the risk of morbidity and mortality from undetected medical conditions is increased. By collaborating with managed care organizations (MCOs), a managed behavioral healthcare organization (MBHO) developed and implemented an integrated approach for managing delirium prior to hospital admission.

Key Points
- A five-year case study shows a 283 percent increase in comprehensive medical evaluations completed in the decision-making process prior to an inpatient admission. Attention in the care-management process to the potential risks of undetected medical conditions in older persons can direct treatment to the appropriate level of care, either acute psychiatric or medical.
- The MBHO experienced a 23 percent reduction in cost per 1,000 member years, from $5,859 in 2000 to $4,492 in 2002, for the target diagnostic categories determined to be the most likely diagnoses for patients with undetected delirium. The cost benefit correlates to reduced utilization.
- Interventions included providing MBHO care managers with guidelines for escalating pre-certification decisions to a psychiatrist, training for care managers to identify persons at risk for delirium, implementation of a joint policy for the MBHO and MCOs on the care of persons at risk for delirium, and outreach to medical and behavioral health clinicians.
- A consumer-centered healthcare system has developed model processes to direct resources to meet consumer needs efficiently and effectively. An integrated approach to care allows clinicians to address the complexities of the differential diagnosis of behavioral and physical disorders in older persons.
over 65 years of age were found with delirium; the ED physician positively identified only 35 percent of those. Another study of older persons diagnosed with depression and psychosis on a university geropsychiatric unit found 34 percent with unrecognized medical disorders. Successful management of medical conditions typically associated with delirium and prevention of adverse outcomes require early identification and intervention, particularly for persons being considered for placement in a psychiatric unit. Common contributors to misdiagnosis of delirium have been identified:

- failure to conduct an appropriate mental status evaluation
- intoxication with alcohol or illicit drugs
- inadequate physical examination
- failure to obtain available history
- failure to obtain indicated laboratory studies.

Processes for the differential diagnosis of delirium vary and lack standardization. An organized approach is recommended to discover symptom causes and in ordering appropriate laboratory studies. Although difficult to achieve, it is possible for multiple entities to work together on managing the process of care, reducing the potential for adverse outcomes with at-risk populations, and improving patient safety. Collaboration and coordination of the assessment and treatment for both behavioral health and physical health are critical. At the micro-level, clinicians involved in the day-to-day care management can implement comprehensive treatment strategies for persons with multiple and complex healthcare needs.

PacifiCare Behavioral Health (PBH) is a network model managed behavioral healthcare organization (MBHO). It administers behavioral health benefits for MCOs and employer-sponsored plans. One of its regional service centers manages benefits for three MCOs serving commercial and Medicare Advantage (formerly Medicare+Choice) enrollees in Washington and Oregon. In 1999, care managers in the regional service center provided anecdotal reports of undetected delirium in older persons. This resulted in longer lengths of stay in psychiatric units, transfers from psychiatric to medical units, increased morbidity, and, in some instances, death. Thorough assessment and triage of persons at-risk for co-morbid conditions became a priority. Seniors (age 65 years and older) enrolled in Medicare Advantage in 1999 represented 24 percent of the PBH region’s membership, and accounted for 46 percent of all psychiatric inpatient days for commercial and Medicare enrollees. The region’s experience was disproportionate to the experience of the organization nationally, where Medicare enrollees represented 10.8 percent of the membership, and accounted for 14 percent of all psychiatric inpatient days.

PBH sought to improve collaboration with relevant medical delivery systems for persons presenting for inpatient psychiatric care, to ensure older persons with acute mental status or behavioral changes receive a comprehensive medical evaluation. Several avenues of system entry exist for a person seeking inpatient behavioral health services:

- Contact PBH via a toll-free telephone number for triage, pre-certification, and referral by a PBH care manager.
- Present at a network facility for triage and admission, if appropriate.
- Present in an emergency department for evaluation and referral.

In the latter scenario, a physician (e.g., the person’s primary care physician, an emergency physician, or a psychiatrist) completes an assessment of the person’s needs. A determination is made as to whether inpatient psychiatric care is indicated. For admission, a facility representative telephones PBH and requests pre-certification. The request is accompanied by a presentation of the patient’s clinical disposition and is reviewed against utilization management criteria. When the person’s clinical disposition satisfies criteria for admission to the level of care requested by the facility representative, care is pre-certified. The person’s clinical disposition and rationale for pre-certification are documented in an electronic database. Considering several opportunities to reduce risk, PBH prioritized changes to its care-management processes, specifically at the point of entry into the behavioral health system.

Methods

Case study series were conducted over a five-year period (1999 to 2003). Using quantitative and qualitative data, the study evaluated PBH’s processes for delivering acute inpatient psychiatric care to older persons at-risk for delirium and the effect of interventions intended to ensure timely detection and treatment for delirium. Baseline data were collected through case review. The case review determined the extent to which PBH care managers considered comprehensive medical evaluation of persons age 65 years and older in decisions about the level and setting of treatment. Using an internally developed audit tool, auditors examined individual case documentation. Audit tool criteria included information related to medical
history, physical, and laboratory studies. This permitted auditors to score each case record based on whether the spectrum of clinical information was considered in the certification decisions prior to a hospital admission. Cases including all three of these elements received a score of 1; those lacking any of these three elements received a score of 0.

At the baseline measurement, records were randomly selected from the database containing 230 records for persons age 65 years and older who were pre-certified for acute inpatient psychiatric care over a 12-month period. The sample was selected from the total number of claims for inpatient admissions for persons age 65 and older. A random number was assigned to each claim, and claims were sorted in ascending order by the randomly assigned numbers. The first 50 percent of the cases (n = 115) were selected for case review. The sample size is sufficient to detect a modest effect size (approximately 10 percent) with a 0.05 significance level with a power of 0.8. Auditors were uniformly trained, provided with instructions on data collection, and tested for Inter-Rater reliability to ensure consistency. Confidentiality of Medicare beneficiary information was protected. Auditors were selected from the organization’s clinical services staff, who had signed confidentiality agreements as a condition of employment. Subsequent measurements applied the same methodology.

Results
Evidence of the audit elements was found in only 17 percent of the cases at the baseline measurement. Qualitative analysis revealed barriers and opportunities for improvement in processes, both internal and external to PBH. Top-priority opportunities included:

1. Improve care manager review skills in assessment of risk for delirium.
2. Increase psychiatric consultation for care managers during pre-certification reviews.
3. Increase comprehensive medical evaluations by healthcare providers to rule out delirium for patients at risk.
4. Clarify delineation of responsibility between medical and behavioral health delivery systems in management of patients at risk for delirium.

PBH subsequently implemented training of its care managers. A 60-minute in-service training conducted by the PBH regional medical director, who was a board-certified geriatric psychiatrist, focused on identifying and managing patients at risk for delirium. Protocols for pre-certification reviews of older persons were added to the Inpatient Care Manager’s Escalation Guide (Exhibit 1).

Training on specific clinical information required to rule out delirium was reiterated in the guide. This enabled inpatient care managers to determine when consultation was needed with the regional medical director. In consultation, the medical director advised whether evaluation was satisfactory or when additional evaluation was needed. The regional medical director facilitated outreach activities to medical providers, increasing their awareness of under-detected delirium and of the opportunity to collaborate with managed care for persons at risk.

A joint policy and procedure on the management of persons at-risk for delirium and dementia with agitation was developed and implemented with contracted health plans. Delineated were the procedures to be followed by both the PBH care managers and the medical delivery system to ensure effective treatment planning. Principal responsibility was placed on primary care physicians (PCPs), or an appropriate proxy, to complete a comprehensive medical evaluation to rule out delirium. In confirmed cases with delirium, treatment was arranged in a medical setting. Psychiatric consultation was pre-certified by PBH for medical settings as needed. Once the person presenting with delirium was medically stable and appropriate for ambulatory care, PBH facilitated ongoing psychiatric treatment to address cognitive disturbances or behavioral dyscontrol.

Remeasurement was conducted for the 12 months subsequent to the baseline period. There was a 15-percentage-point improvement in the medical evaluation completion rate over baseline to 32 percent. A Chi-square test showed the difference in rates for baseline to remeasurement was statistically significant ($\chi^2 = 6.34 [P \leq 0.025]$). Qualitative analysis underscored the need for more comprehensive training of PBH care managers in the steps of identifying at-risk individuals and ensuring delirium was ruled out.

External to PBH, opportunity remained for medical physicians to take initiative in conducting comprehensive medical evaluations to rule out delirium for at-risk persons. This was particularly true of PCPs who may not see the person. Often when hearing of acute changes in the person’s mental status, PCPs would direct caregivers to the nearest ED to request a psychiatric admission. In response, the PBH regional medical director and clinical manager regularly presented the delirium protocol at meetings with MCOs and medical directors of contracted physician groups. In addition, the PBH regional medical director and clinical manager met with staff at psychiatric
hospitals to collaborate on procedures for managing older persons at risk for delirium. This intervention targeted hospitals serving a high-volume of PBH Medicare beneficiaries.

A second remeasurement was conducted for the 12-month period subsequent to the first remeasurement. Actions resulted in a 15-percentage-point improvement over the first remeasurement to 47 percent, a 176 percent relative change over the baseline. Comparing the first remeasurement to the second remeasurement, a Chi-square test demonstrated improvement of statistical significance ($\chi^2 = 6.82 \ [P \leq 0.01]$). Qualitative analysis concluded that comprehensive training was needed for newly hired care managers to ensure procedures to rule out delirium are consistently followed and considered in the process of patient placement. Also, additional interventions with physicians and the delivery system would support the efforts of care managers.

A third remeasurement was conducted for the next 12-month period. The result of 46 percent was not statistically significant from the second remeasurement ($\chi^2 = 0.028 \ [P \leq 1]$). Mapping the process of pre-certification review for acute psychiatric inpatient care for older persons highlighted the lack of a standard tool or template to support care manager adherence to the defined procedures for inpatient pre-certification decisions. Modifying care management software to support this process was proposed as the greatest opportunity for improvement, but has not been implemented.

A fourth remeasurement was conducted for the next 12-month period. The result of 53 percent was not statistically significant over the previous measurement ($\chi^2 = 0.25 \ [P > 0.10]$). However, the result of this latest measurement represents a 283 percent increase ($\chi^2 = 25.34 \ [P \leq 0.001]$) over baseline in pre-certifications for inpatient psychiatric care, taking into consideration a comprehensive medical evaluation in the decision-making process. Improvement of performance over the third remeasurement, although not statistically significant, is attributed to recurring training of care managers to review history, physical, and laboratory studies in the pre-certification process for inpatient psychiatric care. Meaningful attention

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**Exhibit 1: Inpatient Care Manager’s Escalation Guide**

**An Inpatient Care Manager Should Contact the Attending Physician Directly When:**

- The facility’s reviewer has inadequate clinical information and can’t answer questions with sufficient detail. The issue is not necessarily whether inpatient care is necessary, but rather whether an appropriate treatment plan is being implemented. Care managers shape appropriate treatment plans.

- The facility’s reviewer provides information that seems vague and untrustworthy. The concern is that the poor quality of information being provided may result in the consideration of a denial when the member’s clinical status actually warrants inpatient care. Care managers advocate necessary care for members and avoid unnecessary involvement by PBH medical directors as well as inappropriate denials.

- The facility’s reviewer is slow to respond. Care managers work with the facility’s utilization review staff as intermediaries for attending practitioners, ensuring that the practitioner is directly involved in the care management process when the intermediary is not cooperative.

**An Inpatient Care Manager Should Consult With a PBH Medical Director or Psychiatric Advisor When:**

- Acute mental status changes suggest the possibility of delirium that is not being appropriately evaluated by the practitioner or facility; thus, a PBH psychiatrist is needed to review the general medical and psychiatric care provided to the member.

- Significant co-morbid medical conditions exist and a PBH psychiatrist is needed to assess the thoroughness of the diagnostic work-up and treatment planning for the member.

- Anorexia nervosa is the admission diagnosis.

- Autism or Pervasive Development Disorder is the admission diagnosis.

- Dementia is suspected or confirmed and appears to be the basis for the psychiatric symptoms being described.

- The member’s detoxification protocol is unorthodox or it is not familiar to the care manager of clinical operations treatment, or it’s a difficult case that has first been discussed with the team leader and it has been determined that review with a PBH psychiatrist is needed.

- Inpatient care has extended, and the case has not previously been presented to a PBH psychiatrist.
in the care-management process yielded identification of the potential risks of undetected medical conditions and early intervention with older persons presenting for acute psychiatric care. Exhibit 2 summarizes the methods and results for the five years. Exhibit 3 summarizes interventions.

There was an unanticipated cost benefit associated with this study. A retrospective cost analysis for inpatient psychiatric treatment for 2000 through 2002 was conducted using the entire population of inpatient service users age 65 and older. The data showed nearly a 23 percent reduction in cost per 1,000 member years, from $5,859 in 2000 to $4,492 in 2002 for the target diagnostic categories of dementia, depression not otherwise specified (NOS), and psychotic disorder NOS. These diagnoses are determined to be the most likely diagnoses for patients with undetected delirium. The cost benefit correlates

Exhibit 2: Completion Rates for Comprehensive Medical Evaluations

<table>
<thead>
<tr>
<th>Period</th>
<th>Sample Size/Total Population</th>
<th>Sampling Method</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>115/230 Simple random sample</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>117/234 Simple random sample</td>
<td>32% Baseline to Remeasurement 1: ( \chi^2 = 6.34 ) ( P &lt; 0.025 ) †</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>161/321 Simple random sample</td>
<td>47% Remeasurement 1 to Remeasurement 2: ( \chi^2 = 6.82 ) ( P &lt; 0.01 ) † Baseline to Remeasurement 2: ( \chi^2 = 26.29 ) ( P &lt; 0.001 ) †</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>147/292 Simple random sample</td>
<td>46% Remeasurement 2 to Remeasurement 3: ( \chi^2 = 0.028 ) ( P &gt; 0.10 ) Baseline to Remeasurement 3: ( \chi^2 = 24.1 ) ( P &lt; 0.001 ) †</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>130/259 Simple random sample</td>
<td>53% Remeasurement 3 to Remeasurement 4: ( \chi^2 = 0.25 ) ( P &gt; 0.10 ) Baseline to Remeasurement 4: ( \chi^2 = 25.34 ) ( P &lt; 0.001 ) †</td>
<td></td>
</tr>
</tbody>
</table>

*This sample size is sufficient to detect a modest effect size (approximately 10%) with a 0.05 significance level with a power of 0.8.
†The distribution is significant.

Exhibit 3: Key Interventions to Improve Comprehensive Medical Evaluation

- Protocol for management of delirium and dementia for use by PBH care managers
- Medical Evaluation for All Members With Probable Delirium, desktop guide for reviewing inpatient psychiatric admissions for older adults
- Inpatient Care Manager Escalation Guide. The desktop tool directs care managers to consult with the psychiatric physician consultant when acute mental status changes suggest the possibility of delirium.
- Joint Policy on the Management of Delirium and Agitation Associated with Dementia implemented with health plan medical groups by the health plan medical management teams
- Training of all care managers in PBH procedures for identifying and managing persons with delirium
- Delirium Protocol Training with in-network general psychiatric and geropsychiatric facilities
- Orientation to Joint Policy on the Management of Delirium and Agitation Associated with Dementia for 29 health plans’ medical providers and representatives from medical groups. Materials included:
  > Guidelines for a Comprehensive Medical Evaluation of Older Adults for Probable Delirium
  > Rolodex card including the physician consultation service telephone number for consultation with a PBH psychiatric consultant
  > Training of PBH care managers on laboratory studies that should be routinely requested for older adults presenting for acute psychiatric admissions to rule out medical conditions that may be causing psychiatric symptoms
to reduced utilization. In 2002, persons 65 years and older represented 28 percent of the PBH region’s total membership, four percentage points more than in 1999, and utilized 20 percent of all psychiatric inpatient days, down from 46 percent in 1999.

Because this study was non-experimental, it is limited by the absence of case controls for any measurement, and there was no random assignment for the multiple interventions implemented by PBH. The mixing of effects may lead to the incorrect inferences about change in the rate of medical evaluations considered. However, healthcare providers are often at a disadvantage when conducting “research” in natural settings. It is not always possible or ethical to produce a true experimental, or even a quasi-experimental study design.

Discussion

A consumer-centered healthcare system models processes and directs resources to efficiently and effectively meet the needs of consumers. The result is an integrated approach to care, allowing clinicians to address the complexities of the differential diagnosis of behavioral and physical disorders in older persons. Effective interventions likely to make a difference include the adoption and implementation of clinical guidelines with the obligatory mental state examinations, steps for ruling out delirium during the initial assessment of acute mental status and behavioral changes, and training to increase clinical expertise in treatment planning for older persons.

Referenced existing research supports early identification and intervention as effective deterrents to increased morbidity and mortality. More research, advocacy, and action are needed in this area. As declared by the Institute of Medicine, healthcare is fragmented and the persons placed at greatest risk by insufficient coordination of care are those most in need of healthcare. Artificial and real divisions between healthcare disciplines and delivery systems—in particular behavioral and physical medicine—complicate diagnosis and create inefficiencies in the continuity and delivery of care that cannot be easily navigated or overcome by persons seeking care. Collaboration between MBHOs and MCOs can produce processes that ensure collaboration in the differential diagnosis and treatment planning for older persons, improving the integration of care needed to increase patient safety, reduce medical costs, and improve outcomes.

Acknowledgements

The authors wish to acknowledge PacifiCare Health Plans for its contributions to the development of a joint protocol with PacifiCare Behavioral Health for the management of older persons with delirium. Specifically, PacifiCare of Oregon and PacifiCare of Washington are recognized for providing a collaborative environment where opportunities to improve the care of older persons could be explored and pursued. Finally, the authors express gratitude to Gigi Mathew, DrPH, and Eric Hamilton, MS, for statistical analysis.

References


Jon D. Beaty, MSW, LCSW, CPHQ, is corporate manager of quality improvement for PacifiCare Behavioral Health in Hillsboro, Ore. Christy L. Beaudin, PhD, LCSW, CPHQ, is corporate director of quality improvement for PacifiCare Behavioral Health in Van Nuys, Calif.
OSTEOPOROSIS IS A DEGENERATIVE skeletal disease that increases bone fragility and is the cause of more than 1 million painful and often debilitating fractures each year. The World Health Organization defines osteoporosis as a bone mineral density (BMD) >2.5 standard deviations (SDs) below the mean peak BMD of young normal adults measured at any skeletal site. Osteopenia is defined as a BMD >1 but <2.5 SD below the mean for young normal adults. The number of standard deviations that the BMD is above or below the young normal mean is referred to as the T-score.1

Osteoporosis affects mainly post-menopausal women but also men, in either primary or secondary forms. Approximately 50 percent of Caucasian women and a lower percentage of men and non-Caucasian women will experience an osteoporotic fracture in their lifetime.2 Of the 25 million lives affected, four in five are women. Although other sites may be affected, there are three major fracture sites in osteoporosis: the hip, the vertebrae, and the distal radius. Frequently, psychological symptoms such as depression are associated with osteoporotic fractures.3 After the third to fourth decade of life, age-associated bone loss in women occurs at a rate of approximately 1 percent per year and at menopause, due to estrogen deficiency, accelerated bone loss occurs at a rate of approximately 1.5 percent to 3.9 percent per year for a period of about five years.4 Testing for BMD may be appropriate for: 1) diagnosis, to aid in treatment decisions; 2) monitoring response to therapy; or 3) evaluating the effect of concomitant medications like glucocorticoids or medical conditions such as hyperthyroidism on BMD. In addition, testing for BMD may be appropriate for postmenopausal women under age 65 who have >1 risk factors for osteoporotic fractures other than menopause, and postmenopausal women who present with fractures. Hip fractures affect more than 250,000 people in the U.S. and are associated with high morbidity and mortality rates. Approximately 20 percent of patients will die within one year of sustaining an osteoporotic hip fracture. Those who survive their injuries may require placement in a long-term care facility. By the year 2040, it is expected that the number of hip fractures in developed countries will have tripled.
Vertebral fractures total more than 500,000 in the U.S. annually, resulting in back pain and diminished quality of life due to loss of height and kyphosis. Limitations in activity such as bending and reaching are often associated with the postural and height changes seen with kyphosis. Altered thoracic and abdominal anatomy secondary to multiple thoracic fractures may result in additional morbidity.

The financial implications of osteoporotic fractures are significant and account for more than 2 million healthcare practitioner visits each year. The costs of these visits and associated treatments are projected to be in the billions of dollars. Preventive strategies, including the use of both pharmacological therapies as well as scanning devices, are increasingly recognized as important means of averting larger expenses in the future.

Risk Factors
Fracture risk is increased in those individuals with low BMD. The relative risk of vertebral fracture doubles and that of hip fracture increases by 2.5 times for each decrease of one S.D. (SD) in BMD. Numerous nonmodifiable risk factors are associated with the incidence of osteoporosis and low BMD. Some of these include a first-degree family history of osteoporosis, Caucasian or Asian race, female gender, prior vertebral fracture, advanced age, dementia, and frailty. Potentially modifiable risk factors include low body weight or low body mass index (BMI), estrogen deficiency from early menopause or a premenopausal bilateral oophorectomy, chronic corticosteroid use, prolonged bed rest, cigarette smoking, high intake of alcohol or caffeine-containing beverages, low calcium intake, high protein or phosphate intake, and inadequate physical activity.

Prevention and Treatment
There are various medications approved by the United States Food and Drug Administration (FDA) for the prevention and treatment of osteoporosis. (Exhibit 1) At this time there is no cure for osteoporosis, but there are measures that can be taken to halt its onset or slow its progression.

Bisphosphonates
Bisphosphonates provide antiresorptive therapy. They have been shown to reduce bone loss and increase BMD in both the spine and hip. Risedronate (RSN) has been shown to reduce the risk of vertebral and nonvertebral fractures. Hip fracture risk was reduced by 30 percent in a large study with hip fracture as the primary endpoint. Alendronate (ALN) has been shown to reduce the risk of vertebral and nonvertebral fractures and to reduce the risk of hip fracture by 50 percent. Significant risk reduction has been consistently
shown across treatment studies. ALN and RSN are approved for the prevention and treatment of osteoporosis in females. Only ALN has been approved for the treatment of osteoporosis in males. Both agents are approved for treating glucocorticoid-induced osteoporosis. The effect of antiresorptive therapy in reducing nonvertebral fractures in women without osteoporosis is unclear. Also, the efficacy of this therapy in children and young adults has not been evaluated.

Zoledronic acid (Zometa), is a relatively new and potent addition to the bisphosphonates. It has been approved by the FDA for use in hypercalcemia of malignancy and bone metastases associated with cancer. Recently, the role of zoledronic acid has been evaluated in treatment of bone loss associated with androgen deprivation therapy (ADT) and osteoporosis in postmenopausal women. Like other bisphosphonates, zoledronic acid slows osteoclastic activity resulting in decreased bone resorption. Zoledronic acid, however, differs from most bisphosphonates in that it is administered intravenously, every three to four weeks. This route of administration may help in avoiding gastrointestinal adverse effects associated with orally administered bisphosphonates. Accumulated data indicate that the dose of an individual bisphosphonate and the dosing interval are extremely important factors in the determination of fracture prevention efficacy. Osteoporosis studies using tiludronate were stopped due to failure to show an effect on fracture, seemingly because of a lack of proper dose range finding studies. Although the dosing of zoledronic acid for investigational indications is not clearly defined, investigators believe that it may be given every three months or even at yearly intervals. The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) clinical trial program is recruiting participants to determine the safety and effectiveness of once-yearly zoledronic acid for treating osteoporosis. This dosing schedule could be attractive to many patients who currently take oral bisphosphonates on a daily or weekly interval and could result in improved patient adherence.

Bisphosphonate Efficacy Studies

Selected findings from some of the key bisphosphonate antifracture efficacy studies are outlined in Exhibit 2. ALN was introduced to the U.S. market in 1995 and RSN in 2000. The reduction in risk of new vertebral fractures versus placebo for RSN (41 percent, p=0.003) was similar to that of ALN (47 percent, p=0.02). Caution in comparing data among studies has been recommended due to differences in study design and patient populations. For example, 16 types of nonvertebral fracture sites (hip, wrist, shoulder, arm, hand, fingers, other small wrist bones, ribs, chest/sternum, pelvis, coccyx/sacrum, leg, ankle, foot/metatarsal, toes, periprosthetic) were followed in the Fracture Intervention Trial (FIT) trial with ALN compared to six sites in two Vertebral Efficacy with Risedronate Therapy (VERT) trials thus precluding direct comparisons of total nonvertebral fractures reported. Different statistical analyses of fractures, different definitions of vertebral fracture reductions, and different endpoints such as new fracture analysis with RSN versus new and worsening fracture analysis with ALN make it difficult to assess comparability.

Alendronate

In an early major double-blind placebo-controlled multicentered study of ALN by Liberman et al., 994 postmenopausal osteoporotic women 45 to 80 years of age were studied for change in BMD. Fracture presence was not a criterion for study inclusion and only 20 percent of patients had a baseline vertebral fracture. Women were treated with either ALN 5 mg/day or 10 mg/day for three years, ALN 20 mg/day for two years followed by 5 mg/day for one year, or placebo for three years. After three years of treatment, the overall incidence of new vertebral fractures was reduced by 48 percent with ALN versus placebo (p <0.03). Although there was a demonstrated trend in benefit of ALN for prevention of nonvertebral fractures, the risk of nonvertebral fractures was not statistically different than placebo. At the 10 mg dose of ALN, lumbar BMD was increased by 8.8 percent, femoral neck BMD by 5.9 percent, and trochanter BMD by 7.8 percent. In a 24-month continuation of the same study, Favus et al. demonstrated continuation of the increased BMD effect with ALN. In a further two-year extension bringing the duration of use to seven years, ALN 10 mg daily increased BMD at the lumbar spine by 11.4 percent. The proportion of women whose spine BMD increased relative to that at month 0 was 97 percent.

The FIT research group evaluated 2,027 women 55 to 81 years of age with ≥1 vertebral fractures at baseline and a reduced BMD. Patients were randomized to receive either ALN 5 mg/day for two years followed by 10 mg/day in year three or placebo. After three years, the ALN-treated patients had a 47 percent risk reduction in vertebral fractures, a 20 percent risk reduction in nonvertebral fractures, and a 51 percent risk reduction in hip fractures. This study was stopped early by an independent safety and monitoring board due to the dramatic decrease in hip fractures among the ALN-treated patients. In another FIT study, 4,432 women with mildly low BMD (mean total hip T-score -1.6) but no vertebral fractures were randomized to receive ALN 5 mg/day for two years followed by 10 mg/day or placebo. The incidence of vertebral fracture was reduced by 44 percent.
In a multinational double-blind, placebo-controlled trial, 1,908 postmenopausal women with a lumbar BMD $\geq$ 2SDs below the postmenopausal adult mean were randomly assigned to receive either ALN 10 mg or placebo for one year. \(^{21}\) Compared to placebo at one year, mean increases in BMD were 4.9 percent at the lumbar spine, 2.4 percent at the femoral neck, and 3.6 percent at the trochanter. The incidence of non-vertebral fractures was lowered by 47 percent in just one year. In a two-year double-blind study of 241 men aged 31 to 87 years with primary osteoporosis, significant increases in BMD were demonstrated in the group treated with ALN 10 mg/day compared to a placebo-treated group.\(^{22}\) The incidence of vertebral fractures and decreases in height loss were also lower in the ALN-treated group.

To investigate whether the incidence of vertebral fractures is related to the magnitude of change in BMD with ALN therapy, Hochberg et al. enrolled 2,984 women aged 55 to 81 in a study who were already participating in the FIT trial.\(^{23}\) While participating in FIT, patients were treated with ALN 5 mg/day for two years, then 10 mg/day for the remaining 12 to 30 months of the study. After 12 months of therapy, 35 percent of study population experienced increases of $\geq$3 percent in total hip BMD, and 21 percent had either decreased total hip BMD or no change. Only 3.2 percent of women with increases of $\geq$3 percent in

<table>
<thead>
<tr>
<th>Trial/ Investigator</th>
<th>Time Frame (Months)</th>
<th>Methods</th>
<th>% $\Delta$ Lumbar Spine</th>
<th>% $\Delta$ Femoral Neck$^*$</th>
<th>% $\Delta$ Trochanter</th>
<th>$\downarrow$ Risk Vertebral Fracture</th>
<th>$\downarrow$ Risk Nonvertebral Fracture</th>
<th>$\downarrow$ Risk Other Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liberman$^{24}$</td>
<td>36</td>
<td>ALN (n=526)</td>
<td>a) 5 mg/day or 10 mg/day for 3 years b) 20 mg/day for 2 years, then 5 mg/day for 1 year PBO (n=335)</td>
<td>8.8%</td>
<td>5.9%</td>
<td>7.8%</td>
<td>48% (pooled doses) 55%;10 mg</td>
<td>NS</td>
</tr>
<tr>
<td>Favus$^{19}$</td>
<td>24</td>
<td>Same as above</td>
<td>9.4%</td>
<td>4.8%</td>
<td>9.1%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>FIT Black$^{8}$</td>
<td>36</td>
<td>ALN 10 mg/day for 2 years then 10 mg/day for year 3 (n=1,022), or PBO (n=1,005)</td>
<td>6.2%</td>
<td>4.1%</td>
<td>6.1%</td>
<td>47%</td>
<td>–</td>
<td>51% of hip fractures; 90% of multiple vertebral fracture; 48% wrist fracture</td>
</tr>
<tr>
<td>FIT Cummings$^{20}$</td>
<td>48</td>
<td>ALN 10 mg/day (n=2,218) PBO (n=2,214)</td>
<td>8.3%</td>
<td>3.8%</td>
<td>6.8%</td>
<td>44%</td>
<td>NS</td>
<td>78% of multiple vertebral fractures</td>
</tr>
<tr>
<td>FOSIT Pols$^{21}$</td>
<td>12</td>
<td>ALN 10 mg/day (n=950) PBO (n=958)</td>
<td>4.9%</td>
<td>2.4%</td>
<td>3.6%</td>
<td>No X-rays taken</td>
<td>47%</td>
<td>–</td>
</tr>
<tr>
<td>Harris$^{22}$</td>
<td>36</td>
<td>RSN 5 mg/day (n=489) or PBO (n=450)</td>
<td>4.3%</td>
<td>2.8%</td>
<td>3.9%</td>
<td>41%</td>
<td>39%</td>
<td>–</td>
</tr>
<tr>
<td>Reginster$^{23}$</td>
<td>36</td>
<td>RSN 5 mg/day or PBO</td>
<td>5.9%</td>
<td>3.1%</td>
<td>6.4%</td>
<td>49%</td>
<td>33%, p=0.063</td>
<td>–</td>
</tr>
<tr>
<td>McClung$^{7}$</td>
<td>36</td>
<td>Age 70-79 with osteoporosis: RSN 2.5 mg (n=1,812) RSN 5.0 mg (n=1,812) PBO (n=1,821)</td>
<td>2.1%</td>
<td>3.8%</td>
<td>–</td>
<td>–</td>
<td>Reported as relative risk reduction</td>
<td>Significant hip fracture risk reduction in elderly women with confirmed osteoporosis, age 70-79, but not among elderly women selected primarily on the basis of risk factors other than low BMD</td>
</tr>
<tr>
<td>Orwell$^{24}$</td>
<td>24</td>
<td>Males with osteoporosis: ALN 10 mg/day (n=146) PBO (n=95)</td>
<td>7.1%</td>
<td>2.5%</td>
<td>4.3%</td>
<td>–</td>
<td>–</td>
<td>Significantly lower incidence in ALN group</td>
</tr>
</tbody>
</table>

Note: Severity of baseline disease may have an effect on short-term outcome. Baseline hip T scores range from (-1.6) to (-4.0).

It is easier to demonstrate fracture effect at three years in patients with high immediate fracture risk based on bone density due to the larger numbers of events.

BMD (bone mineral density) ALN (alendronate) RSN (risedronate) PBO (placebo) NS (not significant) All p values statistically significant at a minimum of $\leq 0.05$
total hip BMD experienced new vertebral fractures. Fifty percent more women, whose BMD stayed the same or declined, experienced new fractures: 6.3 percent versus 3.2 percent (adjusted odds ratio of 0.45, 95 percent CI 0.27-0.72). Women with increases of ≥3 percent in BMD during the first one or two years of ALN treatment had the lowest incidence of new vertebral fractures. Among women taking ALN, those patients experiencing greater increases in BMD had a decreased risk of new vertebral fractures.

In an alternate dosing schedule of alendronate, Rizzoli et al. looked at 70 mg weekly, 35 mg biweekly, and 10 mg daily of alendronate and the effects on BMD.24 The two-year study enrolled 1,258 postmenopausal women age 42 to 95 with osteoporosis. The results showed increased BMD of the spine in the weekly, biweekly, and daily alendronate by 6.8 percent, 7.0 percent, and 7.4 percent, respectively. Increases in BMD of the hip, femoral neck, and total body were also seen. The study notes that the three treatment groups had similar rates of fractures and adverse events.

**Risedronate**

In the VERT study, a randomized, double-blind, placebo, parallel-group study, Harris et al. placed 2,458 women <85 years of age, ≥5 years postmenopausal, with ≥2 vertebral fractures or one fracture with low BMD into three treatment groups: RSN 2.5 mg/day, RSN 5 mg/day, or placebo.17 After one year the 2.5 mg/day group was discontinued by protocol amendment because of lack of efficacy. After three years of treatment, 450 patients in the placebo group and 489 in the RSN 5 mg/day were compared. Mean BMD increases at three years in the RSN group were 4.3 percent at the lumbar spine, 2.8 percent at the femoral neck, and 3.9 percent at the trochanter. The overall incidence of new vertebral fractures was reduced by 41 percent and new nonvertebral fractures by 39 percent. No difference in hip fractures between the treatment and control groups were reported.

Reginster et al. conducted a double-blind, randomized, placebo-controlled trial in 1,226 postmenopausal women ≥2 vertebral fractures. Fracture rates were compared in patients treated with either 2.5 mg/day or 5 mg/day of RSN with patients receiving placebo.18 At the end of three years, the risk of new vertebral fractures was reduced by 49 percent and new nonvertebral fractures by 33 percent, although the latter did not achieve statistical significance (p=0.063). No difference in hip fracture risk was demonstrated. Mean increases in BMD were 5.9 percent at the lumbar spine, 3.1 percent at the femoral neck, and 6.4 percent at the trochanter.

In a study of two groups of elderly women, McClung et al. evaluated 5,445 women age 70 to 79 with confirmed osteoporosis who were treated with RSN 2.5 mg (n=1,812), RSN 5 mg (n=1,812), or placebo (n=1,821) and a second group of women ≥80 years of age and >1 risk factor for hip fracture treated with RSN 2.5 mg (n=1,281), RSN 5 mg (n=1,292), or placebo (n=1,313).7 The original plan was to compare each individual dose against placebo. The analysis was modified to pool both doses of RSN compared to placebo. There was a significant reduction in the risk of hip fracture in elderly women age 70 to 79 but not among women over age 80 who were selected primarily on the basis of risk factors other than low BMD.

McClung’s findings warrant further examination.7 The reduction in the fracture rate was not observed in women who were selected based on risk factors other than low BMD. The reduction in radiographically confirmed hip fractures included both symptomatic and asymptomatic fractures. The hip fracture results included pooled data from 2.5 and 5.0 mg/day treatment groups. However, in the 70 to 79 age group, when the RSN treatment groups were looked at separately, the 2.5 mg/day treatment group showed a statistically significant increase in hip fracture risk but the 5 mg/day treatment group did not. In the study by Harris et al., the results with the 2.5 mg dose were comparable to placebo.19 Based on NHANES data, the incidence of osteoporosis is very high in women over age 80. Among the 941 older women with known low BMD (T score ≤2.5), the incidence of hip fracture was 7.2 percent with RSN vs. 9.7 percent with placebo (p=n.s.) showing no benefit with RSN therapy.

To determine the effect of risedronate on vertebral fractures in high risk patients, Watts et al. pooled data from previous studies and selected a subset of older patients with prior vertebral fractures or lower BMD.25 Risedronate 5 mg/day was found to reduce the relative risk of a vertebral fracture by 62 percent (p <0.001), and multiple new fractures by 90 percent (p <0.001) when compared to placebo at one year.

A two-year randomized, double-blind study evaluated risedronate 35 mg or 50 mg weekly versus risedronate 5 mg daily in 1,456 postmenopausal women with osteoporosis.13 Measurements at one year showed an increase in BMD of the lumbar spine by 3.9 percent, 4.2 percent, and 4.0 percent for the participants receiving 35 mg weekly, 50 mg weekly, and 5 mg daily regimens, respectively. The study concluded that once weekly regimens of risedronate provided the same safety and efficacy, as measured by gastrointestinal side effects, as daily regimens.

**Zoledronic acid**

A one-year multinational, double-blind, placebo-controlled trial investigated the optimal dosing of zoledronic acid in 351 postmenopausal women with low
BMD of the lumbar spine. Patients were randomized to one of seven regimens, which included zoledronic acid 0.25 mg, 0.5 mg, or 1 mg given every three months; zoledronic acid 2 mg at six-month intervals or a single infusion of zoledronic acid 4 mg at the beginning of the trial; or placebo. All participants received 1 gram oral calcium supplementation daily. The study measured the changes in lumbar spine, femur, forearm, and total body BMD using Dual-Energy X-ray Absorptiometry (DEXA). The results showed that the increased BMD of the lumbar spine (up to 5.1 percent) and femur (up to 3.5 percent) were significantly greater in patients receiving zoledronic acid versus placebo (p <0.001). The total body BMD and forearm also responded favorably to treatment with zoledronic acid but to a smaller degree. The results did not show a significant difference in lumbar spine BMD among the different regimens of zoledronic acid.

In a multicenter, double-blind, placebo-controlled trial, 106 men beginning androgen deprivation therapy (ADT) for nonmetastatic prostate cancer, were randomly assigned to 4 mg zoledronic acid or placebo every three months for one year. ADT reduces testosterone and estrogen and can cause bone loss, or osteoporosis. The study looked at the change in BMD of the lumbar spine, measured by DEXA, after one year of zoledronic acid therapy. The results showed a 5.6 percent increase in BMD of the lumbar spine in patients treated with zoledronic acid versus a BMD decrease of 2.2 percent in the patients receiving placebo (p <0.001).

**Gastrointestinal Side Effects of the Bisphosphonates**

The major safety concern with bisphosphonates is the irritant effect that they may have on the gastrointestinal tract and their association with pain, esophagitis, and gastritis. Details of selected analyses of gastrointestinal side effects can be found in Exhibit 3. Caution is recommended in comparing results among studies because of varying populations and co-morbidities. Of note, many controlled trials for both ALN and RSN, the adverse occurrence rates did not differ between placebo controls and treated patients. Outside of carefully controlled clinical trial environments, patients may not be compliant with instructions to take the drug with a full glass of water upon rising, to remain in the sitting or standing positions, and to avoid any food for 30 minutes. Noncompliance with recommended instructions may affect the potential for adverse effects as well as affecting bioavailability and efficacy.

As the gastrointestinal intolerance to bisphosphonates has been shown to relate in part to its exposure time to the esophageal and stomach mucosa, reducing the dosing interval from daily to biweekly or weekly may help to reduce the iatrogenic effect. In a recent study, Schnitzer et al. compared the effect of dosing of ALN 70 mg/week, 35 mg/twice weekly, and 10 mg/daily on GI side effects. The authors’ findings suggested that, consistent with earlier animal models, once weekly dosing has the potential for improved gastrointestinal tolerability. They concluded that once weekly dosing of 70 mg ALN will provide patients with a more convenient, therapeutically equivalent alternative to daily dosing, and may enhance compliance and long-term persistence with therapy.

**Hormone Replacement Therapy**

In postmenopausal women, estrogen or estrogen in combination with progestin (hormonal replacement therapy, or HRT) has been shown to reduce bone loss, and increase bone density in both the spine and hip. However, fracture benefit has not been established with HRT in a large, prospective, randomized fracture-endpoint study. In the Heart and Estrogen/progestin Replacement Study (HERS), a prospective placebo-controlled trial looking at secondary prevention of cardiovascular disease, no statistically significant reduction in hip or any other fracture was demonstrated among 2,700 women, in up to 4.1 years follow-up. In another large prospective trial, the WHI (Women’s Health Initiative) evaluated the role of HRT in primary prevention of CHD with invasive breast cancer as the primary adverse outcome. The combined HRT component of the study was terminated early due to an increased risk of invasive breast cancer. Somewhat unexpectedly, an increased risk for CHD, stroke, and pulmonary embolism was also seen. Among the benefits observed were a decreased risk of hip fractures, colorectal cancer, and endometrial cancer. HRT is FDA indicated for prevention but not for treatment of osteoporosis.

**Selective Estrogen Receptor Modulators**

Selective estrogen receptor modulators (SERMs), like raloxifene, appear to prevent bone loss at the spine, hip, and total body and are approved for preventing and treating osteoporosis in women. Unlike estrogens, SERMs do not appear to stimulate uterine or breast tissue. Raloxifene has been shown to prevent morphometric vertebral fractures, but has not demonstrated efficacy in preventing hip or other nonvertebral fractures. In a large clinical trial, raloxifene reduced the risk of vertebral fractures among women treated for 36 months by 30 to 50 percent. In the same study, by 40 months raloxifene-treated women had an increased risk of venous thromboembolism versus placebo (RR, 3.1; 95 percent CI, 1.5–6.2) and comparable to that of estrogen (RR ≈ 3) reported in observational trials.
Calcitonin
Calcitonin is a hormone involved in calcium regulation and bone metabolism. The drug compound calcitonin salmon cannot be taken orally due to its low bioavailability and is generally administered as a nasal spray daily. In a five-year double-blind randomized placebo-controlled study, at 200 IU daily, calcitonin salmon nasal spray significantly reduced the risk of new morphometric or radiographic vertebral fractures in postmenopausal women with osteoporosis by 36 percent. In the trial, a dose-response curve was not demonstrated since the reductions in vertebral fractures at the 100-IU and the 400-IU groups were not significantly different from placebo.

Lumbar spine bone mineral density increased significantly from baseline at all three dose levels, but not significantly from placebo. Risk reduction for nonvertebral fractures was not significant. Overall, only 41 percent of subjects completed the five-year trial.

Teriparatide
Teriparatide (rDNA origin) is a 34-amino acid analogue of parathyroid hormone (hPTH [1-34]) and is indicated in the treatment of osteoporosis in postmenopausal women at high risk for fractures as well as men with osteoporosis of hypogonadal or idiopathic origin. It is not currently recommended for more than two years of therapy because clinical

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**Exhibit 3: Bisphosphonate Adverse Gastrointestinal Events**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug/Dose</th>
<th>Trial Type</th>
<th>% GI Tract Events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanza53</td>
<td>ALN 40 mg/day (n=90) RSN 30 mg/day (n=89) PBO (n=36) for 21 days followed by ASA 650 mg q.i.d for last 7 days (n=36)</td>
<td>Randomized, parallel-group, double-blind PBO controlled</td>
<td>Reported as mean change ASA+PBO=2.77 ALN vs. ASA= -2.18 RSN vs. ASA= -2.34</td>
<td>Mean gastric and duodenal erosion score with ALN &amp; RSN similar to PBO and lower than ASA. P value for all three groups was &lt;0.001.</td>
</tr>
<tr>
<td>Lanza54</td>
<td>ALN 5 mg/day (n=22) ALN 10 mg/day (n=21) ASA 650 mg 4x/ day (n=14) PBO (n=22)</td>
<td>Randomized, double-blind, PBO controlled</td>
<td>ALN 5 mg=18.2 ALN 10 mg=23.8 ASA=100 PBO=18.2</td>
<td>Endoscopically confirmed. Trial 14 days. No significant difference between ALN groups and PBO.</td>
</tr>
<tr>
<td>Bauer27</td>
<td>ALN 5 mg &amp; 10/day (n=3,323) PBO (n=3,223)</td>
<td>Randomized, double-blind, PBO controlled</td>
<td>ALN =47.5 PBO=46.2</td>
<td>Follow up 3.8 yrs, no clinical differences in GI AEs or hospitalizations due to PUBs in ALN vs. PBO group.</td>
</tr>
<tr>
<td>Lowe24</td>
<td>ALN 10 mg/day</td>
<td>Randomized, double-blind, PBO controlled</td>
<td>(result numbers not in abstract)</td>
<td>Endoscopically confirmed. Trial 30 days. ALN comparable to PBO.</td>
</tr>
<tr>
<td>Watts59</td>
<td>Phase III Trials ALN 5 mg (n=202) ALN 10 mg (n=196) ALN 0 mg/5 mg (n=199) PBO (n=397)</td>
<td>Primary Phase III Trial Data and Fracture Intervention Trial</td>
<td>Phase III Trials—Overall ALN 5 mg=40.2 ALN 10 mg=42.3 ALN 20 mg/5 mg=36.6 PBO=39.0</td>
<td>In Phase III Trials, of all upper GI AEs only abdominal pain and dysphagia occurred significantly more often with ALN 10 mg than PBO (20%,10% vs. 13.9%,9.6%).</td>
</tr>
<tr>
<td>FIT</td>
<td>ALN 5 mg,10 mg (n=1,022) PBO (n=1,005)</td>
<td></td>
<td>ALN=41.3% PBO=40.1%</td>
<td></td>
</tr>
<tr>
<td>Lanza53</td>
<td>RSN 5 mg (n=255) ALN 10 mg(n=260) X 2 weeks</td>
<td>Randomized controlled</td>
<td>RSN=4.1% ALN=13.2%</td>
<td>Results of gastric ulcer occurrence reported. Difference is significant at p&lt;0.001.</td>
</tr>
<tr>
<td>Graham56</td>
<td>ALN 10 mg/daily PBO</td>
<td>Randomized, crossover</td>
<td>ALN=38% PBO=13%</td>
<td>Therapy evaluated at 7 and 14 days. Endoscopic presence of mucosal damage evaluated.</td>
</tr>
<tr>
<td>Schnitzer20</td>
<td>ALN 10 mg/day (n=370) ALN 35 mg twice/ week (n=369) ALN 70 mg/week (n=519)</td>
<td>One-year randomized blind, multi-center</td>
<td>Daily=23.5% Twice weekly=23.8% Weekly=22.4%</td>
<td>Overall similar incidence. Trend to fewer serious GI and esophageal events with weekly dosing.</td>
</tr>
<tr>
<td>Graham57</td>
<td>ALN 10 mg/day or Naproxen 500 mg twice daily or the combination of ALN 10 mg/day plus Naproxen 500 mg twice daily</td>
<td>Randomized, single center, crossover</td>
<td>ALN=8% Naproxen=12% Combination=38%</td>
<td>P&lt;0.5 for the combination vs. either drug regimen. Results conflict with large body of clinical data looking at patients treated with NSAIDS while on ALN.</td>
</tr>
</tbody>
</table>
trials have not been conducted to provide outcomes of long-term efficacy and safety. Teriparatide is a peptide that must be injected on a daily basis. Teriparatide has been shown to restore bone and increase BMD. Its actions are similar to those of endogenous PTH, regulating calcium resorption in bone, calcium, and phosphate excretion in the kidney, and intestinal calcium absorption. Teriparatide has also been shown to reduce the relative risk of vertebral and nonvertebral fractures in postmenopausal women by up to 65 percent and 47 percent respectively, as measured by radiographic assessment. Reported side effects were mild and included nausea and headache. Osteosarcoma was observed in rats treated with high doses of teriparatide, but neoplastic activity has not been observed in humans. Teriparatide use is contraindicated in pediatric patients and in the treatment of Paget's disease because these populations have an increased rate of bone turnover, and may be at higher risk of developing osteosarcomas. Because of this potentially serious association with osteosarcoma, teriparatide carries a black box warning.

**Teriparatide Efficacy Studies**

In a three-year randomized controlled trial of 34 postmenopausal women with osteoporosis, Lindsay et al. examined the effect of hPTH [1-34] on vertebral bone mass measured by DEXA. The study compared the effects of hPTH [1-34] and HRT versus HRT only, with lumbar vertebral BMD as the primary endpoint. BMD of the hip, forearm, and total body were also measured. The 17 patients randomized to take 25 mcg hPTH daily in addition to HRT showed a significant 13 percent increase in BMD of the vertebral bone, whereas the group receiving only HRT showed no increase in vertebral BMD (p <0.001). There was a small but significant increase (2.7 percent) in BMD of the hip in the hPTH treated group versus no change in the control group (p=0.05). The study also showed an increase in total body BMD increase of 7.8 percent in the hPTH treated group versus no change in the control group (p <0.002). Although a reduction in vertebral fractures was not a defined endpoint of this study, a difference was noted. Of the 13 vertebral fractures occurring during the study, 10 (77 percent) were noted in the control group (p <0.03). The authors of the study note, however, that these findings should be validated in a larger study with vertebral fractures as a defined endpoint.

In a multinational, double-blind, placebo-controlled trial, 1,637 postmenopausal women with known vertebral fractures were randomly assigned to 20 mcg or 40 mcg teriparatide, or placebo. All participants also received 400 IU Vitamin D and 1,000 mg calcium supplements daily. The primary endpoint was new radiographically diagnosed vertebral fractures. The average follow-up time was 19 months. Results indicated that teriparatide reduced the relative risk of a new vertebral and nonvertebral fracture by 65 percent and 53 percent, respectively. Teriparatide was also shown to significantly increase BMD of the lumbar spine, hip, neck, as well as total body BMD.

**Combination Therapy**

More recent studies sought to examine the potential benefits of concomitant therapy with parathyroid hormone and alendronate. A 12-month randomized, double-blind, placebo-controlled trial of 238 women with osteoporosis compared the benefits of using each agent alone daily (10 mg alendronate or 100 mcg of parathyroid hormone, PTH (1-84)) versus a daily combination of parathyroid hormone and alendronate. In contrast to the hypothesis that a combination of these agents would provide benefits superior to those produced with either agent alone, a synergistic effect between alendronate and parathyroid hormone was not evident. A second study investigated the use of alendronate, parathyroid hormone (synthetic hPTH(1-34), or a combination of these medications in men. This trial involved 83 men who were randomly assigned to alendronate 10 mg/day, parathyroid hormone 40 µg, or a combination of these treatments. Because parathyroid hormone increases bone formation, it was theorized that combining hPTH (1-34) with an antiresorptive agent would increase BMD more than either agent alone. At the conclusion of the trial, however, it appeared that alendronate may actually decrease parathyroid hormone’s beneficial effects on bone mineral density. Another study treating men and women with osteoporosis compared daily versus cyclic PTH 25 mcg with alendronate to alendronate alone in treating osteoporosis. In the interim analysis of the study of 83 patients completing nine months of therapy, PTH was shown to increase BMD and stimulate bone growth in patients already established on long-term alendronate therapy. The authors conclude that short cyclic challenges with PTH might be an efficient and economical way to use PTH in treating osteoporosis.

**Treatment of Glucocorticoid-Induced Osteoporosis**

Although it is well known that therapy with high-dose glucocorticoids can cause osteoporosis, it has recently become evident that low-dose glucocorticoids can also induce bone loss, particularly of trabecular bone. Bone loss occurs rapidly during the
first six months of glucocorticoid use, and persists thereafter at a slower rate, with overall bone loss occurring at a rate of 3 percent to 10 percent per year. Daily doses of prednisone or its equivalent as low as 5.0 mg can result in substantial bone loss and increased fracture risk. Up to one quarter of patients receiving long-term glucocorticoid therapy sustain osteoporosis fractures. Some, but not all, studies suggest that calcium supplementation alone may help to maintain bone mass in patients treated with low to medium doses of glucocorticoids. Vitamin D3 and its analogs improve calcium absorption and stabilize bone mineral density of the lumbar spine. Hormone replacement therapy may also maintain bone mineral density in postmenopausal women with glucocorticoid-induced osteoporosis. The bisphosphonates also maintain or modestly improve lumbar spine and maintain bone mass, and are the only agents that have been shown to reduce fracture rates in patients on glucocorticoid therapy. In July 2001, the American College of Rheumatology Task Force on Osteoporosis updated guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis. The Task Force recommended that all patients maintain an adequate intake of calcium (1,000 mg daily) and Vitamin D (800 IU daily). Bisphosphonates are recommended to prevent and treat bone loss in men and postmenopausal women. In hypogonadal patients for whom long-term glucocorticoid therapy (>3 months) at doses ≥5 mg/day is being initiated, HRT is recommended. It is reasonable to predict that the guidelines will be updated to reflect new findings from clinical trials, as well as information regarding new agents and combination therapies.

Several retrospective and prospective cohort studies regarding the treatment of corticosteroid-induced osteoporosis with bone-sparing agents exist, but these studies are open to more types of bias than are controlled trials. Exhibit 4 presents a number of controlled clinical trials utilizing bisphosphonates and showing good evidence for reducing bone loss in patients with glucocorticoid-induced osteoporosis. There is considerable variation in the magnitude of the effects of bisphosphonate therapy across studies and in the baseline and placebo fracture rates. Therefore, Homik and colleagues

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug/Dose</th>
<th>Control</th>
<th>Duration</th>
<th>Patient Type</th>
<th>% ∆ BMD Lumbar Spine</th>
<th>% ∆ BMD in Femoral Neck</th>
<th>% ∆ BMD in Trochanter</th>
<th>Risk Vertebral Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saag*</td>
<td>ALN 5 mg/day (n=161)</td>
<td>Ca + VitD</td>
<td>48 weeks</td>
<td>477 men and women, age 17-83</td>
<td>2.1%</td>
<td>1.2%</td>
<td>1.1%</td>
<td>Overall incidence of 2.3% in ALN-treated group and 3.7% in PBO group</td>
</tr>
<tr>
<td></td>
<td>ALN/10 mg/day (n=157)</td>
<td>PBO (n=159)</td>
<td></td>
<td></td>
<td>2.9%</td>
<td>1.0%</td>
<td>2.7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PBO (n=159)</td>
<td></td>
<td></td>
<td></td>
<td>-0.4%</td>
<td>-1.2%</td>
<td>-0.7%</td>
<td></td>
</tr>
<tr>
<td>Adachi (Extension of Saag study)</td>
<td>ALN 5 mg/day (n=68)</td>
<td>Ca + VitD</td>
<td>24 months</td>
<td>208 patients, age 21-79</td>
<td>2.84%</td>
<td>0.11%</td>
<td>2.16%</td>
<td>Overall incidence of 0.7% in ALN-treated group and 6.8% in PBO group, 90% reduction in vertebral fracture</td>
</tr>
<tr>
<td></td>
<td>ALN/10 mg/day (n=55)</td>
<td>PBO (n=61)</td>
<td></td>
<td></td>
<td>3.85%</td>
<td>0.61%</td>
<td>3.91%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PBO (n=61)</td>
<td></td>
<td></td>
<td></td>
<td>-0.77%</td>
<td>-2.93%</td>
<td>-1.21%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ALN 2.5 g/10 mg/day (n=29)</td>
<td></td>
<td></td>
<td></td>
<td>3.69%</td>
<td>-0.43%</td>
<td>1.73%</td>
<td></td>
</tr>
<tr>
<td>Cohen**</td>
<td>RSN 2.5 mg/day (n=75)</td>
<td>Ca</td>
<td>12 months</td>
<td>228 men and women, age 18-85</td>
<td>-0.1%</td>
<td>-4</td>
<td>-2%</td>
<td>Trend toward reduction in number of fractures</td>
</tr>
<tr>
<td></td>
<td>RSN 5.0 mg/day (n=74)</td>
<td>PBO (n=77)</td>
<td></td>
<td></td>
<td>0.6%</td>
<td>0.8</td>
<td>1.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PBO (n=77)</td>
<td></td>
<td></td>
<td></td>
<td>-2.8%</td>
<td>-3.1%</td>
<td>-3.1%</td>
<td></td>
</tr>
<tr>
<td>Eastell**</td>
<td>RSN 2.5 mg/day (n=43)</td>
<td></td>
<td>24 months</td>
<td>120 women</td>
<td>1.4%</td>
<td>-1.0%</td>
<td>-0.4%</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>RSN 15 mg/day for 2, then PBO daily for 10 weeks, then repeat (n=40)</td>
<td>PBO (n=40)</td>
<td>12-month no-treat follow-up*</td>
<td></td>
<td>-0.05%</td>
<td>0.9%</td>
<td>1.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PBO (n=40)</td>
<td></td>
<td></td>
<td></td>
<td>-2.3%</td>
<td>-4.0%</td>
<td>-4.0%</td>
<td></td>
</tr>
<tr>
<td>Reid**</td>
<td>RSN 2.5 mg/day (n=66)</td>
<td>Ca + VitD</td>
<td>12 months</td>
<td>290 men and women, age 18-75</td>
<td>1.9%</td>
<td>-0.2%</td>
<td>0.1%</td>
<td>Though not powered to show fracture efficacy, 70% reduction in vertebral fractures</td>
</tr>
<tr>
<td></td>
<td>RSN 5 mg/day (n=100)</td>
<td>PBO (n=95)</td>
<td></td>
<td></td>
<td>2.9%</td>
<td>1.8%</td>
<td>2.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PBO (n=95)</td>
<td></td>
<td></td>
<td></td>
<td>0.4%</td>
<td>-0.3%</td>
<td>1.0%</td>
<td></td>
</tr>
</tbody>
</table>

BMD (bone mineral density) T (treatment group) RA (rheumatoid arthritis)
Conducted a meta-analysis on the use of bisphosphonates in corticosteroid-induced osteoporosis that included studies using cyclic etidronate, pamidronate, and some but not all of the studies presented in Exhibit 4. Homik et al. concluded that bisphosphonates are effective at preventing and treating corticosteroid-induced bone loss at the lumbar spine. Bone density changes are correlated with fracture risk and bisphosphonates while demonstrating a statistically significant treatment effect on femoral BMD, the magnitude was less than that seen at the lumbar spine.

Conclusion

There is no cure for osteoporosis, but there are preventive measures that can be taken to halt its onset or slow its progression. Therapeutic options include bisphosphonates, estrogens alone or in combination with progestins, calcitonin, SERMs, and parathyroid hormone (hPTH[1-34]). Of the therapeutic options, most data on fracture risk reductions have been reported with bisphosphonates. Caution in comparing data among studies should be exercised due to differences in study design and patient populations.

Bisphosphonates provide antiresorptive therapy, which reduces bone loss and increases BMD in both the spine and hip. Although estrogen alone or in combination with progestin in postmenopausal women has been shown to reduce bone loss and increase bone density and reduce fractures in both the spine and hip without noted fracture benefit, concern has been noted with its combined use due to an increased risk of invasive breast cancer, CHD, stroke, and pulmonary embolism. Salmon calcitonin nasal spray significantly reduced the risk of new morphometric or radiographic vertebral fractures in postmenopausal women with osteoporosis. Selective estrogen receptor modulators appear to prevent bone loss at the spine, hip, and total body and are approved for preventing and treating osteoporosis in women. Unlike estrogens, SERMs do not appear to stimulate uterine or breast tissue. Raloxifene has been shown to prevent morphometric vertebral fractures, but has not demonstrated efficacy in preventing hip or other nonvertebral fractures. Teriparatide has been shown to restore bone and increase BMD. JMCM

Saira A. Jan MS, PharmD, is director of clinical programs in pharmacy management and associate professor at Rutgers State University of New Jersey. Jan is also the director of research program at Horizon Blue Cross Blue Shield of New Jersey. At Rutgers, her areas of expertise are managed care, pain management and connective tissue disorders. Alan F. Kaul, PharmD, MS, MBA, FACC, is president of Medical Outcomes Management Inc. and has more than 30 years of healthcare clinical, management and consulting experience. He holds appointments as adjunct professor of pharmacy practice at the Massachusetts College of Pharmacy and Health Sciences (Boston) and as adjunct professor of pharmacy practice at the University of Rhode Island College of Pharmacy.

Acknowledgement

The authors wish to thank Brandon Cherenzenz, PharmD candidate, for his assistance in the preparation of this manuscript.

Data Sources

A MEDLINE literature search (1966–2004) was conducted using the key words of osteoporosis, osteopenia, bisphosphonates, alendronate, risedronate, calcitonin, selective estrogen receptor modulators, raloxifene, and parathyroid hormone. Information provided by established un-based organizations such as the National Osteoporosis Foundation were also researched. Additional references were added based on the bibliographies of the articles selected for inclusion.

References


OSTEOARTHRITIS IS THE MOST prevalent chronic joint disorder worldwide and is associated with significant pain and disability. It has been estimated that OA costs approach $150 billion annually in the U.S. and affects 20 million people. The disease is two times more frequent in females than males, and it affects 70 percent of the population over age 65. This is a relentlessly progressive disease that continues to worsen with aging.

Osteoarthritis Overview
Focusing on the knee, OA is progressive deterioration of the articular cartilage of the tibiofemoral and/or patellofemoral compartments. The etiology of OA is thought to be multifactorial, with genetics being one of the driving forces. Some common contributors to OA development are trauma to the articular cartilage, poor alignment of the joint, anatomy of the patella, joint instability, meniscus tear, obesity, athletic training, and smoking. Typical symptoms of OA of the knee include diffuse activity-related pain, localized pain that may radiate up or down the leg, pain exacerbated by activity, stairs, squats, or hills, clicking, catching, grinding, grating sounds, mechanical symptoms, night pain, recurrent swelling, post inertial dyskinesia, pseudoinstability/pseudo locking of the joint.

Summary
Osteoarthritis of the knee is a common, costly disorder. The etiology is multifactorial, with genetics playing a large role. Treatment should be individualized and may include nonpharmacologic, pharmacologic, and surgical treatments or surgery to improve pain. Of the pharmacologic options, glucosamine and chondroitin supplements and hyaluronans may promote cartilage growth and possibly alter the disease process. Future research will focus on combination therapy, gene therapy, and cartilage transplants.

Key Points
• Osteoarthritis (OA) affects 20 million people in the United States.
• OA of the knee is progressive deterioration of the articular cartilage of the knee joint, which is important for optimal functioning of the knee joint.
• Significant pain results from changes in the joint. Although analgesics can help relieve the pain, they do not alter the course of the disease.
• Hyaluronans are as effective as NSAIDs for pain relief and have a longer duration of action than articular steroid injections.
• Growing evidence suggests that glucosamine, chondroitin supplements, and hyaluronans may promote cartilage growth and possibly alter the OA disease process.
source of pain is joint contracture secondary to fibrosis. Irritation of the synovium by osteophytes (bone spurs) that form can sometimes be a source of pain. Muscle spasms surrounding the joint can cause discomfort.

The evaluation of a patient with knee OA would include a history of symptoms and injuries, an examination of the knee, and radiographs. Because articular cartilage is not visible on X-ray, OA of the knee is identified on radiographs as a narrowing of the joint space.

**Articular Cartilage**

Articular cartilage covers the ends of the bones within the joint. The cartilage facilitates joint movement by providing a smooth surface, absorbs forces of impact and weight delivered to the joints, and helps maintain joint structure. Articular cartilage is composed of chondrocytes, matrix, and water. Articular cartilage is primarily water, as is the rest of the body. Chondrocytes make up about 1 to 5 percent of the tissue volume. The extra cellular matrix is 70 percent type II collagen and 30 percent proteoglycans. Under normal circumstances, articular cartilage undergoes continuous breakdown and renewal. Chondrocytes control the rate of cartilage synthesis and breakdown in part through secretion of proteolytic enzymes. Chondrocytes use amino acids, carbohydrates, and water to make glycosaminoglycans (GAGs), which are the building blocks of the matrix. Chondrocytes release GAGs, which combine with collagen fibrils to form the matrix. The predominant GAGs in cartilage are chondroitin sulfate, keratan sulfate, and hyaluronic acid. With the exception of hyaluronic acid, all GAGs bond with a core protein to form proteoglycan monomers that provide compressive strength. Collagen in the matrix provides tensile strength.

When considering treatment, it’s especially important to consider that the articular cartilage has no blood, nerve, or lymphatic supply. Its nutrition comes either from the subchondral bone or from the synovial fluid.

With aging, the matrix experiences an increase in water, a decrease in the quality of the proteoglycans, smaller aggrecan molecules, a decrease in collagen content, and a conversion from type II to type I (scar) cartilage. Numerous changes occur that ultimately result in a decrease in articular cartilage strength, increased stiffness, and increased nitric oxide, an oxidating agent. Nitric oxide leads to cell death, or apoptosis of the chondrocyte. Metalloproteinases, which basically destroy articular cartilage, also increase with aging. With the onset of OA, hyaluronic acid—a component that gives the joint fluid elasticity and compression qualities—tends to be smaller and produced in smaller quantities, and works less efficiently. The aging process, unfortunately, means that synovial fluid is less effective because of alterations in hyaluronic acid function and production. Aging also decreases the ability of chondrocytes to maintain and restore articular cartilage and, thereby, increases the risk of degeneration of the articular cartilage surface.

**Treatment of Osteoarthritis**

The two major objectives of treatment are to decrease pain and attempt to delay the progression of osteoarthritis. The management of osteoarthritic pain involves nonpharmacologic, pharmacologic, and surgical modes of therapy.

**Nonpharmacologic Therapy**

The American College of Rheumatology (ACR) guidelines recommend patient and family education, support groups, weight loss, physical therapy, exercise, and occupational therapy.

Helping overweight patients with knee OA lose weight will improve pain and may prevent progression of the disease. Assistive devices, such as heel wedges and neoprene sleeves to correct abnormal biomechanics of the knee joint, may also be used.

**Pharmacologic Treatment**

Oral pharmacologic options for pain management include acetaminophen, nonsteroidal anti-inflammatory agents (NSAIDs), and cyclooxygenase type 2 (COX-2) inhibitors (see Exhibit 2). Acetaminophen (Tylenol) is recommended as first line therapy for mild to moderate pain. Over the counter NSAIDs and topical analgesic creams are also options. The ACR guidelines recommend COX-2 inhibitors and prescription NSAIDs for moderate to severe pain. Because of the adverse effects associated with these agents, many clinicians are avoiding their long-term use. Short courses are used during flare-ups.

Corticosteroid injections are also used for acute flare-ups. Although the role of corticosteroid injections in OA is not well defined, many times these agents are used to decrease inflammation in a joint so that the patient can move better and be able to fully participate in and benefit from physical therapy.

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**Exhibit 1: Changes in Articular Cartilage**

**Microscopic**

- Chondrocytes
  - Increase cell activity
  - Decrease beta-1 integrin expression
- Matrix
  - Increase water content
  - Decrease PG content
  - Decrease collagen content/quality
Hyaluronan Injections

Because of the many significant systemic adverse effects of analgesics and the fact that they only control pain and do not alter the course of the disease, many clinicians have begun using intra-articular hyaluronan injections earlier in the course of the OA disease process. The ACR guidelines also recommend early considerations of these agents. When initially approved, these agents were primarily used for patients who had failed other forms of therapy.

Five hyaluronan injection products are available in the U.S. (see Exhibit 3). The products differ in size of the hyaluronan and origin. Four products are extracted from rooster combs. The fifth, Euflexxa®, is different in that it’s bioengineered through bacteria fermentation, thereby avoiding patient exposure to proteins from an animal source. These agents are FDA approved for the treatment of pain in OA of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics (e.g., acetaminophen).

Hyaluronan has many action mechanisms (see Exhibits 4 and 5). There is laboratory evidence that hyaluronan injections may stimulate synovial membrane cells to make more hyaluronan and aggrecan, which, theoretically, may be reversing osteoarthritis. Hyaluronan injections also have been shown to have disease-modifying activity. This stems from 1) the complex biochemical effects of hyaluronans in the synovium and extracellular matrix of the articular cartilage, including interactions between exogenously administered hyaluronans and articular cartilage, subchondral bone, matrix proteoglycans, and collagens; 2) the effects of hyaluronan administration in animal models of OA, including total or partial meniscectomy and anterior cruciate ligament transection; and 3) results of clinical trials using one product, Hyalgan (sodium hyaluronate, molecular weight 500-730 kDa) that evaluated structural outcomes, such as joint-space width, chondrocyte density and vitality, and arthroscopic evaluation of chondropathy. Growing evidence supports the notion that, in addition to relieving the symptoms of OA, hyaluronans also modify the structure of the diseased joint and the rate of OA disease progression, at least early in the evolution of the disease process. Viscosupplementation does not appear to be very effective when used late in the disease process.

Modawal and colleagues conducted a meta analysis of 11 trials of hyaluronan injections or derivatives. Their conclusion was that intra-articular viscosupplementation with hyaluronan injections was moderately effective in relieving knee pain in patients with osteoarthritis for up to 10 weeks after the last injection but not at 15 to 22 weeks.

A Cochrane analysis published in 2005 found that at 5 to 13 weeks post-injection there was an 11 to 54 percent improvement in pain and a 9 to 15 percent improvement in function. This analysis concluded that viscosupplementation is an effective treatment for OA of the knee with beneficial effects on pain, function and patient global assessment, and at different post-injection
Pharmacoeconomics of Hyaluronans

Torrance and colleagues evaluated the cost effectiveness and cost utility of hyaluronan injections using data from a one-year double-blind trial conducted in Canada. Pharmacoeconomic analyses in U.S. dollars have not been published. Over the year, the hyaluronan treatment group had higher costs ($2,125 to $1,415 = CAN$710, $0.05), more patients improved (69 percent to 40 percent = 29 percent, $0.0001), and increased quality-adjusted life years (QALYs) (0.071, $0.05). The incremental cost-effectiveness ratio was $2,505/patient improved. The incremental cost-utility ratio was $10,000/QALY gained. The authors stated that their results provide strong evidence for adoption of hyaluronan treatment in Canada in the patients and settings similar to those studied in the trial.

Supplements

The supplements glucosamine and chondroitin sulfate have some clinical evidence to support their use in altering the course of OA. Both are building blocks of articular cartilage. Both also appear to have some anti-inflammatory activity. Although not all patients appear to gain benefit, many do and are able to decrease their dosage of analgesics. The adverse effects of these agents tend to be minor gastrointestinal reactions. Based on other studies that looked at joint space narrowing over time, the combination of these two supplements appears to slow the progression of joint space narrowing, periods, but especially at the 5–13-week post-injection period. It should be noted that the magnitude of the clinical effect is different for different products, comparisons, time points, variables, and trial designs. However, there are few randomized head-to-head comparisons of different viscosupplements, and conclusions regarding the relative value of different products cannot be made.

In general, hyaluronan injection has comparable efficacy against NSAIDs and longer-term benefits when compared against intra-articular corticosteroids. Few significant adverse events are reported with hyaluronans. The majority of adverse effects are local reactions at the injection site. There is a potential for allergic reactions with the rooster-derived products in patients with avian allergies.

Whether this is the disease slowing or a rebuilding of articular cartilage is unknown at this time.

Conclusion

Pain is a significant part of the OA disease process. Current therapy aims to reduce pain and alter the progression of the disease. Analgesics, which have many adverse effects, improve pain. Hyaluronan injections and glucosamine and chondroitin supplements appear to reduce pain and improve the disease process.

Robert Dimoff, MD, is medical director of sports medicine at The Cleveland Clinic Foundation and director of the Primary Care Sports Medicine Fellowship. He is associate professor of Orthopedic Surgery at the Cleveland Clinic Lerner College of Medicine at Case Western Reserve University, assistant clinical professor of Family Practice at Case Western Reserve University and associate professor or Family Practice at the Ohio State University.

References

Heart failure (HF) is a significant national problem, in terms of morbidity, mortality, and costs. Today, a number of beta-blockers are being used to improve symptoms, reduce remodeling, reduce hospitalization, reduce sudden death, and improve HF survival rates. Three agents have been extensively studied and shown to be effective in treating HF. These include metoprolol succinate extended release (Toprol-XL®), bisoprolol (Zebeta®), and carvedilol (Coreg®). Although beta-blockers are currently underused in HF treatment, increasing appropriate use should improve clinical outcomes and reduce costs.

Key Points
- Beta-blockers are underused in HF, especially in the elderly.
- Three agents (bisoprolol, stain-release metoprolol succinate, and carvedilol) have proven effects on reducing morbidity and mortality related to HF.
- Based on current data, all beta-blockers do not appear to be effective for HF.
- Improved use of beta-blockers would reduce costs related to HF.

HEART FAILURE IS A SIGNIFICANT problem, with 5 million people affected in the United States. The incidence of HF in the U.S. has doubled in the last decade. The prevalence is particularly high in people over 65 years of age, with 6 percent to 10 percent having some degree of heart failure. It accounts for about 6.5 million hospital days a year and 300,000 deaths per year. Heart failure also causes two thirds of all cardiovascular disease deaths. Eighty percent of men and 70 percent of women who have heart failure under the age of 85 will die within eight years. Heart failure accounts for $30 billion in annual costs.

Overview of Heart Failure
Fifty percent of patients with HF have hypertension as a contributing factor. In addition to hypertension, smoking, obesity, diabetes, and lipid disorders contribute to the development of left ventricular hypertrophy or myocardial infarctions, which both lead to HF. Numerous factors aggravate HF (see Exhibit 1), while Exhibit 2 illustrates the pathologic progression from an insult to the myocardium to the development of HF, arrhythmias, and, ultimately, death. The American College of Cardiology/American Heart Association (ACC/AHA) has characterized symptoms, clinical characteristics, and treatment for the evolutionary stages of heart failure (see Exhibit 3). In this example, the A and B groups are asymptomatic, while the C and D groups are symptomatic. Group A is at risk of HF. Group B has heart disease with left ventricular dysfunction but does not yet exhibit symptoms. Group C is the typical heart failure group, exhibiting symptoms as well as structural heart disease or a history of symptomatic HF. Group D has severe refractory HF.

Although evidence-based guidelines for HF have existed for several years, there is still variation in
actual heart failure management. A study of 2,000 patients with heart failure found that 23 to 79 percent of eligible HF patients had standard therapy with an angiotension converting enzyme inhibitor (ACE-I) prescribed. A similar trend was seen in terms of counseling on salt intake. Other studies have shown that only 30 percent of post-MI patients with HF actually receive beta-blocker therapy.

In general, the treatment objectives in HF are to

- increase survival
- decrease morbidity
- increase exercise capacity
- increase quality of life
- decrease neurohormonal changes
- decrease progression of CHF

All HF patients should have risk factors controlled, lifestyle changes, treatment for underlying causes, and standard medications. As noted in Exhibit 3, standard medications include ACE inhibitors and beta-blockers as tolerated. Additional agents that may be used include diuretics, digoxin, aldosterone inhibition, vasodilators, and angiotension receptor blockers. For patients with severe disease, other therapies that may be used include revascularization, implantable cardiac defibrillator, ventricular resyncronization, ventricular assist devices, heart transplant, and artificial heart.
Beta-Blocker Under-Use

Although beta-blocker use after a heart attack is one of the most scientifically substantiated, cost-effective medical services, they are substantially underused, especially in the elderly. A beta-blocker used after a heart attack decreases cardiovascular mortality and reinfarctions by 20 to 40 percent. Beta-blocker under-use leads to excess two-year mortality and re-hospitalization for cardiovascular disease.

In a survey of New Jersey Medicare beneficiaries, only 21 percent received beta-blocker therapy post-MI. Calcium channel blockers were used almost three times more often than beta-blockers despite a lack of efficacy evidence. The use of a calcium channel blocker instead of a beta-blocker doubled the risk of death. Patients on beta-blockers were re-hospitalized 22 percent less often and had 43 percent lower mortality.

Efficacy of Beta-Blockers in Heart Failure

In HF, beta-blockers improve symptoms, reduce remodeling, reduce hospitalization, reduce sudden death, and improve survival. Not all beta-blockers are effective for, or have been studied for, HF. Three agents have been extensively studied and shown to be effective in treating HF. These include metoprolol extended release (Toprol-XL®), bisoprolol (Zebeta®), and carvedilol (Coreg®). As noted in the ACC/AHA guidelines, positive findings with these three agents, however, should not be considered indicative of a beta-blocker class effect, as shown by the lack of effectiveness of bucindolol and the lesser effectiveness of short-acting metoprolol in clinical trials.

Data from landmark beta-blocker studies in HF appear in Exhibits 4-7. The U.S. Carvedilol Heart Failure Trials Program study showed a 65 percent reduction in death for patients with class I and class II heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS-II) and Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) trials showed a 34 percent reduction in all-cause death with bisoprolol and metoprolol therapy in patients with class II-III heart failure. Data from Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS), with a 35 percent mortality reduction, extended this benefit to class IV patients treated with carvedilol who do not require intravenous diuretics or positive inotropes.

Metoprolol extended release, bisoprolol, and carvedilol are indicated for symptomatic heart failure, asymptomatic ventricular dysfunction (left ventricular ejection fraction [LVEF] < 35 to 40 percent) and recent or remote MI regardless of LVEF. Patients who have Stage C HF should be treated with one of these three beta-blockers. The relative efficacy among these three agents is not known, but available evidence does suggest that beta-blockers can differ in their effects on survival. In the COMET trial, carvedilol (target dose 25 mg twice daily) was compared with immediate-release metoprolol tartrate (target dose 50 mg twice daily). In that trial, carvedilol was associated with a significantly reduced mortality rate compared with metoprolol tartrate.

Although both the dose and the formulation of metoprolol (metoprolol tartrate) used in the above-referenced trial are commonly prescribed by physicians for the treatment of HF, they were neither the dose nor the formulation used in the controlled trials that show that sustained-release metoprolol (metoprolol succinate) reduces the risk of death. To date, there are no published head-to-head comparisons with any of the three preferred agents.
Beta-blockers should be prescribed to all patients with stable HF due to reduced LVEF unless they have a contraindication to their use or have been shown to be unable to tolerate treatment with these drugs. Because of the favorable effects of beta-blockers on survival and disease progression, treatment with a beta-blocker should be initiated as soon as LV dysfunction is diagnosed. Even when symptoms are mild or have responded to other therapies, beta-blocker therapy is important and should not be delayed until symptoms return or disease progression is documented during treatment with other drugs. Therefore, even if patients do not benefit symptomatically because they have little disability, they should receive treatment with a beta-blocker to reduce the risk of disease progression, future clinical deterioration, and sudden death.

Cost Effectiveness of Beta-Blockers
Several studies have examined the cost effectiveness of beta-blocker therapy in HF. Two of these analyzed data from two carvedilol studies, COPERNICUS and U.S. Carvedilol Heart Failure Trials Program. One estimated an 11.1 percent reduction in healthcare costs in favor of carvedilol. The
Exhibit 7: β-Adrenergic Blockers

COPERNICUS

 surviving NYHA III-IV n=2,289

Exhibit 8: AHRQ Study–Cost of Beta-Blockers in CHF

Major Finding: Decision model indicates that Medicare costs would decrease if the use of beta-blockers were more widespread for patients with heart failure.

Estimated cost for Medicare to treat heart failure per-person over a five-year period

<table>
<thead>
<tr>
<th></th>
<th>No beta blocker</th>
<th>with beta blocker</th>
<th>savings of $6,000 per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient</td>
<td>$37,294</td>
<td>$29,697</td>
<td></td>
</tr>
<tr>
<td>Outpatient</td>
<td>$12,817</td>
<td>$14,000</td>
<td>$1,183</td>
</tr>
<tr>
<td>Medication</td>
<td>$2,888</td>
<td>$5,343</td>
<td>$2,455</td>
</tr>
<tr>
<td>TOTAL</td>
<td>$52,999</td>
<td>$49,040</td>
<td>$3,959</td>
</tr>
</tbody>
</table>


Exhibit 9: Cost Savings With Beta-Blocker

<table>
<thead>
<tr>
<th></th>
<th>No BB</th>
<th>+BB</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient</td>
<td>$37,294</td>
<td>$29,697</td>
<td>-$7,597</td>
</tr>
<tr>
<td>Outpatient</td>
<td>$12,817</td>
<td>$14,000</td>
<td>$1,183</td>
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<tr>
<td>Medication</td>
<td>$2,888</td>
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<td>$2,455</td>
</tr>
<tr>
<td>TOTAL</td>
<td>$52,999</td>
<td>$49,040</td>
<td>-$3,959</td>
</tr>
</tbody>
</table>

Total societal costs over five years
cost effectiveness of carvedilol for HF compared favorably to that of other generally accepted medical interventions, even under conservative assumptions regarding the duration of therapeutic benefit.

In a retrospective cohort study based on claims and medical chart data, carvedilol use in HF resulted in a significant economic reduction in the overall expenditures by approximately $14,530. Hospital expenditures were approximately $9,000 lower for the carvedilol group than for the control group. Carvedilol-treated patients had less frequent hospital admissions and shorter lengths of stay compared with patients not receiving carvedilol.

In a cost analysis by Cowper and colleagues, beta-blocker therapy increased survival in HF patients by 0.3 years per patient and reduced societal costs by $3,959 per patient over five years (see Exhibit 8).20 Medicare costs declined by $6,064 per patient, due primarily to lower hospitalization rates (see Exhibit 9).20

Hospitalization contributes between 60 and 75 percent of the total expenses related to HF. The addition of β-blockers to conventional HF therapy results in a significant reduction in hospitalization. Beta-blocker therapy in heart failure is cost-effective and compares favorably to that of other generally accepted medical interventions.

Conclusion

Long-term treatment with beta-blockers can lessen the symptoms of HF, improve the clinical status of patients, and enhance patients’ overall sense of well being. Like ACE-IIs, beta-blockers can reduce the risk of death and the combined risk of death or hospitalization. These benefits are seen in patients with or without coronary artery disease and in patients with or without diabetes mellitus, as well as in female and black patients. The favorable effects of beta-blockers are also observed in patients already taking ACE-IIs, which suggests that a combined blockade of the two neurohormonal systems can produce additive effects.

Jay Johnson, MD, FACC, is a board-certified cardiologist and currently a staff attending physician at Stanford University. He also serves as chief medical officer to WorldDoc Inc., an online consumer education and decision support service based in Las Vegas.

References

HIGHLIGHTS

Keynote Presentations
The Future of Managed Care and Healthcare Delivery
Peter Kongstedt, MD, Partner, Health & Life Sciences, Accenture

Managed Care and Disease Management: Challenges and Opportunities
Tom Morrow, MD, President, NAMCP

General Sessions
Provider Preparation for Pay for Performance
Managed Medicare 2006: Implications for Providers
Consumer Driven Health Plans
New Trends in Health Plan Medical Management

Concurrent Track Sessions (Business Track)
Advanced Managed Care Contracting
Clinical Integration: Step-by-Step
Legal Issues Affecting Managed Care
Clinical Integration Panel Discussion
The Changed Nature of Physician/Hospital Relationships
Provider Contracting and Conflict Theory
Creating the Value You Need to Succeed With a Hospitalist Program (B2)

Concurrent Track Sessions (Clinical Track)
Post MI Left Ventricle Disorder
Managed Care’s Concern with the Treatment of Multiple Sclerosis
Changing Treatment Paradigms
New Treatment in Bladder Control
Current Issues in HIV Treatment and the Implications for Managed Care
Chronic Inflammatory Disease

Who Should Attend
Attendees include Vice Presidents and Directors of Managed Care, Contracting and Provider Relations Managers, Medical Directors, Hospital and Health System Chief Executive Officers, Senior Management Teams, and Governing Board Members of Managed Care Organizations, and Integrated Delivery Systems such as Physician Hospital Organizations and Independent Practice Associations. Also, Executive Directors, Administrators, Case Managers, Utilization Managers, Quality Managers, Medical Management Directors and Clinical Managers associated with a variety of Managed Care Organizations.

Accommodations
The Spring Managed Care Forum will be held at Loews Coronado Bay Resort, located at 4000 Coronado Bay Road, Coronado, California 92118. To make your hotel reservations, please call 800-815-6397 prior to April 2, 2006. A special conference rate of $185 per night has been secured. To reserve this rate, mention the Spring Managed Care Forum.

For more information or to register go to www.namcp.org or call 804.527.1905.
Save 20% off your registration fee when you register by April 15, 2006 using Value Code JM0306. Hurry, offer expires April 15, 2006. *Limit 1 per person (group discounts available). Registration required. May not be combined with any other offer. You MUST enter your Value Code JM0306 when registering to receive your 20% discount.
At Teva Neuroscience, our inspiration to achieve comes from knowing we help people who live with neurological diseases.

We first made that happen in multiple sclerosis (MS), and today we are expanding our reach with a vision to be the North American leader in neurology through the quality of our people, our products, and our focus on the patient. Each has a critical role, but the patient is at the center of everything we do.

We are committed – through our own research and by supporting other organizations – to continue to improve treatment for MS and other neurological diseases with the ultimate goal of finding a cure.
A LOT HAS CHANGED SINCE THE FIRST biopharmaceutical—recombinant human insulin—was approved by the FDA in 1982. Approximately 175 biotechnology products are currently marketed.1 Around 33 products are making their way through the filing process for FDA approval. Another 426 products are in phase I, II, or III trials. All of these products are targeting more than 200 diseases including cancer, Alzheimer’s, cardiovascular diseases, multiple sclerosis, HIV/AIDS, and arthritis. The rate of growth of biotechnology product approvals has skyrocketed in the last decade (see Exhibit 1).

Growth of Biotech Companies
As shown in Exhibit 2, biotechnology company revenues grew by 17 percent and personnel increased 5 percent between 2003 and 2004. Despite revenue growth, the companies continue to lose money overall. Ninety percent of biotech companies are surviving on venture capital, do not yet have a single product on the market, and are working hard to move products through preclinical discovery and chemistry to clinical investigation and then through FDA approval.

One of biotechnology’s greatest strengths is its breadth of coverage. Biotechnology companies focus on health, food and agriculture, and industrial and environmental applications. Within the healthcare-focused portion of biotechnology, many technologies are at work; see Exhibit 3. Relative to food and agriculture, companies are working on genetically modified foods and animals and a whole slate of issues that are designed to improve food supply. Industrial and environmental applications of biotechnology include renewable bio-fuels.

Products in Development
Seventy-eight vaccines for cancer are currently under development,2 including dendritic, antigen-specific, and polyvalent vaccines. Antigen-specific vaccines dominate the research, representing 63 of the vaccines now in the pipeline. Of these vaccines, 18 percent are in Phase II trials; 14 cancer vaccines are in Phase III development, including five for melanoma, two for pancreatic cancer,
three for non-Hodgkin’s lymphoma, two for prostate cancer, and two for breast cancer. Given that approximately 50 percent of products in Phase III development eventually gain FDA approval, it is likely that seven of these vaccines will make it to market.

In addition to vaccines, there are monoclonal antibodies and antisense oligonucleotides under development for breast cancer (see Exhibit 4). Beyond a curative treatment, the future in breast health needs to be focused on chemo-prevention, advances in diagnosis, and the potential role of complementary and alternative medicine. Several studies are evaluating alternatives to surgery and chemoprevention.

A large number of products are under development for prostate cancer (see Exhibit 4). One is a gene therapy agent. Because of serious adverse effects in some of the early trials with gene-altering agents, this type of research is proceeding quite slowly. Looking toward the end of this decade and moving into the next, there likely will be more focus on gene therapies because of expanding knowledge about the genetic basis of disease. In the arena of prostate cancer research, an immediate goal is to determine whether widespread prostate specific antigen (PSA) screening is effective in the reduction of prostate cancer morbidity and mortality, so as to establish effective guidelines and begin implementing them worldwide. A second priority is to develop effective treatments for metastatic, hormone-refractory disease.

As with prostate and breast cancer, a tremendous number of products are under development for lung cancer (see Exhibit 4). Beyond the possibility of these products, an immediate goal for improving survival rates for lung cancer is the design and implementation of national screening programs for early detection of disease. Equally as important is the need to reduce tobacco consumption through effective educational programs. Smoking cessation, together with experimental chemo-preventive strategies, perhaps represent the most promising areas for meaningful immediate impact in this particular disease area.

In addition to the many products under development...
for diabetes mellitus (see Exhibit 4), inhaled insulin was recently approved by the FDA. Exubera, an inhaled powder form of recombinant human insulin (rDNA) for the treatment of adult patients with type 1 and type 2 diabetes, is the first new insulin delivery option introduced since the discovery of insulin in the 1920s. Exubera delivers short-acting insulin via an inhaler. The safety and efficacy of Exubera have been studied in approximately 2,500 adult patients with type 1 and type 2 diabetes. In clinical studies, Exubera reached peak insulin concentration more quickly than regular insulin administered by an injection. Peak insulin levels were achieved at 49 minutes (range 30 to 90 minutes) with Exubera inhaled insulin, compared to 105 minutes (range 60 to 240 minutes) with regular insulin, respectively. In type 1 diabetes, inhaled insulin may be added to longer-acting insulins as a replacement for short-acting insulin taken with meals. In type 2 diabetes, inhaled insulin may be used alone, with oral therapy, or with longer-acting insulins. In addition to hypoglycemia, other side effects associated with Exubera therapy seen in clinical trials included cough, shortness of breath, sore throat, and dry mouth. The FDA recommends that patients have lung function tested before beginning treatment and every six to 12 months while treatment continues.

In the nearer term, the development of oral and additional inhaled forms of insulin will significantly improve the quality of life for insulin-requiring patients. New targets based on the insulin-signaling cascade are being studied, and preliminary results may have implications for the development of new therapies for diabetes. The importance of improved, patient-friendly treatment for diabetes cannot be stressed enough, given that tight control of blood glucose levels is essential for avoiding the often-devastating complications of the disease.

Autoimmune disorders, including rheumatoid arthritis and lupus, are another active area of biotechnology research. Many of the agents in various stages of development are listed in Exhibit 4. Promising future treatments for rheumatoid arthritis include gene therapy and cytokine antagonists, as well as various combination therapies. Considerable research still needs to take place in determining the causes of autoimmune diseases. It is hoped that future developments will help prevent these devastating diseases and also be able to reverse the damage already wrought in patients.

Turning to infectious diseases, two areas of significant research are hepatitis C and HIV/AIDS (see Exhibit 4). Interferons, monoclonal antibodies, immunoglobulins, and therapeutic vaccines are all under development for hepatitis C. In addition to other products, exciting but slow work is transpiring on a vaccine for HIV.

Another topical issue is the avian influenza vaccine. Because of the potential for an avian influenza pandemic, many companies in multiple countries are working to develop an effective vaccine in as timely a manner as possible.

**Controversial Issues**

A great unanswered question in biotechnology involves what to do about biologic products reaching the end of patent. This year, there will be about a dozen major biopharmaceuticals coming off patent, affecting $10 billion worth of product, including several of the most lucrative biopharmaceuticals.

Copies of biologic agents have been referred to by many names: follow-on protein products (FOPP), post-patent biologics, follow-on biologics, biogenerics, generic biologics, and biosimilars. The latter term is most common in the European Union. For this article, the term follow-on biologics will be used.

The 1984 enactment of the Drug Price Competition and Patent Term Restoration Act, popularly known as the Waxman-Hatch Act, established the process of an abbreviated new drug application (ANDA) for generic versions of all chemical drugs approved after 1962. Manufacturers need only to provide manufacturing process data to show bioequivalence to the branded drug. No comparable legislation governing biopharmaceuticals has yet been enacted. While consumer groups and purchasers clamor for cheaper biopharmaceuticals, and biotech companies fiercely guard their hard-won expertise, patents, production processes, and clinical know-how, regulation remains unsettled. Laws governing follow-ons are changing, but not as fast as the science, which is as convoluted as a folded protein.

The difficulty in approving follow-on biologics is that most biologics are not well characterized. The exact structure is not known, so it is difficult to copy, unlike more traditional drug molecules that are easy to duplicate through chemistry. The major production issues with follow-on biologics is characterizing the protein and being able to duplicate the production process. The production process is 90 percent of the
### Breast Cancer

<table>
<thead>
<tr>
<th>Type of Product</th>
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<tbody>
<tr>
<td>Monoclonal antibodies</td>
<td>• Bevacizumab (Genentech) – phase III</td>
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<tr>
<td></td>
<td>• Adocetumabum (Micromet) – phase II</td>
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<tr>
<td></td>
<td>• Ipilimumab (Medarex) – phase II</td>
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<td></td>
<td>• Pertuzumab (Genentech) – phase II</td>
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<td>Immunotherapeutic vaccines</td>
<td>• IGN-101 (Igenon) – phase III</td>
</tr>
<tr>
<td></td>
<td>• Theratope (Biomira) – phase III</td>
</tr>
<tr>
<td></td>
<td>• GrnRH Pharmaccine (Apton) – phase II</td>
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<tr>
<td>Antisense oligonucleotides</td>
<td>• GTI-2040 (NCI) – phase II</td>
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### Prostate Cancer

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<td>• CG-1940/CG-8711 (Cell Genesys) – phase III</td>
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<td>• DCVraxProstate (Northwest Biotherapeutics) – phase II</td>
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<td>• Globo H-KLH Vaccine (Sloan Kettering Institute) – phase II</td>
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<td>• Ipilimumab (BMS/Medarex) – phase II</td>
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### Lung Cancer

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<td>• Cetuximab (ImClone) – phase II</td>
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<td>• Desoxysome vaccine (Ansysys) – phase II</td>
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<td>• EGF Vaccine (Center of Molecular Immunology) – phase II</td>
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<td>• EP-2101 (Epimmune) – phase II</td>
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<td>• L-BLP-25 (Biomira) – phase II</td>
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<td></td>
<td>• MVA-Muc1-IL-2 (Transgene) – phase II</td>
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### Diabetes

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<td>Insulin</td>
<td>• Inhaled (Jelly; Novo Nordisk; Aventis/Pfizer; others) – phase III</td>
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<td></td>
<td>• Oral (Genelex; Emsphere) – phase II (US)</td>
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<td></td>
<td>• Intranasal (Bentley Pharmaceutical) – phase I</td>
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<td>Growth Factors</td>
<td>• Mecasermin rinfabate (Insmed) – phase II</td>
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<td>• TH-9507 (Theratechnologies) – phase II</td>
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<td>Plant-derived compounds</td>
<td>• LL-2113AD (Lupin) – phase II</td>
</tr>
<tr>
<td>Regenerative therapies</td>
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### Rheumatoid Arthritis

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<td>Monoclonal antibodies</td>
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<td>• Rituximab (Roche/Genentech) – phase III</td>
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<td></td>
<td>• Certolizumab pegol (UCB/Nektar) – phase III</td>
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<tr>
<td>Cytokine inhibitors</td>
<td>• AD-452 (Arakira) – phase II</td>
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<td></td>
<td>• AMG-162 (Amgen) – phase II</td>
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<td></td>
<td>• IL-1 cytokine trap (Regeneron) – phase II</td>
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<td>Chemokine antagonists</td>
<td>• INCB-003284 (IncYte) – phase II</td>
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<tr>
<td></td>
<td>• MLN-1202 (Millennium Pharmaceuticals) – phase II</td>
</tr>
</tbody>
</table>
intellectual property related to the product. How this debate will be resolved is unknown. Savings related to follow-on biologics also are unknown but are unlikely to be of the same magnitude as traditional generics. In fact, because of costs related to manufacturing biologics, the savings may be quite small.

Other hot-button issues in the biotechnology industry are cloning, stem cell research, patient access to biologics, post-marketing surveillance, and safety issues. Each issue requires more public education on the value of biotechnology, including stem cells, cloning, and genetically modified plants and animals, as well as food animals that are now being cloned. The withdrawal of the multiple sclerosis drug natalizumab (Tysabri) last year because of fatal adverse effects in patients receiving the agent highlights the importance of post-marketing surveillance with biopharmaceuticals.

Conclusion

Biotechnology is improving therapies through better delivery systems, better diagnostics, safer and more effective medicines, more patient access, and enhanced therapeutic options for physicians and patients. In coming years, much potential exists for more effective, more targeted, even more individualized medical treatments that can cure or at least slow or halt disease progression. It also will be easier to determine in advance which patients will actually benefit. The 21st century is poised to be the biomedical century.

Debra Weintraub, PharmD, MPA, FAPhA, is president and founder of Veracis LLC, a clinical pharmacy and business strategy consultant to the pharmaceutical industry. Weintraub previously worked in hospital and retail pharmacy practice and was the pharmacy director at Suburban Hospital in Bethesda, Md.

References


Exhibit 4: Biotechnologies Under Development (continued)

**Lupus**

<table>
<thead>
<tr>
<th>Type of Product</th>
<th>Name/Manufacturer/Clinical Trial Phase</th>
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<tbody>
<tr>
<td>Cytokine modulators</td>
<td>IFN-alpha kinase (NeoVacs) – phase I</td>
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<td></td>
<td>Tocilizumab (Roche) – phase I</td>
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<tr>
<td>B cell targets</td>
<td>Epratuzumab (Immunomedics) – phase III</td>
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<td>Belimumab (Human Genome Sciences) – phase II</td>
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<td>Lupus nephritis</td>
<td>Abetimus sodium (La Jolla Pharm.) – NDA filed</td>
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<td>Rituximab (Roche) – phase II</td>
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**Hepatitis C**

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<td>Interferon beta-1a (Serono) – phase III</td>
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<td>Interferons</td>
<td>Interferon gamma-1b (InterMune) – phase II</td>
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<td>Interferon omega (Intarcia) – phase II</td>
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<td>Monoclonal antibodies</td>
<td>XTL-002 (XTL Biopharm.) – phase II</td>
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<td>InnoVax C (Innogenetics) – phase II</td>
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**HIV/AIDS**

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<tr>
<td></td>
<td>2G12 (Polymun) – phase I/II</td>
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<td>B1-201 (BioInvent) – phase I/II</td>
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<td></td>
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<tr>
<td>Cytokines</td>
<td>Aldesleukin (NIAID) – phase III</td>
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<td></td>
<td>Adargileukin (Bayer) – phase I/II</td>
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<td></td>
<td>Human leukocyte interferon alpha (HemispherRx) – phase II/III</td>
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<tr>
<td>Vaccines</td>
<td>ALVAC HIV vaccine (sanofi-aventis) – phase III</td>
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<td></td>
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<td></td>
<td>Tat Toxoid (NeoVacs) – phase II</td>
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<td>Ad5 HIV-1 (Merck) – phase II</td>
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<tr>
<td></td>
<td>IR-103 (Immune Response Corp.) – phase II</td>
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</table>
NEW INDICATION: PSORIATIC ARTHRITIS

Tuberculosis (TB), invasive fungal and other opportunistic infections have been observed in patients receiving HUMIRA. Some infections have been fatal. Anti-TB treatment of patients with latent TB infection reduces the risk of reactivation in patients receiving HUMIRA. However, active TB has developed in patients receiving HUMIRA whose screening for latent TB infection was negative. Patients should be evaluated for latent TB with a tuberculin skin test. Treatment of latent TB should be initiated prior to therapy with HUMIRA. Physicians should monitor patients receiving HUMIRA for signs and symptoms of active TB including patients who are TB skin test negative.

Important Safety Information

Tuberculosis (TB), invasive fungal and other opportunistic infections have been observed in patients receiving HUMIRA. Some infections have been fatal. Anti-TB treatment of patients with latent TB infection reduces the risk of reactivation in patients receiving HUMIRA. However, active TB has developed in patients receiving HUMIRA whose screening for latent TB infection was negative. Patients should be evaluated for latent TB with a tuberculin skin test. Treatment of latent TB should be initiated prior to therapy with HUMIRA. Physicians should monitor patients receiving HUMIRA for signs and symptoms of active TB including patients who are TB skin test negative.

Serious infections and sepsis, including fatalities, have been reported with the use of TNF-blocking agents, including HUMIRA. Many of these infections occurred in patients predisposed to infections because of concomitant immunosuppressive therapy in addition to their underlying disease. Patients who develop a new infection while using HUMIRA should be monitored closely. Treatment should be discontinued if a patient develops a serious infection. Do not start HUMIRA in patients with active infection (including chronic or localized), or allergy to HUMIRA or its components. Exercise caution in patients with a history of recurrent infection or with underlying conditions, which may predispose patients to infections or patients who have resided in regions where TB and histoplasmosis are endemic.

The combination of HUMIRA and anakinra is not recommended. TNF-blocking agents, including HUMIRA, have been associated in rare cases with new onset or exacerbation of demyelinating disease. Exercise caution when considering HUMIRA for patients with these disorders. More cases of malignancies have been observed among patients receiving TNF blockers, including HUMIRA, compared to control patients in clinical trials. These malignancies, other than lymphoma and non-melanoma skin cancer, were similar in type and number to what would be expected in the general population. In the controlled and open-label portions of HUMIRA clinical trials, there was an approximately four fold higher rate of lymphoma than expected in the general population. The potential role of TNF-blocking therapy in the development of malignancies is not known.

Anaphylaxis has been reported rarely following HUMIRA administration. Rare reports of pancytopenia including aplastic anemia have been reported with TNF-blocking agents. Medically significant cytopenia (e.g. thrombocytopenia, leukopenia) has been infrequently reported with HUMIRA. The causal relationship of these reports to HUMIRA remains unclear. Worsening congestive heart failure (CHF) has been observed with TNF-blocking agents, including HUMIRA, and new onset CHF has been reported with TNF-blocking agents.

Most frequent adverse events vs placebo from rheumatoid arthritis placebo-controlled studies were injection site reactions (20% vs 14%), upper respiratory infection (17% vs 13%), injection site pain (12% vs 12%), headache (12% vs 9%), rash (15% vs 6%), and sinusitis (11% vs 8%). Discontinuations due to adverse events were 7% for HUMIRA vs 4% for placebo.

The safety profile for patients with psoriatic arthritis treated with HUMIRA was similar to the safety profile seen in patients with rheumatoid arthritis.
HUMIRA® (adalimumab)

WARNING
RISK OF INFECTIONS
TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE Fungal INFECTIONS, and OTHER OPPORTUNISTIC INFECTIONS have been observed in patients receiving HUMIRA. Some of these infections have been fatal. (See WARNINGS). ANTI-TUBERCULOSIS TREATMENT of PATIENTS WITH LATENT TUBERCULOSIS INFECTION REDUCES THE RISK OF REACTIONS IN PATIENTS RECEIVING TREATMENT WITH HUMIRA. LATENT TUBERCULOSIS INFECTION has been observed in patients receiving HUMIRA whose screening for LATENT TUBERCULOSIS INFECTION was NEGATIVE.

PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION WITH A TUBERCULIN SKIN TEST. TREATMENT OF LATENT TUBERCULOSIS INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH HUMIRA. PHYSICIANS SHOULD MONITOR PATIENTS RECEIVING HUMIRA FOR SIGNS AND SYMPTOMS OF ACTIVE TUBERCULOSIS, INCLUDING PATIENTS WHO ARE TUBERCULIN SKIN TEST NEGATIVE.

INDICATIONS AND USAGE
HUMIRA is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. HUMIRA can be used alone or in combination with MTX or other DMARDs.

HUMIRA is indicated for reducing signs and symptoms of active arthritis in patients with psoriatic arthritis. HUMIRA can be used alone or in combination with DMARDs.

CONTRAINDICATIONS
HUMIRA should not be administered to patients with known hypersensitivity to HUMIRA or any of its components.

WARNINGS
SERIOUS INFECTIONS
SERIOUS INFECTIONS, SEPSIS, TUBERCULOSIS AND RARE CASES OF OPPORTUNISTIC INFECTIONS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF TNF BLOCKING AGENTS INCLUDING HUMIRA. MANY OF THE SERIOUS INFECTIONS HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR RHEUMATOID ARTHRITIS, COULD PRE- DISPOSE THEM TO INFECTION.

TREATMENT WITH HUMIRA SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS INCLUDING CHRONIC OR LOCALIZED INFECTIONS. PATIENTS WHO DEVELOP A NEW INFECTION WHILE UNDERGOING TREATMENT WITH HUMIRA SHOULD BE MONITORED CLOSER. ADMINISTRATION OF HUMIRA SHOULD BE SUSPENDED IN PATIENTS WHO DEVELOPS A SERIOUS INFECTION. PHYSICIANS SHOULD EXERCISE CAUTION WHEN CONSIDERING THE USE OF HUMIRA IN PATIENTS WITH A HISTORY OF RECURRENT INFECTION OR UNDERLYING CONDITIONS WHICH MAY PREPONE THEM TO INFECTIONS, OR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE TUBERCULOSIS AND HISTOPLASMOSIS ARE ENDEMIC (see PRECAUTIONS, Tuberculosis and ADVERSE REACTIONS, Infections). THE BENEFITS AND RISKS OF HUMIRA TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF HUMIRA THERAPY.

Use with Anakinra
Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent, with no added benefit. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from combination of anakinra and other TNF blocking agents. Therefore, the combination of HUMIRA and anakinra is not recommended (see PRECAUTIONS, Drug Interactions).

Neurologic Events
Use of TNF blocking agents, including HUMIRA, has been associated with rare cases of new onset or exaggerated neurologic abnormalities. Many of these cases have involved patients with pre-existing neurologic abnormalities. It is not known if these events are causally related to HUMIRA treatment. Increased mortality has been observed in patients with severe neurologic conditions treated with TNF inhibitors. Patients should be monitored for signs and symptoms suggestive of neurologic disorders. Discontinuation of HUMIRA therapy should be considered in patients with confirmed significant hemato logic abnormalities.

Malignancies
In the controlled portions of clinical trials of some TNF blocking agents, including HUMIRA, more cases of malignancies have been observed among patients receiving those TNF blockers compared to control patients. During the controlled portions of HUMIRA trials in patients with moderately to severely active RA, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.4, 1.3) 1/100 patient-years among 1922 HUMIRA-treated patients versus a rate of 0.4 (0.1, 1.2) 1/100 patient-years among 947 control patients (median duration of treatment of 5.6 months for HUMIRA-R treated patients and 5.2 months for control-treated patients). The size of the control group and limited number of patients receiving HUMIRA limits the ability to draw inferences from these trials. In a meta-analysis of 84 patients with rheumatoid arthritis treated with HUMIRA, there was no evidence of increased risk of developing malignancies compared to control patients. Because of the lack of direct comparative data, patients who develop malignancies should be followed closely and the relationship of the malignancy to treatment with HUMIRA should be assessed. The role of TNF blockers in the development of malignancies is not yet known.

In the controlled portions of clinical trials of all of the TNF blocking agents, more cases of lymphoma have been observed among patients receiving TNF blockers compared to control patients. In controlled trials in patients with rheumatoid arthritis, 2 lymphomas were observed among 1922 HUMIRA-treated patients versus 1 among 947 control patients. In combination the controlled and uncontrolled open-label portions of these clinical trials, the rate of lymphoma per patient-years of therapy, the observed rate of lymphomas is approximately 0.15/100 patient-years. This is approximately 4-fold higher than expected in the general population. Rates in clinical trials for HUMIRA remain lower than rates observed in a broader patient population. Patients with rheumatoid arthritis, particularly those with highly active disease, are at a higher risk for the development of lymphoma.

Hypersensitivity Reactions
In postmarketing experience, anaphylaxis has been reported rarely following HUMIRA administration. If anaphylactic or other serious allergic reaction occurs, administration of HUMIRA should be discontinued immediately and appropriate therapy instituted. In clinical trials of HUMIRA, allergic reactions overall (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specific drug reaction, urticaria) have been reported in approximately 1% of patients.

Hematologic Events
Rare reports of pancytopenia including aplastic anaemia have been reported with TNF blocking agents, especially anakinra (an interleukin-1 antagonist). In severe refractory cases, 1 TNF-blocking agent has been reported to be more effective than the other TNF-blocking agent (see PRECAUTIONS, Drug Interactions). The causal relationship of these reports to HUMIRA remains unclear. Other TNF-blocking agents should be avoided to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g. persistent fever, bruising, bleeding, pallor) while on HUMIRA. Discontinuation of HUMIRA therapy should be considered in patients with confirmed significant hematologic abnormalities.

PRECAUTIONS
Information to Patients
The first injection should be performed under the supervision of a qualified health care professional. If a patient or caregiver is to administer HUMIRA, he/she should be instructed in injection techniques and their ability to inject subcutaneously should be assessed to ensure the proper administration of HUMIRA (see HOW SUPPLIED/ PATIENT INFORMATION LEAFLET).

Before initiation of therapy with HUMIRA, patients should be evaluated for active or latent tuberculosis using a tuberculin skin test. If latent infection is diagnosed, appropriate prophylaxis in accordance with the Centers for Disease Control and Prevention guidelines should be instituted. Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur.

Patients with Heart Failure
Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. Cases of worsening CHF have also been observed with HUMIRA. HUMIRA has not been formally studied in patients with CHF; however, in clinical trials of another TNF blocker, a higher rate of serious CHF-related adverse events was observed. Physicians should exercise caution when using HUMIRA in patients who have heart failure and monitor them carefully.

Immunosuppression
The possibility exists for TNF blocking agents, including HUMIRA, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a meta-analysis of 84 patients with rheumatoid arthritis treated with HUMIRA, there was no evidence of increased risk of developing type-1 diabetes and type-1 diabetes-like clinical presentation), invasive fungal infections, and other opportunistic infections, including malignancies. Because animal reproduction and developmental studies have not been conducted with HUMIRA, there is no information on the effects of HUMIRA on the development and course of malignancies, as well as active and/or chronic infections in non-human primates (Ames) assay, respectively. The safety and efficacy of HUMIRA in patients with immunosuppression have not been evaluated.

Immunizations
No data are available on the effects of vaccination in patients receiving HUMIRA. Live vaccines should not be given concurrently with HUMIRA. Data are available on the secondary transmission of infection by live vaccines in patients receiving HUMIRA.

Autoimmunity
Treatment with HUMIRA may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with HUMIRA, treatment should be discontinued (see ADVERSE REACTIONS, Autoantibodies).

Drug Interactions
Methotrexate
HUMIRA has been studied in rheumatoid arthritis patients taking concomitant MTX (see CLINICAL PHARMACOLOGY: Drug Interactions). The data do not suggest the need for dose adjustment of either HUMIRA or MTX.

Anaemia
Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocking agent has been associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to these medicinal products alone. Therefore, the combination of anakinra and another TNF-blocking agent, including HUMIRA, may also result in similar toxicities (see WARNINGS, SERIOUS INFECTIONS).

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Long-term animal studies of HUMIRA have not been conducted to evaluate the carcinogenic potential or its effect on fertility. No clastogenic or mutagenic effects of HUMIRA were observed in the mouse micronucleus test or the Salmonella-Escherichia coli (Ames) assay, respectively.

Pregnancy
Pregnancy Category B - An embryo-fetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at doses up to 100 mg/kg (266 times human AUC when given 40 mg subcutaneous with MTX every week or 373 times human AUC when given 40 mg subcutaneous without MTX) and there was no evidence of harm to the fetus due to adalimumumab. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, HUMIRA should be used during pregnancy only if clearly needed.

Pregnancy Registry: To monitor outcomes of pregnant women exposed to HUMIRA, a pregnancy registry has been established. Physicians are encouraged to register patients by calling 1.877.311.8972

Nursing Mothers
HUMIRA should not be administered during breastfeeding. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions, HUMIRA should be discontinued immediately and appropriate therapy instituted. In clinical trials of HUMIRA, allergic reactions overall (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specific drug reaction, urticaria) have been reported in approximately 1% of patients.
Infections

In placebo-controlled rheumatoid arthritis trials, the rate of infection was 1 per patient-year in the HUMIRA-treated patients and 0.9 per patient-year in the placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, bronchitis and urinary tract infections. Most patients continued on HUMIRA after the infection resolved. The incidence of serious infections was 0.04 per patient-year in HUMIRA-treated patients and 0.02 per patient-year in placebo-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis (see WARNINGS).

In completed and ongoing global clinical studies that include over 13,000 patients, the overall rate of tuberculosis is approximately 0.26 per 100 patient-years. In over 4,500 patients in the US and Canada, the rate is approximately 0.07 per 100 patient-years. These studies include reports of myelitis, lymphocytic, as well as pulmonary tuberculosis. Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect reactivation of latent disease. Cases of opportunistic infections have also been reported in these clinical trials at an overall rate of approximately 0.075/100 patient-years. Some cases of opportunistic infections and tuberculosis have been fatal (see WARNINGS). In postmarketing experience, infections have been observed in association with viral, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving HUMIRA alone or in combination with immunosuppressive agents.

Malignancies

More cases of malignancy have been observed in HUMIRA-treated patients compared to control-treated patients in clinical trials (see WARNINGS).

Autoantibodies

In the rheumatoid arthritis controlled trials, 12% of patients treated with HUMIRA and 7% of placebo-treated patients had negative baseline ANA titers developed positive titers at week 24. Two patients out of 381 treated with HUMIRA developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with HUMIRA on the development of autoimmune diseases is unknown.

Immunogenicity

Patients in Studies I, II, and III were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1,062) of adult rheumatoid arthritis patients receiving HUMIRA developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing in vitro. Patients treated with concomitant MTX had a lower rate of antibody development than patients on HUMIRA monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse events was observed. With monotherapy, patients receiving every other week dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg every other week as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of HUMIRA is unknown.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

The data described below reflect exposure to HUMIRA in 2,486 patients, including 2,073 exposed for 6 months, 1,497 exposed for greater than one year and 1,380 in adequate and well-controlled studies (Studies I, II, III, and IV). HUMIRA was studied primarily in placebo-controlled trials and in long-term follow-up studies of up to 18 months duration. The population had a mean age of 54 years, 77% were female, 91% were Caucasian and had moderately to severely active rheumatoid arthritis. Most patients received 40 mg HUMIRA every other week.

Table 8 summarizes events reported at a rate of at least 5% in patients treated with HUMIRA 40 mg every other week compared to placebo and with an incidence higher than placebo. Adverse event rates in patients treated with HUMIRA 40 mg weekly were similar to rates in patients treated with HUMIRA 40 mg every other week. In Study III, the types and frequencies of adverse events in the second year open-label extension were similar to those observed in the one-year double-blind portion.
MULTIPLE SCLEROSIS (MS) IS AN inflammatory and neurodegenerative autoimmune disorder of the central nervous system (CNS), and the most common disabling neurologic disease of young adults, with a lifetime risk of 1 in 400. The peak age of onset for MS is the third decade of life, with most cases striking between ages 15 and 45. Like many other autoimmune diseases, women with MS outnumber men by a ratio greater than 2:1. One of the more puzzling aspects of MS is the increase in prevalence with distance from the equator, which is noted in both hemispheres and similar in Europe and the U.S. There are between 8,500 and 10,000 new cases of MS diagnosed in the U.S. each year, and the disease affects a total of approximately 350,000 people.

Overview of MS
The clinical diagnosis of the disease is based on demonstrating the dissemination of lesions in the CNS in time and space (i.e., the occurrence of a second clinical episode at a different site in the CNS). Although the cause of MS is unknown, studies support a complex interaction of environmental and genetic factors. There are four MS subtypes:

- Relapsing-remitting MS (RRMS)
- Secondary progressive MS (SPMS)
- Primary progressive MS (PPMS)
- Progressive-relapsing MS (PRMS)

The majority of MS patients (approximately 85 percent) initially present with RRMS, characterized by clearly defined episodes of neurologic disturbance...
(also known as attack or relapse) with full recovery, or with sequelae and residual deficit upon recovery. RRMS is not classified as a progressive form of MS, but residual deficits can be established with each exacerbation. At least 50 percent of patients with RRMS will transition into SPMS, characterized by disease progression with or without occasional relapses, minor remissions, and plateaus. Approximately 10 percent of the MS population present with a disease progression from onset, with occasional plateaus and temporary improvements (PPMS). The least common form, PRMS, is a progressive disease from onset with acute relapses, with or without full recovery, and with periods between relapses characterized by continuous progression. Although the course of the disease is variable, the average patient experiences two exacerbations (of about two to three weeks’ duration) every three years.

Simplistically, MS is an imbalance between inflammatory (e.g., tumor necrosis factor [TNF], interleukin 12 [IL-12], interferon gamma [IFNg]) and anti-inflammatory (e.g., interleukin 4 [IL-4], interleukin 10 [IL-10], transforming growth factor beta [TGFb]) cytokines in the body (Exhibit 1). When inflammation is severe, damage goes beyond demyelination. Axonal degeneration occurs, which leads to permanent loss of axonal function. The cumulative loss of axons is the probable cause of permanent and progressive neurological dysfunction and disability with MS.

Normal CNS axons are surrounded by an insulating myelin sheath that speeds the conduction of action potentials that carry a signal from one neuron to another. During the relapse phase of RRMS, activation of the immune system results in migration of T-cells and macrophages, as well as increased amounts of tumor necrosis factor, nitric oxide, and antemyelin antibodies within the CNS. The macrophages and inflammatory cytokines act together to destroy myelin. As the myelin sheath is damaged, conduction velocity within the axon decreases, and severe damage can lead to nerve conduction block. Remodeling of the demyelinated axon membrane is hypothesized to increase the number of sodium channels in the remission phase of RRMS, resulting in improved conduction of action potentials. Remission may also result from remyelination.

In patients with MS, damage to white matter occurs throughout the CNS, often near ventricular zones, which results in a broad spectrum of signs and symptoms. During a relapse, a patient will suddenly get much worse along one or more functional dimensions for a few weeks to a few months. Fatigue is the most common symptom reported by 75 to 90 percent of persons with MS. Fifty to 60 percent of patients report fatigue as the worst symptom of their disease. Up to 80 percent of MS patients suffer from pain syndromes, such as extremity dysesthesia, back pain, leg spasms, or abdominal pain. Other common signs or symptoms associated with MS are spasticity, bladder and bowel dysfunction, sexual dysfunction, and optic neuritis.

Depression is another serious issue for MS patients. Forty to 50 percent of MS patients will experience significant clinical depression at some point in time. Furthermore, MS patients are seven times more likely than the general population to commit suicide. Depression is a side effect of several medications used in the management of MS or its symptoms, particularly glucocorticoids, interferon (IFN) beta, and benzodiazepines.

The natural history of MS is that the majority of patients will exhibit a progressive neurologic deterioration. Approximately 90 percent of MS patients will transition to a progressive form of the disease 25 years from the time of diagnosis, and can be characterized as having substantial clinical disability. The timing of accrued disability is strongly influenced by the number of exacerbations during the early phases of

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Exhibit 1: Immune Imbalance in MS

<table>
<thead>
<tr>
<th>Normal</th>
<th>MS</th>
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</thead>
<tbody>
<tr>
<td>( \text{TH}_1 )</td>
<td>( \text{TH}_1 )</td>
</tr>
<tr>
<td>Inflammatory IFN( \gamma ), IL-12, TNF</td>
<td>Anti-inflammatory IL-4, IL-10, TGF( \beta )</td>
</tr>
<tr>
<td>( \text{TH}_2 )</td>
<td>( \text{TH}_2 )</td>
</tr>
<tr>
<td>Anti-inflammatory IL-4, IL-10, TGF( \beta )</td>
<td>Inflammatory IFN( \gamma ), IL-12, TNF</td>
</tr>
</tbody>
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the disease.\textsuperscript{20} Irreversible deficits can be established with each exacerbation. Consequently, MS treatment should be initiated at the earliest possible time to prevent disability.\textsuperscript{1}

Disability related to MS is most commonly assessed using the Kurtzke Expanded Disability Status Scale (EDSS) (see Exhibit 2).\textsuperscript{22} A standard neurologic exam is used to evaluate functional abnormalities involving several systems: pyramidal, cerebellar, brain stem, sensory, bladder and bowel, visual, and mental. For example, an EDSS score of 4.0 to 4.5 means disability is moderate. The patient can only walk 330 to 550 yards without assistance or rest.\textsuperscript{22}

**Treatment of MS**

The therapeutic approaches to the various forms of MS have changed dramatically over the past decade, and various disease-modifying therapies have successfully been introduced and established.\textsuperscript{23-25} Five agents are FDA approved for treating RRMS: subcutaneous IFN beta-1b, Betaseron\textsuperscript{®}; intramuscular IFN beta-1a, Avonex\textsuperscript{®}; subcutaneous IFN beta-1a, Rebif\textsuperscript{®}; glatiramer acetate, Copaxone\textsuperscript{®}; and mitoxantrone, Novantrone\textsuperscript{®}.\textsuperscript{25-29} Mitoxantrone is reserved for severe MS because of its cumulative cardiac toxicity.

**Interferon Beta**

Interferon (IFN) beta currently is recommended by the American Academy of Neurology guidelines for the management of patients with relapsing-remitting MS, relapsing forms of secondary progressive MS, and in patients at high risk of developing clinically definite MS.\textsuperscript{25} Its precise mechanism of action, however, remains unclear. Nevertheless, several biological activities have been described such as inhibitory effects on the proliferation of leukocytes and antigen presentation, the modulation of cytokine production, and the potential to inhibit T-cell migration across the blood-brain barrier by down-regulating the expression of adhesion molecules and inhibiting the activity of T-cell matrix metalloproteinases.\textsuperscript{30-33}

Although not curative, interferon beta appears to reduce the frequency of relapses and produces a beneficial effect on several magnetic resonance imaging (MRI) measures of disease activity.\textsuperscript{33} Immunomodulators, such as interferon beta, appear to be of little use once axonal degeneration has reached a critical threshold and clinical progression of the disorder is established.\textsuperscript{33} Decisions to initiate interferon beta therapy in clinical practice, however, must be tempered by an understanding that the magnitude of the reported clinical benefits of interferon beta is modest. The rate of neurologic attacks and disease severity measures used as outcomes in clinical trials has an uncertain relationship with long-term disability outcome. Some patients will experience notable adverse effects to therapy, and some patients with MS (even without specific therapy) may have a relatively benign disease course.\textsuperscript{33} Although many patients subjectively report

![Exhibit 2: Progression to Disability—EDSS\textsuperscript{22}](image)
improvement in various manifestations following initiation of interferon beta therapy, the drug is ineffective in the treatment of some common symptoms of MS (e.g., bladder dysfunction, spasticity, fatigue), for which other pharmacologic agents (e.g., antispasmodic agents, skeletal muscle relaxants) generally are indicated.33

There currently are two types of recombinant interferon beta commercially available in the U.S., interferon beta-1a and interferon beta-1b. Important differences in beneficial effects (clinical, MRI measures of response) between these different types of interferon beta have not been reported.33

The optimal preparation, dosage, and route of administration of interferon beta for the management of MS has not been determined. In addition, interferon beta preparations and other disease-modifying agents (e.g., glatiramer acetate, mitoxantrone) have not been compared in well-designed, controlled studies.

IFN beta therapy often causes side effects, such as flu-like symptoms, injection site reactions, and laboratory abnormalities, such as elevation in liver function tests or lymphopenia.26–28 However, these side effects are generally mild and tend to disappear within the first months of treatment. The adverse effects frequently can cause patients to discontinue therapy. Several switch studies have demonstrated effectiveness of glatiramer acetate if side effects or inadequate response have caused a patient to discontinue interferons.

Glatiramer Acetate
Glatiramer acetate, a mixture of synthetic polypeptides composed of random sequences of the amino acids L-alanine, L-glutamine, L-lysine and L-tyrosine, inhibits the binding of some myelin proteins to the major histocompatibility complex.24 Its immunological mechanisms of action are not completely understood, and some differ from those known for IFN beta. Glatiramer acetate reduces the rate of exacerbation and improves mean disability scale scores in patients with RRMS.35–40 Exacerbation rate is decreased approximately 30 percent in patients with mild relapsing-remitting disease. The number of CNS lesions decreases with treatment, and there is a tendency for the disease to progress in fewer patients with relapsing-remitting disease who receive glatiramer acetate than in placebo recipients. Mean disability status scores improve with treatment and deteriorate without it.41 In patients with secondary progressive multiple sclerosis, the rate of disease progression was reduced, but not significantly, by treatment with glatiramer acetate compared with placebo; however, further trials with larger patient numbers may be warranted.41

Potential limitations to glatiramer use are 1) the number of patients with relapsing-remitting disease progression is not significantly different between active and placebo treatment groups at 30 months, six years, and eight years; 2) reactive antibodies to glatiramer acetate form in most patients receiving long-term therapy; the effect on efficacy is unclear; and 3) efficacy still has to be established in patients

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**Exhibit 3: MS Treatment Steps**

Patient meets diagnostic criteria for RRMS

**STEP 1**
- Glatiramer acetate

**STEP 2**
- Interferon #1 or mitoxantrone

**STEP 3**
- Consider other options or check for NABs if interferon was used in step 1 or step 2 and was given at a low dosage

- No NABs present

- NABs present

**STEP 4**
- Interferon #2

**OR**

- If treatment fails or patient is intolerant

- STEP 1 Interferon #1

**STEP 2**
- Glatiramer acetate or mitoxantrone

**STEP 4**
- Evaluate NAB titer and consider other treatment options
with secondary progressive multiple sclerosis.\textsuperscript{41}

Glatiramer acetate, which is injected, is well tolerated. Local injection site reactions are the most common adverse effect and are usually mild. A transient benign systemic reaction occurs in some patients; the influenza-like symptoms commonly associated with IFN-beta treatment have not been reported.\textsuperscript{29}

**Comparison of Agents**

There have been no direct comparisons of glatiramer, interferon-\textbeta-1a, and interferon-\textbeta-1b. Direct comparisons of these drugs in well-designed trials are obviously necessary before conclusions may be drawn about their relative advantages and disadvantages. The potential advantages of combining these agents need to be evaluated. Glatiramer acetate and interferon-\textbeta-1b, both of which cause immunomodulatory changes in T helper-1 cell lines, have been studied in combination in one study. Their action was found to be additive.\textsuperscript{42}

Based on available evidence, any of the three agents could be chosen for initial therapy for RRMS. If the initial choice fails, then one of the other agents can be selected. A treatment algorithm for MS is presented in Exhibit 3.\textsuperscript{43}

**Future Agents**

Thirty-six percent of agents in late-stage development are for MS.\textsuperscript{44} A significant number of these agents are targeted toward altering the immune system response and are injectable agents that will be expensive.

**Disease Management of MS**

The cost of treating MS, particularly since the development of immunomodulators, is significant. In the United States, the annual per-patient cost of MS has been estimated at $34,000, with a total lifetime per-patient cost of $2.2 million; a conservative estimate of the national annual cost is $6.8 billion.\textsuperscript{45} The annual cost for immunomodulators for MS is $2 billion.

As more biological agents become available for treating MS, managed care organizations (MCOs) are applying various strategies to control costs and improve outcomes in their MS populations. Some of these possible strategies include

- appropriateness of therapy
- cost sharing
- formulary management
- reimbursement management
- disease management/outcome improvement.

When managing any disease category, one of the first goals is to determine whether therapy is appropriate for a given patient. Cost sharing by increasing co-pays or through tiered co-pays is one way to manage the costs, but it will not change the outcome and may worsen it. Formulary management is tied into cost sharing, but it too will not change the clinical outcome. Reimbursement management decreases the reimbursement for different products, but does not change the outcome. A disease management program involves more than just drug maximization (i.e., appropriate therapy, adherence, compliance). A true disease management program targets various issues to improve clinical outcomes with the result of reducing acute care costs (e.g., hospitalizations) significantly more than the increased cost of medications when patients comply with appropriate therapy.

One method that may both improve outcomes and manage costs of MS is the use of specialty pharmacy providers for biologic agents. Distribution of biologics through a specialty pharmacy may seem unrelated to disease management, but a specialty pharmacy may actually be the best site of care for disease management because of the way it operates.

Use of a specialty pharmacy by an MCO can assist physician providers by helping them avoid the many administrative and legal issues related to obtaining and stocking medications within a physician’s office. These include ordering, up-front costs, collection of co-pay or co-insurance, insurance billing, and legal storage and handling requirements.

In addition to reducing workload issues related to biologics, specialty pharmacies have other significant advantages (see Exhibit 4). One of the most important roles specialty pharmacies perform is to communicate by phone with the patient every month. At its essence, disease management is good personal communication between two parties. Specialty pharmacy companies routinely call each patient every month to check in before sending a refrigerated, expensive medication through the mail.

Beyond offering a communication system, other advantages of specialty pharmacies include a ready distribution system and the ability to bill both pharmacy and medical benefit portions of a health plan. Forty to 60 percent of specialty pharmacy charges are paid through the medical claim system, not pharmacy benefits.\textsuperscript{46}

**Exhibit 4: MS Disease Management–Most Efficient Site**

**Specialty Pharmacies**

- Dispensing site for much of the medication
- Already knowledgeable
- Monthly calls to patients
- Integration of medical and pharmacy benefits
- Ability to collect/track data over time
- Differentiation opportunity
Specialty pharmacies address the reasons for noncompliance and achieve savings for the payer by helping to avoid the consequences of noncompliance. For one MCO, the mean unit cost in 2002 of a “low-intensity” MS relapse, which could result in physician office visits and symptom-related medications, was $243 per patient. Adherence rates for injectable MS medications achieved by one specialty pharmacy were reported to be 98 percent for Avonex® and Rebiq®. Adherence rates for Copaxone® and Betaseron®, the other two common MS therapies, were around 95 percent.

Disease Management Process

The initial step in building a disease management program for MS is to identify and assess the plan’s MS population (see Exhibit 5). Interventions to alter the disease outcomes can then be developed and implemented. The components of a disease management program for MS include drug management (adherence and compliance to the medication, safety, tolerability), tracking of patient outcomes including relapses and disease progression, data analysis, and outcome improvement (see Exhibit 6).

The major reasons MS patients stop taking medications are intolerable side effects and a perceived lack of treatment efficacy. An estimated 20 percent of

![Exhibit 5: Disease Management Process](image-url)

**Exhibit 6: Component of MS Disease Management**

- **Monitoring/Documenting:**
  - Adherence
  - Relapses
  - Disease Progression
  - Safety/Tolerability
  - EDSS

- **Interventions:**
  - Co-morbid condition(s)
  - Symptom management assistance

- **Data Analysis**

- **Outcome Improvement**

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**Exhibit 7: Suboptimal Treatment Response Lack of Efficacy**

- **Clinical Event**
  - Increase in severity and/or number of relapses
  - Recovery time after a relapse
  - Progression of EDSS

- **MRI**
  - Increased lesion load (especially if Rx > 6 months)

- **Neutralizing Antibodies**
  - Present with clinical change (especially if Rx > 6 months)
  - Cross reactivity with interferons (1a & 1b)
MS patients in the U.S have been on therapy but have stopped for some reason. Patients often have an unrealistic expectation of their MS therapy and are likely to drop their injectable medications because they don’t feel they’re getting better, or they are having adverse effects such as flu-like symptoms. In many such cases, education about the common side effects of the biologic agents will help patients complete the initial treatment period when these effects are most prominent. Encouraging patients to stay on therapy through the initial tolerance building phase may help patients stay on therapy long enough to determine if efficacy has occurred. Although many of the adverse effects of biologic agents are transient, some, such as liver function and blood cell abnormalities, are only amenable to therapy discontinuation.

Once patients have remained on therapy for an adequate amount of time, efficacy must be assessed. The only way for an MCO to know if medications are working in a particular population is to develop a tracking and intervention process. Markers of suboptimal treatment response in MS are provided in Exhibit 7.

A claims base analysis published in 2000 found that the yearly cost of MS increases with each exacerbation (see Exhibit 8). Economically, reducing relapses leads to fewer acute care costs, decreases ancillary costs (i.e., occupational therapy, physical therapy), and improves patient productivity. The biologic agents, as discussed earlier, will reduce relapses.

Additionally, direct costs increase as the severity of relapses worsen. There is currently no data that the biologic agents vary in ability to control severity of relapses. Because relapses are associated with increasing disability, a disease management program needs to monitor the severity of individual relapses, the recovery time, and how much therapy is required. Relapses may also indicate the need to switch to immunologic therapy.

Using data from pre-marketing studies involving biologic agents, Ollendorf and colleagues published an analysis of the clinical and economic impact of these agents (see Exhibit 9). Study results indicate that use of glatiramer therapy in patients with MS results in a lower rate of relapse relative to those receiving interferon-beta therapies. In addition, therapy with glatiramer acetate appeared to be more “durable” than that of the interferon-beta—patients receiving the

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**Exhibit 8: Total MS Costs by Number of Exacerbations**
- No exacerbations ...................... $6,007
- One exacerbation ....................... $8,180
- Two exacerbations ..................... $14,521
- Three to eight exacerbations ........ $20,519

(Claim-based analysis, 1996 dollars)

**Exhibit 9: Cost of MS Related Care**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Galtiramer acetate</th>
<th>IFN -1a</th>
<th>IFN -1b</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1,674</td>
<td>$6,740</td>
<td>$7,547</td>
<td>$7,648</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Study Therapy</td>
<td>$516</td>
<td>$445</td>
<td>$435</td>
<td>0.764</td>
</tr>
<tr>
<td>N=5,031</td>
<td>$7,256</td>
<td>$7,992</td>
<td>$8,083</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other MS-Related Medication</td>
<td>$1,291</td>
<td>$1,202</td>
<td>$1,083</td>
<td>0.459</td>
</tr>
<tr>
<td>N=1,752</td>
<td>$9,522</td>
<td>$9,957</td>
<td>$10,185</td>
<td>0.004</td>
</tr>
</tbody>
</table>

(Claim-based analysis, 1996 dollars)
former did not switch or add on immunomodulatory therapy, while nearly 10 percent of those receiving interferon beta therapy did experience a therapy change. Finally, total costs of MS-related care were reduced by $1,100 to $700 among glatiramer acetate patients relative to the interferon-beta; findings persisted in multivariate analyses controlling for age, sex, and propensity scores for immunomodulatory therapy. Based on this analysis, six years is required to prevent one relapse with interferon beta-1a (Avonex®) and two years is required with interferon beta-1b (Betaseron®) and glatiramer (Copaxone®). One and a third years are required with interferon beta-1a (Rebi®) but because it is a high-dose therapy, few patients tolerate it well. This analysis illustrates a key point that pharmacy and total medical costs are different for different biologics. To identify the true costs and outcomes, the MCO should monitor relapses and how each medication is being used.

Implementation of an MS disease management program requires a database for tracking patients and outcomes, telephone-based assessments and interactions, patient-based symptom and medication tracking (e.g., patient diary), procedures manual, and adequate personnel resources to implement the program and provide programmed interventions. A patient diary is a way to get the patient involved in his or her care. For example, the diary can be used to track symptoms, medication and other therapy compliance, side effects, laboratory tests, relapses, and preventive health measures such as an annual influenza vaccination. This author has published the MS Clinician’s Guidebook as a resource for MCOs in developing a MS disease management program (see Exhibit 10).

The average total annual costs for MS patients in remission are directly related to the level of disability present (see Exhibit 11). By preventing disability progression through various interventions, the patient can be maintained at a lower direct cost level. If disability is delayed, there are fewer lost productive years and lower indirect costs. Programmed interventions that can help delay disability progression in an MS population include:

• compliance monitoring
• fall prevention
• urosepsis prevention
• side-effect management
• depression screening/referral.

Falls related to neurologic deficits in MS patients can have devastating consequences. Preventing urosepsis secondary to bladder dysfunction can avoid hospitalizations and a potentially life-threatening event. Since depression is frequent in MS patients, screening, referral, and treatment will help avoid the costly consequences of untreated depression.

Benefits of Disease Management

A disease management program for MS offers numerous benefits for patients and MCOs (see Exhibit 12). One benefit is the ability of the MCO to market their MS management program with proven outcomes.

<table>
<thead>
<tr>
<th>Exhibit 10: Multiple Sclerosis Clinician’s Guidebook</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Overview</strong></td>
</tr>
<tr>
<td>&gt; Medical and Pharmacy Directors</td>
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<tr>
<td>&gt; Case Managers</td>
</tr>
<tr>
<td><strong>Patient Education</strong></td>
</tr>
<tr>
<td>&gt; Depression</td>
</tr>
<tr>
<td>&gt; Fall Prevention</td>
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<tr>
<td>&gt; Bowel Dysfunction</td>
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<tr>
<td>&gt; Fatigue</td>
</tr>
<tr>
<td>&gt; Stress Reduction</td>
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<tr>
<td>&gt; Exercise</td>
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<tr>
<td>&gt; Communicating With Your Physician</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exhibit 11: Average Annual Costs per Patients While in Remission50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Medical Costs</td>
</tr>
<tr>
<td>Patient Time Losses-work</td>
</tr>
<tr>
<td>Patient Time Losses-leisure</td>
</tr>
<tr>
<td>Unpaid caregiver time</td>
</tr>
<tr>
<td>TOTAL</td>
</tr>
</tbody>
</table>
such as improved productivity for employers. Another significant benefit for an MCO is the ability to identify significant adverse events with new therapies.

For example, in 2004 a new biologic, natalizumab (Tysabri), was approved for treating RRMS. Use of this agent skyrocketed from November 2004 to February 2005 until the agent was removed from the market because of significant adverse effects (including several deaths).31 Intense tracking of adverse effects through a disease management program will identify significant and potentially life-threatening events early. A disease management program will allow the needed data collection to manage inappropriate use of a new or unproven medication.

Conclusion

The aim of an effective therapy in MS is to reduce the frequency and severity of relapses, shorten their duration, limit side effects, relieve symptoms, prevent disability arising from disease progression, and promote tissue repair. Progress has been made during the last decade in treating MS, especially for RRMS. Benefit and risk need to be weighed carefully in each individual patient. It is hoped that even more powerful therapies will be available in the near future to fight this disabling disease. Disease management programs, whether incorporating a specialty pharmacy or not, can help improve clinical and financial outcomes.

Tom Morrow, MD, is president of the National Association of Managed Care Physicians and has more than 20 years’ experience as a managed care executive. He also has served as an NCQA surveyor overseeing disease management programs such as inflammatory arthritis, depression, chronic pain syndrome, and multiple sclerosis, as well as common chronic diseases.

References

BRIEF SUMMARY
Please consult package insert for full Prescribing Information.

INDICATION
EUFLEXXA™ (1% sodium hyaluronate) is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics (e.g., acetaminophen).

CONTRAINDICATIONS
• Do not use EUFLEXXA™ to treat patients who have a known hypersensitivity to hyaluronan preparations
• Do not use EUFLEXXA™ to treat patients with knee joint infections, infections or skin disease in the area of the injection site

WARNINGS
• Mixing of quaternary ammonium salts such as benzalkonium chloride with hyaluronan solutions results in formation of a precipitate. EUFLEXXA™ should not be administered through a needle previously used with medical solutions containing benzalkonium chloride. Do not use disinfectants for skin preparation that contain quaternary ammonium salts
• Do not inject intravascularly because intravascular injection may cause systemic adverse events

PRECAUTIONS
General
• Patients having repeated exposure to EUFLEXXA™ have the potential for an immune response; however, this has not been assessed in humans
• Safety and effectiveness of injection in conjunction with other intra-articular injectables, or into joints other than the knee has not been studied
• Remove any joint effusion before injecting
• Transient pain or swelling of the injected joint may occur after intra-articular injection with EUFLEXXA™
• Do not use after expiration date
• Protect from light
• Do not re-use—dispose of the syringe after use
• Do not use if the blister package is opened or damaged

Information for Patients
• Transient pain and/or swelling of the injected joint may occur after intra-articular injection of EUFLEXXA™
• As with any invasive joint procedure, it is recommended that the patient avoid any strenuous activities or prolonged (i.e., more than 1 hour) weight-bearing activities such as jogging or tennis within 48 hours following intra-articular injection
• The safety and effectiveness of repeated treatment cycles of EUFLEXXA™ have not been established

ADVERSE EVENTS
Adverse event information regarding the use of EUFLEXXA™ as a treatment for pain in OA of the knee was available from two sources; a multicenter clinical trial conducted in Germany and a single center clinical trial that was conducted in Israel.

Multicenter Clinical Investigation
This clinical investigation was a prospective randomized, double blinded, active control (commercially available hyaluronan product) study conducted at 10 centers. Three hundred twenty-one patients were randomized into groups of equal size to receive either EUFLEXXA™ (n=161) or the active control (n=161). A total of 119 patients reported 196 adverse events; this number represents 54 (33.9%) of the EUFLEXXA™ group and 65 (44.4%) of the active control group. There were no deaths reported during the study.

Incidences of each event were similar for both groups, except for knee joint effusion, which was reported by 9 patients in the active control group and one patient in the EUFLEXXA™ treatment group. A total of 160 patients received 478 injections of EUFLEXXA™. There were 27 reported adverse events considered to be related to EUFLEXXA™ injections: arthralgia – 11 (6.9%); back pain – 1 (0.63%); blood pressure increase – 3 (1.88%); joint effusion – 1 (0.63%); joint swelling – 3 (1.88%); nausea – 1 (0.63%); paresthesia – 2 (1.25%); feeling of sickness of injection – 3 (1.88%); skin irritation – 1 (0.63%); tenderness in study knee – 1 (0.63%). Four adverse events were reported for the EUFLEXXA™ group that the relationship to treatment was considered to be unknown: fatigue – 3 (1.88%); nausea – 1 (0.63%).

Single Center Study
In a single-center, single-blinded, placebo controlled, prospective, two parallel treatment arm clinical trial a total of 49 (25 EUFLEXXA™, 24 placebo) patients were randomized into two treatment groups in a ratio of 1:1 EUFLEXXA™ or placebo. A total of 65 adverse events were reported by 17 (68%) of the patients in the EUFLEXXA™ group and 15 (63%) in the placebo group. Of the 65 total events reported, 20 were regarded as treatment related. Knee pain, hypokinesia of the knee, knee swelling, and rash were considered to be treatment related adverse events.

DETAILED DEVICE DESCRIPTION
Each syringe of EUFLEXXA™ contains:
- Sodium hyaluronate 20 mg
- Sodium chloride 17 mg
- Disodium hydrogen phosphate dodecahydrate 1.12 mg
- Sodium dihydrogen phosphate dihydrate 0.1 mg
- Water for injection q.s.

HOW SUPPLIED
EUFLEXXA™ is supplied in 2.25 ml nominal volume, disposable, pre-filled glass syringes containing 2 ml of EUFLEXXA™. Only the contents of the syringe are sterile. EUFLEXXA™ is nonpyrogenic.

CAUTION
Product contact parts of the syringe contain natural rubber latex, which may cause allergic reactions.

DIRECTIONS FOR USE
• Store refrigerated at 2°C–8°C (36°F–46°F). Protect from light.
• EUFLEXXA™ is administered by intra-articular injection into the knee synovial capsule using strict aseptic injection procedures. The full content of the syringe is injected into the affected knee at weekly intervals for 3 weeks, for a total of 3 injections.
• Twenty to thirty minutes before use, remove the product box from the refrigerator, remove the blister pack from the box and allow the syringe to come to room temperature. Be sure to return any syringes not intended for use to the refrigerator.

Toll free number for providers and patients to call with questions: 1-(888)-FERRING (1-(888)-337-7464).

MANUFACTURED FOR:

FERRING

PHARMACEUTICALS

FERRING PHARMACEUTICALS INC.
SUFFERN, NY 10901

MANUFACTURED BY:
Bio-Technology General (Israel) Ltd.
Be’er Tuvia Industrial Zone, Kiryat Malachi 83104, Israel

Issue date: 10/05

Important Treatment Considerations

EUFLEXXA™ (highly purified hyaluronan) is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics (e.g., acetaminophen). EUFLEXXA™ is contraindicated in patients who have a known hypersensitivity to hyaluronate preparations or who have knee joint infections or skin diseases in the area of the injection site. In a randomized, double-blind, multicenter clinical trial, the only adverse event reported with EUFLEXXA™ at an incidence greater than 5% was arthralgia (8.7%). Transient pain and swelling of the injected joint may occur after intra-articular injection with EUFLEXXA™. The safety and effectiveness of injecting EUFLEXXA™ in conjunction with other intra-articular injectables or into joints other than the knee have not been studied. The safety and effectiveness of treatment cycles of fewer than 3 injections or of repeated treatment cycles with EUFLEXXA™ have not been established. Strict aseptic technique must be followed to avoid joint infection.

Please see brief summary of Prescribing Information on adjacent or following page.
Introducing EUFLEXXA™
Bioengineered* for
unprecedented purity

In a prospective, randomized, double-blind, multicenter head-to-head study vs Synvisc®† (N=321)†

- Proven efficacy in knee OA relief
- Significantly lower incidence of joint effusions

EUFLEXXA™

![Graph showing 0.6% of patients vs 8.1% for Synvisc®](P=0.0015)

Percent of Patients

0 2 4 6 8 10

0.6% Synvisc® 8.1%

Significantly more patients were symptom-free at study end (P<0.04)

Patients centrally randomized to receive EUFLEXXA™ (n=160) or Synvisc® (n=161) in three 2 mL intra-articular injections administered weekly. Patients screened at baseline and at 1, 2, 3, 6, and 12 weeks.

Primary end point: mean change in visual analog scale (VAS: 0-100 mm) score on the WOMAC Index pain subscale. Secondary end points: full WOMAC Index, patient global assessment, consumption of simple analgesics.

*Derived through bacterial fermentation.
†Synvisc is a registered trademark of Genzyme Corporation.

www.euflexxa.com