REPORT

Managing the Expanded Use of Biologics Across Therapeutic Areas: An Example From B-Cell Targeted Therapies

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Abstract

Greater understanding of disease pathology at the molecular and cellular level has enhanced the roles of various proteins in disease pathogenesis. Because so many diseases have common physiologic pathways, many biologic therapies have been found to work in multiple therapeutic areas, particularly cancer, inflammation, infections, and metabolic and blood disorders. Thus, the search for agents to inhibit or block these critical therapeutic agents has been accelerated.

This supplement reviews the factors contributing to the enormous growth of biotechnology drugs—both those currently marketed and those in late-stage development—from a clinical and managed care perspective. Specifically, the growth of expanded indications for drugs approved by the US Food and Drug Administration (FDA) will be examined, along with the challenges of managing biotechnology therapies being used beyond their original indications.

A review of currently marketed biologics under investigation for new indications will be presented, along with a discussion of the implications of expanding indications and the resultant impact on managed care organizations in terms of cost, benefit design, access management strategy, safety and efficacy, and other pertinent issues. Managed care executives will face the challenge of making critical formulary decisions within the context of ever-increasing biologic options, including greater utilization of biotechnology drugs, more biologics for common conditions, and expanded indications for FDA-approved drugs.

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The biologics market is growing at an unprecedented rate, comprising the fastest growing segment of the pharmaceutical marketplace. Of the 101 late-stage biopharmaceuticals in the pipeline for 169 indications in 2004, 27% were already approved by the US Food and Drug Administration (FDA), representing one quarter of the pipeline indications.[1] According to various sources, sales of biologics in 2005 are projected to reach from $45 billion to $50 billion compared with $15 billion to $20 billion in 2000.[2-4] Specialty pharmaceuticals now account for about 5% of overall drug costs and could rise to 15% by the end of 2006.[5] As biologics become more widespread, managed care will not only be tasked with staying abreast of these developments, but also adjusting policies and benefit designs to respond to them.

This supplement examines those key factors contributing to the rapid growth of biologics, with particular emphasis on the role of expanding indications for FDA-approved drugs. The challenges and opportunities payers face in managing biologics approved for multiple indications will be explored, along with how unique mechanisms of action of biotechnology drugs are paving the way for new indications that go well beyond the original therapeutic intent of many drugs. As an example, rituximab, a B-cell targeted therapy approved for relapsed or refractory low-grade non-Hodgkin's lymphoma and currently under investigation for the treatment of rheumatoid arthritis, will be highlighted.

Background

Biopharmaceuticals are most commonly defined as drugs that are produced through biological processes that structurally mimic compounds within the body.[6] These include recombinant proteins, monoclonal and polyclonal antibodies, peptides, antisense oligonucleotides, and therapeutic genes and vaccines—all requiring far more complex

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administration, distribution, and reimbursement methodologies than conventional oral medications. Most biologics fall into the category of specialty pharmaceuticals, which are premium-priced infused or injected drugs that require special handling and are indicated primarily for long-term and/or life-threatening diseases. Typically, there is a high unmet need for specialty pharmaceuticals.[6]

As payers struggle to realign their policies and procedures to accommodate the influx of these expensive high-tech drugs, health plans are increasingly turning to specialty pharmacy providers to manage the acquisition, administration, and distribution of injected and infused biologics and to gain some control over the significant impact on overall pharmacy expenditures. In a poll of major health plans conducted in 2005, 81.4% of the payer groups reported using specialty pharmacy providers—an increase from 74.3% over a 6-month period.[7] In addition, the recent acquisitions of specialty pharmacy providers by major pharmacy benefit companies, such as Express Scripts (Priority) and Medco (Accredo), and the growing consolidation of the specialty pharmacy provider industry in general, point to the current and anticipated growth within the specialty pharmacy segment.[4]

Growth Drivers

Although there are many economic and clinical factors driving the rapid growth of biologics, some key contributors from a managed care perspective include:

- Increased availability of targets for biologic agents
- Increased utilization of approved drugs
- Increased approval of biotechnology drugs for more common conditions
- Expanded indications for approved drugs

The Burgeoning Pipeline

Innovations in biomedical technology continue to drive the development of new and innovative therapies.[8] In April 2003, there were 102 biopharmaceuticals in late-stage development (defined as completing a phase 2 clinical trial or higher) for 156 indications in 36 disease categories.[5] As of March 2004, there were 101 late-stage biopharmaceuticals in the pipeline for 169 indications and 43 disease categories.[1] Estimates of the number of biologics in the pipeline at all stages of clinical development run anywhere from 600 to 800.[3,4]

Biologics for More Common Conditions

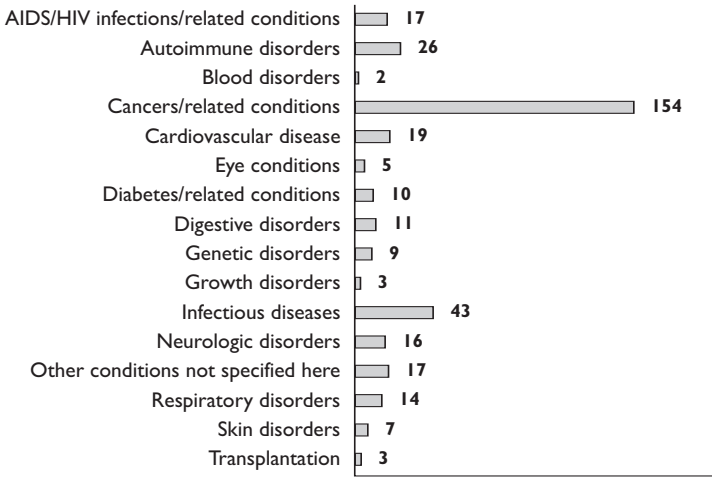
By 2010, it is estimated that between 325 and 400 biotechnology drugs will reach the market, including new drugs for such common conditions as diabetes, cardiovascular disease, digestive disorders, and asthma, as the biotech industry increasingly turns its focus toward long-term conditions.[9] Currently, omalizumab, an immunoglobulin E-blocking agent approved for allergic asthma, is under investigation for peanut allergy, the most common food allergy in the United States, affecting 1.5 million people.[10] Exenatide, an injectable incretin mimetic, was approved for the adjunctive treatment of type 2 diabetes in May 2005.

Although biologics improve patients' quality of life and enhance clinical outcomes, they also generate tremendous costs for third-party payers, costs which many consumers have thus far been insulated from. As these high-priced drugs become available for more common conditions, further questions will undoubtedly arise among managed care organizations (MCOs) regarding how to contain costs as well as deal with the access, management, and ethical issues in delivering biologics to large-scale patient populations.

Increased Utilization

Biologics are used to treat a wide range of long-term and/or life-threatening conditions that cut across therapeutic areas, most commonly cancer, acquired immunodeficiency syndrome/human immunodeficiency virus, rheumatoid arthritis, multiple sclerosis, anemia, hepatitis C, transplantation medicine, and complications caused by human growth hormone. Cancer is by far the top target disease of biopharmaceuticals in late-stage development, followed by infectious diseases and autoimmune disorders and rheumatoid arthritis (**Figure 1**). In May 2001, the National Cancer Institute and the FDA announced a joint program to streamline

Figure 1. Biotechnology in the Pipeline



AIDS indicates autoimmune deficiency syndrome; HIV, human immunodeficiency virus.
Source: 2004 Survey. Medicines in Development: Biotechnology. Available at: http://www.phrma.org/files/Biotech%20Survey.pdf. Accessed February 15, 2006.

anticancer drug development, thus portending that anticancer drugs will be released at a faster pace in the near future, with some of them being distributed through some specialty pharmacy providers.[5]

In a study sponsored by the Blue Cross Blue Shield Foundation on Health Care, 17.8 million people in 10 Blue Cross Blue Shield plans recorded a 12.1% increase in the use of specialty pharmaceuticals from 2002 to 2003, making specialty pharmaceuticals the fastest growing element in the plans' drug budgets.[3] In 2004, Medco, one of the leading pharmacy benefit management companies in the United States, reported that specialty drug spending for its clients grew by 20.4%, a rate significantly faster than the 8.5% average trend for drug spending as a whole.[11] According to Medco, this spending was driven in part by increased utilization of specialty products for current and new indications and as part of combination therapy.

Expanding Indications for Biologics

FDA-approved biologic therapies are gaining approvals for additional indications beyond their original therapeutic targets (**Table 1**). The success of inflammatory cytokines tumor necrosis factor (TNF) inhibitors in the management of the systemic inflammatory features of rheumatoid arthritis has led to extensive investigation (and approvals) of these agents for the treatment of other autoimmune diseases, including Crohn's disease, juvenile rheumatoid arthritis, plaque psoriasis and psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis.[12] Newer oncology drugs, such as erlotinib, approved as a second-line treatment for patients with locally advanced or metastatic non–small-cell lung cancer (NSCLC), was recently approved in combination with gemcitabine for the first-line treatment of patients with advanced pancreatic cancer.[13] Bevacizumab, approved in 2004 for the first-line treatment of colon or rectal cancer, is now in phase 3 clinical trials for a wide range of cancers, including NSCLC, breast cancer, and pancreatic cancer.[14] Rituximab, a B-cell targeted therapy that is currently approved for the treatment of relapsed or refractory low-grade non-Hodgkin's lymphoma and is under investigation for the treatment of rheumatoid arthritis, is even more wide ranging in terms of its potential expanded indication.

One Agent, Multiple Indications—Challenges for Managed Care

Expanding indications for FDA-approved drugs present unique challenges for MCOs. A drug that is used for multiple therapeutic areas may have different dosing regimens, routes of administration, cost structures, and benefit designs. Choosing the appropriate drug in a given indication may be daunting. For example, etanercept, a TNF inhibitor with multiple indications, is dosed at 50 mg per week as 1 subcutaneous injection for adult rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. In adult plaque psoriasis—the most common form of psoriasis—etanercept is given at a dose of 50 mg twice weekly (administered 3 or 4 days apart) for 3 months followed by a reduction to a maintenance dose of 50 mg per week.[15]

This discrepancy may translate into added expenditures for payers, because of the increased frequency of administration and longer duration of therapy. For patients, it may result in higher copays and more restrictive access management strategies, particularly the use of prior authoriza-

tion. Compounding the choice of treatment issues is that many other biologics are indicated for the treatment of moderate-to-severe plaque psoriasis, including adalimumab, alefacept, and efalizumab, all with varying acquisition costs, clinical effectiveness, safety, and patient tolerability.[16] Furthermore, infliximab, an infused agent, is currently under investigation for plaque psoriasis as well as the nonbiologic agents pioglitazone and rosiglitazone, which are currently indicated for the treatment of type 2 diabetes.[11]

Pharmacy versus medical benefit. Another key issue for health plans is determining the benefit classification for a new indication with a different mode of administration. Infused drugs administered in physicians' offices or clinics have traditionally been covered under the medical benefit. The same drug reformulated into an injectable agent will most likely be covered under the pharmacy benefit, resulting in differences in contracts, limits, and exclusions.[5] Given the growing trend in managed care toward shifting biologics from the medical benefit to the pharmacy benefit, how an agent is administered will have important implications for plans.[16] This has created inconsistencies in how coverage is provided for etanercept (injected) and infliximab (infused) by some health plans, as well as how these agents should be tracked.[17] Not only are injectable drugs covered under the pharmacy benefit eligible for more rebates and/or discounts, but the standardized coding also makes processing easier and provides more detailed information for future analysis.[4]

Tier placement, copays, and access management strategies. Another issue for payers will be differences in copays and tier placement. The growing category management of TNF inhibitors by health plans can be evidenced by the many variations in tier placement and copays for agents within the same class of drugs that have different indications and cannot be used interchangeably.[6] Given the high cost of biologics, it is likely that MCOs will require further strategies for managing variations in patient access and cost sharing for a drug approved for multiple disease states. As shown in **Figure 2**, increased use of prior authorization, limited access to specialty therapies, and significant cost sharing are increasingly used as management tools by plans.

Because tiered formulary and patient copay approaches encourage the use of lower-cost medications, they may also result in payer and patient preferences based on cost alone. In the case of multiple indications, when higher-tiered, higher-priced options become available for a prescription, the patient may opt for a lower-priced option or choose not to fill the prescription, increasing the possibility of more expensive healthcare utilization in the future, such as hospitalizations or emergency department visits.

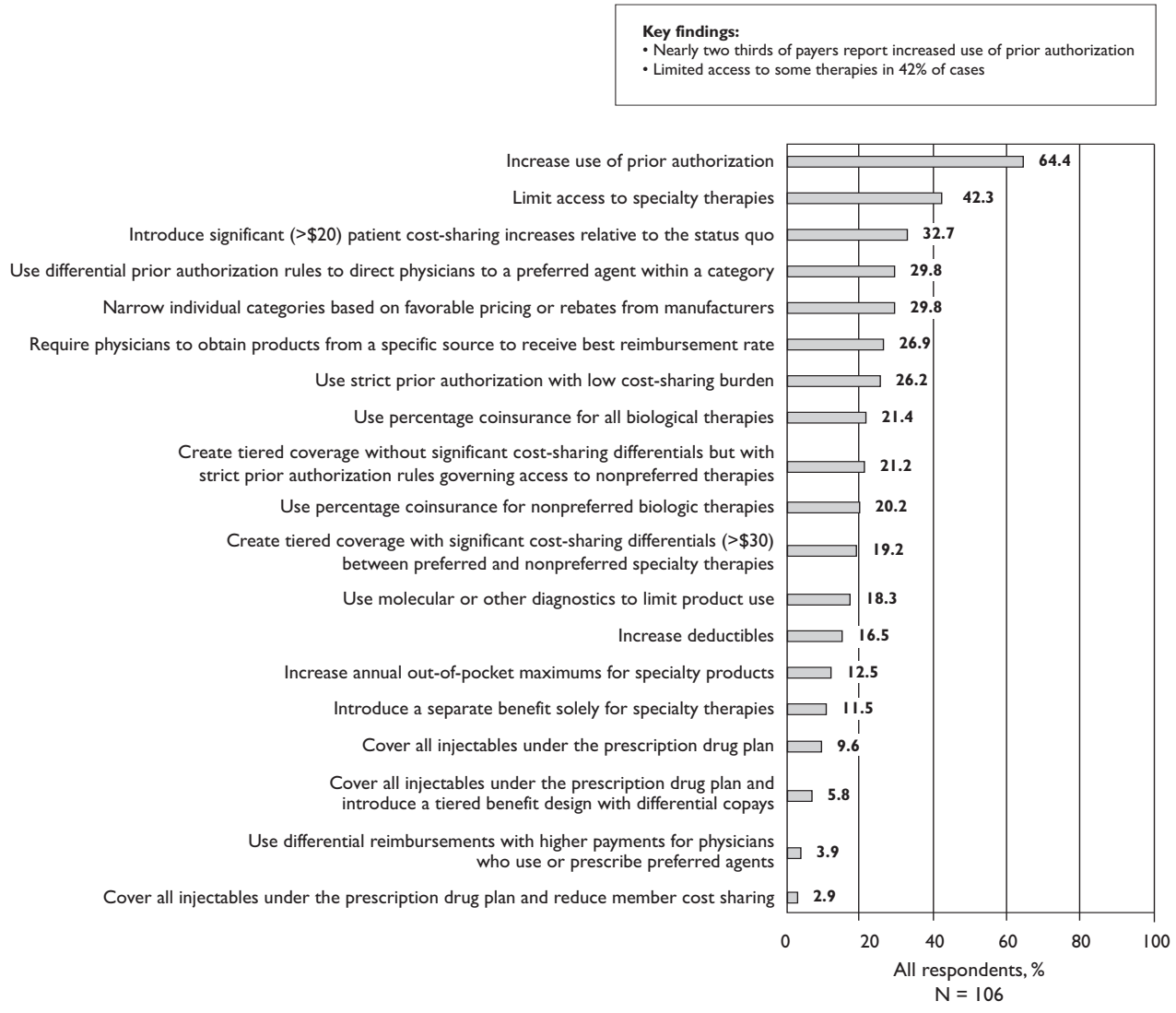
Safety and efficacy. As in the case of TNF inhibitors, although there are many agents with different indications, there are no head-

Table 1. Partial List of New Indications Pending FDA Approval in Phase 2 and 3 Clinical Trials

Drug	Indications
Bevacizumab	Nonsquamous, NSCLC, pancreatic cancer, metastatic renal cell carcinoma
Etanercept	Idiopathic pulmonary fibrosis, juvenile rheumatoid arthritis, ankylosing spondylitis
Cetuximab	Pancreatic cancer, NSCLC, colorectal cancer
Adalimumab	Crohn's disease, juvenile rheumatoid arthritis, ankylosing spondylitis, chronic plaque psoriasis
Efalizumab	Atopic dermatitis
Infliximab	Pediatric Crohn's disease, plaque psoriasis, polyarticular-course juvenile rheumatoid arthritis, cancer-related cachexia in pancreatic cancer, psoriatic arthritis
Rituximab	Rheumatoid arthritis, primary progressive multiple sclerosis, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, intermediate-grade aggressive non-Hodgkin's lymphoma, chronic lymphocytic leukemia, lupus nephritis, antineutrophil cytoplasmic antibody-associated vasculitis
Erlotinib	Ovarian cancer, inoperable advanced squamous cell carcinoma of the head and neck, glioblastoma multiforme, bronchioloalveolar cell carcinoma, metastatic renal cell carcinoma, malignant glioma, NSCLC

FDA indicates US Food and Drug Administration; NSCLC, non–small-cell lung cancer.
Sources: Reference 12; Available at: www.ndapipeline.com. Accessed February 15, 2006.

Figure 2. Current Access Management Strategies



Source: Reference 7.

to-head trials directly comparing safety and efficacy of these agents.[18] Undoubtedly, questions regarding safety, cost effectiveness of treatment, patient selection, rate of adverse events, and treatment guidelines will all vary based on indication. Furthermore, again using the example of rheumatoid arthritis, comparing the safety data of a TNF inhibitor with limited exposure against an agent with greater exposure may produce bias in favor of the former, because in these agents there is less opportunity for uncommon events to occur.[19]

Lack of knowledge/lack of best practices. Few managed care decision makers understand molecular medicine. Without in-depth knowledge of biologics, or established best practices for coverage decisions and benefit designs, formulary decision makers will also increasingly be faced with:

- Appropriate patient selection and drug utilization
- Additional concerns about safety and efficacy caused by off-label use of biologics
- Determining formulary acceptance and

placement in a category where there may be multiple agents of proven efficacy, such as rheumatoid arthritis and multiple sclerosis
- Lack of formal training on the part of Pharmacy and Therapeutics (P&T) Committee and support staff in the pharmacology, pharmacodynamics, and pharmacokinetics of biologics[8]

Further, for some indications, pharmacy expenditures may bear the added cost burden of combination therapy and genetic testing and monitoring.

Other Trends

Complicating these issues for formulary decision makers will be the potential impact of Part D of the Medicare Modernization Act of 2003 on reimbursement and benefit classification. Evolving biologics management strategies, such as greater patient cost sharing, more aggressive access management strategies (eg, increased use of prior authorization), limited access to biologics, the use of differential prior authorization rules to direct physicians to a preferred agent within a category,[7] and continuing movement toward the use of specialty pharmacy providers for drug distribution and case management functions may also challenge these decision makers.

Opportunities for Managed Care

Overall, biologics are transforming medicine by improving survival rates, enhancing quality of life, and delaying or halting disease progression and disability. Despite the added challenges of managing drugs with multiple indications, they still represent critical therapeutic advances. For managed care, the positive aspects of these expanded indications include:

- The potential for increased leverage with contracting as new agents enter already crowded categories
- Known pricing based on previous indications
- Large populations of prior users that allay safety concerns
- The possibility of accruing dual clinical benefits in patients with comorbid conditions
- The ability to gauge real-world use (ie, dosage, concurrent therapies) gleaned from payer databases

Some MCO Considerations in the Off-label Use of Biologics

For biologics with multiple indications, the established safety and efficacy of an agent in several disease states may well lead to its use in related disorders with the same therapeutic target. One retrospective review of the off-label use of chemotherapy for cancer, a well-documented and widespread phenomenon, suggests that off-label usage is more prevalent in patients who have multiple comorbidities, have failed other therapies, and have advanced disease.[20] Issues surrounding the off-label use of biologics range from concerns about safety and adverse events to the anticipated costs of using a biologic for an indication not approved by the FDA either as a first-line treatment or in combination with another therapy. Extrapolated from the off-label use of chemotherapeutics in cancer, a summary of managed care's dilemma in assessing the off-label use of biologics in a variety of diseases includes:

Reasons for the Off-label Use of Biologics

- Small population size and/or assessed cost of clinical trials may negate marketers seeking formal FDA approval
- Potential of newer therapies for better efficacy and outcomes
- Proven safety and efficacy in other disease states
- Potential for increased quality of life
- Thought leader advocacy/patient demand
- Better understanding of disease pathways, particularly immune-modulating diseases

Managed Care's Concerns

- Safety/efficacy questions
- Differing dosing and administration
- Potential for adverse reactions
- Potential for inappropriate care
- Potential for cost increase
- Paucity of data
- Lack of uniform guidelines/best practices
- Legal/ethical issues

Expanding Indications: B-Cell Targeted Therapies

Rituximab is a recombinant monoclonal antibody that is currently approved for the

treatment of B-cell non-Hodgkin's lymphoma.[21] It specifically targets a surface antigen (CD20) that is present only on pre–B-cells and mature B-cells.[22] In so doing, rituximab selectively depletes B-cells from the circulation of patients with lymphoma. By virtue of the central role played by B-cells in the inflammatory cascade of autoimmune diseases, rituximab is currently being investigated for use in the treatment of rheumatoid arthritis as well as other disorders such as multiple sclerosis, antineutrophil cytoplasmic antibodies-associated vasculitis, and systemic lupus erythematosus.

Epidemiology of Rheumatoid Arthritis

Rheumatoid arthritis is a long-term, systemic inflammatory disorder of unknown etiology. The primary targets of rheumatoid arthritis are synovial membranes and articular structures. The condition is associated with irreversible destruction of cartilage, tendons, and bones, which results in significant morbidity. Rheumatoid arthritis may also affect major organ systems, causing premature mortality. In fact, at a given age, the risk of death in patients with rheumatoid arthritis is twice that of the general population.[23]

In addition to its clinical consequences, rheumatoid arthritis has important economic implications. In a systematic review of the literature conducted in 2000, a study found that the direct medical costs of rheumatoid arthritis averaged $5700 per patient per year.[24] In 2004, another study reported annual direct medical costs ranging from $2298 to $13 549 per patient.[25] The indirect costs of rheumatoid arthritis—those associated with lost productivity and employee absenteeism—range from $10 000 to $16 000 per patient per year.[26]

Although the cause of rheumatoid arthritis is unknown, it is believed to be an autoimmune disease initiated in genetically predispositioned individuals by antigenic triggers.[27] There is evidence that the inflammatory cascade in rheumatoid arthritis involves multiple cell types, including T-cells, monocytes, macrophages, and endothelial cells, as well as proinflammatory cytokines.[27] B-cells may also play a prominent role in the inflammatory process, including antigen processing and presenting, autoantibody formation, T-cell activation, and secretion of cytokines.

Treatment of Rheumatoid Arthritis

There have been important changes in the past decade with respect to the management of patients with rheumatoid arthritis. It is now recognized that irreversible joint damage occurs early in the course of rheumatoid arthritis, underscoring the need for early diagnosis and aggressive treatment.[18] A current treatment approach to rheumatoid arthritis is illustrated in **Figure 3.**

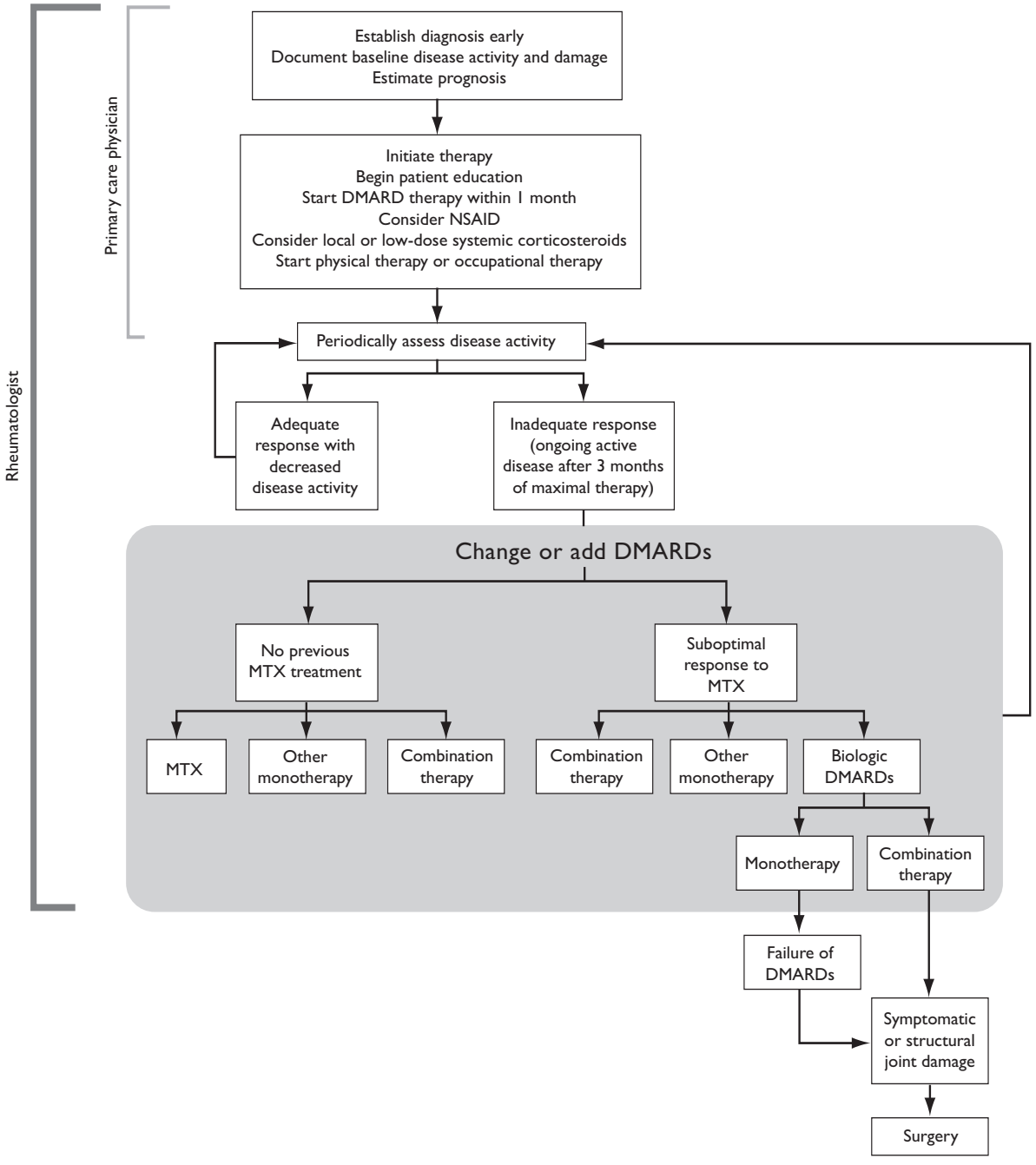
Medications used in the treatment of rheumatoid arthritis include nonsteroidal anti-inflammatory agents, corticosteroids, and disease-modifying antirheumatic drugs (DMARDs). DMARDs should be initiated within 3 months of diagnosing rheumatoid arthritis to prevent or minimize irreversible joint destruction.[18] In recent years, the latter group of agents has been expanded to include biological response modifiers that target specific components of the inflammatory cascade. For example, etanercept, infliximab, and adalimumab are TNF-blocking agents that bind TNF-α in the circulatory system and joints.[18] Similarly, a human recombinant interleukin (IL)-1 receptor antagonist (anakinra) acts by blocking the activity of IL-1.

Other Approaches to Rheumatoid Arthritis in Patients Refractory to TNF-α Inhibitors: Modulation of T-Cell Activation

Another novel approach to the treatment of rheumatoid arthritis is represented by abatacept, a recombinant protein that blocks a costimulatory signal required for T-cell activation. In the Abatacept Trial in the Treatment of Anti-TNF INadequate Rheumatoid Arthritis Responders (ATTAIN), Genovese et al evaluated the efficacy and safety of abatacept in 393 patients with rheumatoid arthritis who were refractory to TNF-α inhibitors.[28]

Patients with rheumatoid arthritis with an inadequate response to 3 months or more of TNF-α inhibitor therapy were randomized to abatacept 10 mg/kg or placebo for 6 months. Study medication was administered on days 1, 15, and 29, and every 28 days thereafter. After 6 months, the rates of

Figure 3. Approach to the Treatment of Rheumatoid Arthritis



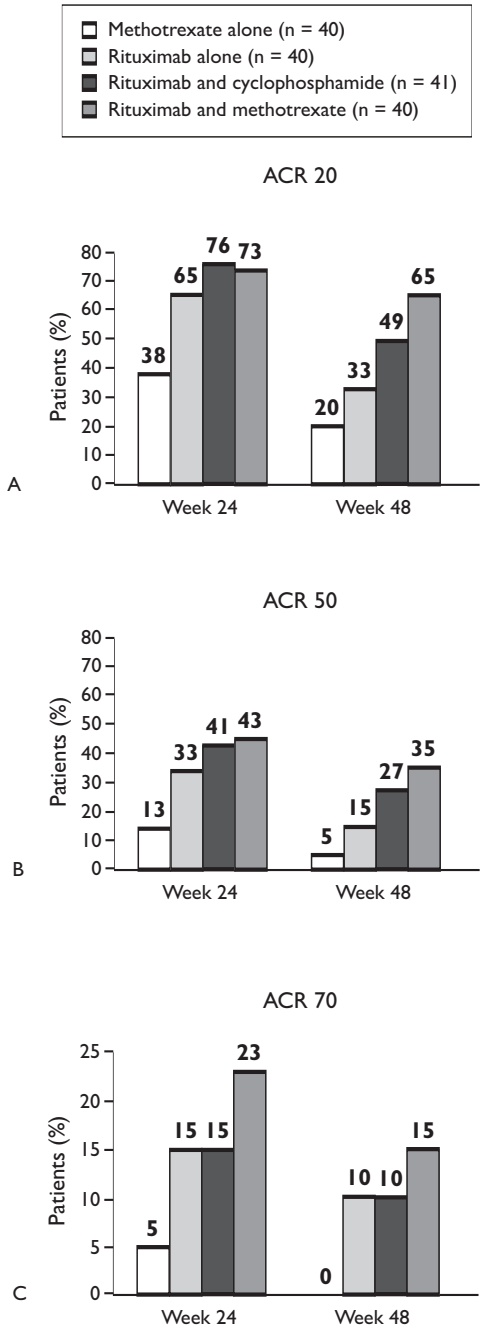
DMARD indicates disease-modifying antirheumatic drug; NSAID, nonsteroidal anti-inflammatory drug; MTX, methotrexate.
Source: Reprinted with permission from Wood A, et al. *N Engl J Med.* 2004;350:2591-2602.

American College of Rheumatology (ACR) 20 responses were 50.1% in the abatacept group and 19.5% in the placebo group (P <.001). According to the study authors, "abatacept is clinically efficacious and has an acceptable safety profile in patients with rheumatoid arthritis and an inadequate response to anti–TNF-α therapy."

The Role of B-Cell Depletion in the Treatment of Rheumatoid Arthritis

Another potential approach to the treatment of rheumatoid arthritis is to interrupt the inflammatory cascade by specifically targeting B-cells. B-cells play a major role in autoimmune disorders, such as rheumatoid arthritis, regulating the activation of tissue-invading T-cells.[29] Thus, they are important potential therapeutic targets; depletion of B-cells would be expected to reduce the pro-inflammatory activity of T-cells in the synovium and elsewhere.

Figure 4. ACR Clinical Responses at Weeks 24 and 48



ACR indicates American College of Rheumatology.
Source: Reprinted with permission from Reference 22.

Rituximab and Rheumatoid Arthritis

In a double-blind, controlled study, Edwards et al randomly assigned 161 patients with active rheumatoid arthritis, despite methotrexate therapy, to 1 of 4 treatments[22]:

- Oral methotrexate (≥10 mg/week; control)
- Rituximab infusion (1000 mg on days 1 and 15)
- Rituximab plus cyclophosphamide (750 mg on days 3 and 17)
- Rituximab plus methotrexate

Clinical assessments according to the ACR core set of disease-activity measures were made at baseline and at weeks 12, 16, 20, and 24. Responses according to the European League Against Rheumatism (EULAR) criteria were also recorded. A secondary analysis evaluated responses at week 48.

Responses at weeks 24 and 48 are shown in **Figure 4**. In all groups treated with rituximab, a significantly higher proportion of patients demonstrated a 20% improvement in symptoms according to ACR criteria (65%-76% vs 38%; $P \leq .025$) or had EULAR responses (83%-85% vs 50%; $P \leq .004$). At week 24, significantly more patients treated with the rituximab-methotrexate combination (43%; $P = .005$) and with the rituximab-cyclophosphamide combination (41%; $P = .005$) demonstrated a 50% improvement in symptoms compared with methotrexate alone (13%).

The majority of adverse events were infusion-related, occurring most frequently in connection with the first infusion. The overall incidence of these reactions was similar in the rituximab-containing regimens (36%) and the placebo infusions (30%) in the control group. Most were mild-to-moderate in intensity. Despite the profound and pro-

longed depletions of B-cells that occurred with rituximab treatment, the overall incidence of infections in rituximab-treated subjects and the control group was similar at weeks 24 and 48.

The Dose-Ranging Assessment International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) study was designed to evaluate the efficacy and safety of varying doses of rituximab in combination with methotrexate in patients with active rheumatoid arthritis currently experiencing an inadequate response to methotrexate.[30,31] The effect of premedication with corticosteroids was also assessed. The study included a total of 465 patients with rheumatoid arthritis who were randomized to treatment with a stable dose of methotrexate plus either placebo, rituximab 500 mg on days 1 and 15, or rituximab 1000 mg on days 1 and 15. Efficacy assessments included ACR 20, ACR 50, and ACR 70 at week 24.[32] Results appear in **Table 2**. Regardless of dose, subjects receiving rituximab demonstrated statistically significant improvement in rheumatoid arthritis symptoms compared with placebo. Premedication with corticosteroids had no significant impact on effectiveness.[33] All regimens were generally well tolerated. The majority of adverse events were infusion-related, and the incidence and severity of these reactions were reduced by corticosteroid premedication.

Future of Rheumatoid Arthritis Therapy

Abatacept, along with the potential approval of rituximab, will give rheumatologists 3 mechanistically distinct biologic treatments for rheumatoid arthritis: a B-cell target (rituximab), a T-cell target (abatacept), and a proinflammatory target (TNF blockers).[34]

Other treatments for rheumatoid arthritis in the phase 3 clinical trials include tocilizumab, an antibody to the IL-6 receptor that is active in juvenile rheumatoid arthritis and is also under investigation for systemic lupus erythematosus. Certolizumab pegol, a pegylated TNF inhibitor administered once per month, is also in phase 3 clinical trials. Treatments for rheumatoid arthritis in late-stage development are shown in **Table 3**.

Recommendations for Managing Expanding Indications

Better safety and efficacy, as well as more specific targeting, have opened the door for many expanded indications of approved biologics for the treatment of a wide range of disorders. Yet, expanded indications also raise concerns about the ability of health plans to manage differing biologics, both clinically and cost effectively. Further, innovations in biologic therapies that hold promise for many difficult-to-treat conditions will also require new strategies for managing costs to enable patients to access these potentially more efficacious therapies. According to Medco's 2005 drug trend analysis, although TNF inhibitors are only a small fraction of utilization in the musculoskeletal and rheumatology category, they contribute to almost 50% of the cost and continue to grow at a rate of 15% to 20% per year.[12]

When pharmacy and medical directors from leading health plans were polled on the management of the expanded use of biologics, the vast majority (92%) agreed that biologics with multiple indications will improve the quality of care for patients overall. Yet, approximately 25% agreed that their organizations would be capable of managing a given therapy with multiple indications, whereas roughly 50% indicated that their organizations would not be capable of managing such a therapy. The remaining respondents indicated that it would depend primarily on benefit classification. When the same group was asked how they would rate the financial

Table 2. ACR Responses (% Subjects) at 6 Months in Patients with Active Rheumatoid Arthritis Currently Experiencing an Inadequate Response to Methotrexate

	Placebo (n = 122)	Rituximab 500 mg (n = 123)	Rituximab 1000 mg (n = 122)
ACR 20	28	55*	54*
ACR 50	13	33*	34*
ACR 70	5	13†	20†

*P <.001.
†P <.05.
ACR indicates American College of Rheumatology.
Source: Reprinted with permission from Reference 33.

Table 3. Rheumatoid Arthritis Development Pipeline: Partial List of Agents in Development

Product	Company	Phase	Indication	Mechanism of action
Rituximab	Genentech	NDA filed August 2005, approval expected in 2006	Patients with rheumatoid arthritis who are refractory to anti–TNF-α therapies	MAb targeting the CD20 antigen
Tocilizumab	Hoffmann-La Roche	3; BLA filing slated for 2007	Monotherapy and in combination for DMARDs for treatment of rheumatoid arthritis	Humanized anti–IL-6 receptor MAb
Certolizumab pegol	Celltech/UCB	3	Moderate-to-severe rheumatoid arthritis	Pegylated humanized antibody fragment TNF-α
AD-452	Arakis	2a complete; 2b in active rheumatoid arthritis began 2005	In combination with methotrexate for disease-modifying treatment of early-stage rheumatoid arthritis	Single-isomer version of a cytokine modulator
SCIO-469	Scios	2b as of 2005	Rheumatoid arthritis	First-generation p38-α MAP kinase inhibitor
DPC-333	Bristol-Myers Squibb	2a	Rheumatoid arthritis	TACE for reduction of TNF production to reduce inflammation
Belimumab	GlaxoSmithKline/ Human Genome Sciences	2 completed; fast-track designation from the FDA	Patients with moderate-to-severe active rheumatoid arthritis who have failed prior therapy	Fully human MAb that inhibits BLyS, a protein required for development of mature plasma B-cells
AT-001 (dnaJP1)	Androclus Therapeutics/NIH	2 completed 2005	Rheumatoid arthritis	Short engineered peptide with epitope-specific immunomodulatory activity that induces tolerization of the autoimmune process in patients with rheumatoid arthritis without changing immune responses to unrelated antigens
AMG-714	Amgen	2 completed 2005	Rheumatoid arthritis	Human MAb targeting IL-15
Golimumab	Centocor	2 met primary end point as of November 2005	Rheumatoid arthritis	Fully human TNF-α IgG1 MAb
VX-702	Vertex Pharmaceuticals	2 initiated June 2005	Rheumatoid arthritis	Second-generation p38 MAP kinase inhibitor that inhibits the cytokines TNF-α and IL-1 beta
HuMax-CD20	Genmab A/S	2 initiated August 2005	Patients with rheumatoid arthritis who have failed treatment with ≥1 DMARD	Human antibody targeting the CD20 antigen on B-cells
PRO-70769	Genentech	2 as of 2005	Patients with moderate-to-severe rheumatoid arthritis	Humanized MAb targeting the CD20 antigen on the surface of mature B-cells
MLN-1202	Millennium Pharmaceuticals	2 as of 2005	Rheumatoid arthritis	MAb targeting the MCP-1/CCR2 chemokine pathway
R-1594	Hoffmann-La Roche	2 as of 2005	Rheumatoid arthritis	Anti-CD20 molecule
AG-284	Organon/Corixa	2	Rheumatoid arthritis	MHC-derived protein and disease-specific autoantigenic peptide
Denosumab (formerly AMG-162)	Amgen	2	Rheumatoid arthritis	MAb targeting the RANKL

NDA indicates new drug application; TNF, tumor necrosis factor; MAb, monoclonal antibody; BLA, biological license application; DMARDs, disease-modifying antirheumatic drugs; IL, interleukin; MAP, mitogen-activated protein; TACE, transarterial chemoembolization; FDA, US Food and Drug Administration; NIH, National Institutes of Health; IgG1, immunoglobulin G1; MCP, monocyte chemotactic protein; MHC, major histocompatibility complex; RANKL, receptor activator of nuclear factor-κβ ligand.
Source: www.ndapipeline.com.

impact of expanding indications for biologic therapies, many of the participants responded that the impact will be very negative "because costs will grow greatly." Yet, a significant percent (40%) responded that the impact would be somewhat negative "because more price competition will offset greater utilization" (unpublished audience polling data from a nonsanctioned symposium held in conjunction with the 2005 Annual Meeting of the Academy of Managed Care Pharmacy, *Managing the Expanded Use of a Biologic Across a Therapeutic Area*).

Clearly, the appropriate utilization of a biologic will be key to the management of expanded indications. Proper utilization will ensure improved clinical outcomes and potential cost savings in the long term.

Organizing an Approach

Developing and implementing an organized approach to managing expanded indications is critical in addressing the complexities of drug utilization. Recommendations include:

Scanning the pipeline. MCOs need to be aware of pending launches of drugs with a major expanded indication that could have significant budgetary ramifications.[8]

Increasing education for P&T committees. Decision-making support for P&T committee members should be provided in the form of increased medical and pharmacy education on biologics' novel mechanisms of action and the roles of these agents in various disease states.

Defining a process and creating clear criteria. Plans need to develop processes for clearly defining whether drugs will be covered under the medical or pharmacy benefit, how patient cost sharing will be determined, and what access management strategies will be put into play. Once developed, the plan should then be prepared to assure that the criteria are appropriate, fair, and justifiable in the court of public opinion.[8]

Developing and/or augmenting treatment guidelines for expanded indications. Specific treatment guidelines should be used to guide prescribers to the most cost-effective therapies. This is particularly true when multiple drug therapies are available and the disease may be exceptionally costly to treat.[16] For drugs with expanded indications, this also means ensuring that prescribers understand critical differences in safety, efficacy, dosing, administration, duration of treatment, and monitoring.

Increasing case management/disease management. Because biologics are more complex, the need for patient education is significant. Many of the diseases they treat are progressive and have changing manifestations and symptoms, requiring close monitoring and follow-up on a regular basis.[35] Specialty pharmacies are likely to play a pivotal role in therapeutic management, because they regularly contact patients to distribute self-injectable medications and have large numbers of patients with diseases treated with biologic drugs.

Striving for innovative management strategies that contain cost and maintain access. Although there is no single approach that is likely to work, experts point to some possible solutions that health plans may use, including:

- Involving marketing and sales executives to ensure that benefit designs are appropriate, ethical, and reasonable[8]
- Shifting more business to specialty pharmacy providers
- Linking patient cost sharing and drug tier level to indication
- Greater use of evidence-based medicine to ensure that treatment decisions and patient selection are based on proved clinical outcomes as well as cost effectiveness

CONCLUSION

Managed Care's Response to the Challenges of Expanded Indications

The challenges of managing expanding indications will grow in complexity as the FDA continues to approve drugs for indications far beyond their original therapeutic intent. Thus far, the predominant payer

response to the influx of new biologics has been to attempt to control costs. However, cost is only one of many considerations in the use of agents with multiple uses—particularly in those disease states where there is still a highly unmet need, despite the availability of other interventions. For example, almost 10% (130 000) of the estimated 1.5 million patients diagnosed with moderate-to-severe rheumatoid arthritis fail anti-TNF therapy.[34]

The biotechnology industry will continue to race to find new therapeutic targets for its marketed drugs, resulting in an even greater influx of agents for once-difficult-to-treat diseases. To effectively manage costs and provide patients with the best quality care, MCOs will need to look beyond their current emphasis on managing the distribution and purchasing of specialty pharmaceuticals to contain costs.[5] Whether these expanded indications represent breakthrough therapies or another tool in the treatment arsenal, MCOs will continually be faced with these following challenges:

- *Ensuring that drugs with expanded indications are used appropriately to promote optimal patient outcomes.* Inappropriate off-label usage, errors in dosing and administration, and over- or underutilization can potentially expose patients to adverse reactions and/or poor outcomes.
- *Maintaining focus on the reduction in disease progression and disability potentially associated with the use of these agents, rather than solely on patient copays and aggressive management strategies.* Again, this will require sound clinical decision making driven by evidence-based medicine. The current focus on costs will need to shift to determining how evidence-based medicine can be incorporated into formulary decision making and provider treatment paradigms.
- *Adequately planning for agents with multiple indications.* Most health plans are not ready to deal with the onslaught of specialty pharmaceuticals overall. Although there is no doubt that specialty pharmacy providers will play a far greater role in their management, payers and providers need to understand and differentiate the safety and efficacy of these drugs across disease states. Establishing more definitive criteria for evaluating expanded indications and their potential for cost savings in the future will be essential. Head-to-head trials and pharmacoeconomic studies will be critical to accurate clinical decision making as well as determining the true value of these therapies.

Without adequate understanding of the challenges associated with managing drugs with multiple indications, MCOs may encounter inappropriate use of these drugs as well as squandered opportunities to affect genuine improvements in patients with serious, long-term conditions.

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