

The Use of Therapeutic Interchange For Biologic Therapies

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PROLOGUE

On Sept. 29, 2006, an expert panel of physicians, pharmacists, and third-party payer representatives met in Chicago to develop a consensus on the appropriateness of therapeutic interchange with respect to biologic therapies for rheumatoid arthritis and psoriasis. During this process, the interdisciplinary group — comprising a rheumatologist, a dermatologist, a medical researcher with an interest in health policy, a managed care pharmacy director, a managed care pharmacy consultant, and the president of a specialty pharmacy — reviewed current approaches to the management of these chronic diseases, utilization trends, and pharmacy management techniques. The expert panel's recommendations, rooted in common ground among health care professionals and third-party payers, lend themselves to cost control but leave room for physician judgment and patient considerations.

ABSTRACT

Therapeutic interchange is the practice of switching or dispensing drugs that are chemically distinct but therapeutically similar in terms of their efficacy, safety, and tolerability profiles. The stated goal of therapeutic interchange is to achieve an improved or neutral outcome with the new agent while reducing overall treatment costs. Until recently, most interchange programs have been limited to switches within drug classes, such as angiotensin-converting enzyme (ACE) inhibitors, proton pump inhibitors (PPIs), HMG-CoA reductase inhibitors (statins), and selective serotonin reuptake in-

hibitors (SSRIs), and generally to drugs that use the same routes of administration. Therapeutic interchange now is being applied to some biologic agents, such as those used to treat psoriasis and rheumatoid arthritis (RA). In some cases, these agents differ in structure and mode of administration. Patients who require a biologic agent are often difficult to manage, and the comorbidities that are prevalent in these patients further complicate management and agent selection. Population-based outcomes among various agents may not appear notably different, but because there is no *a priori* means to determine the effects of a given biologic agent on any individual patient, therapeutic interchange is inadvisable once a patient receiving RA or psoriasis therapy has been stabilized. However, if a biologic agent has been designated as preferred on a formulary, it is reasonable to initiate treatment with that agent in a patient who is naïve to biologic therapy if that agent is not contraindicated. Respectful, two-way communication between health care professionals and managed care organizations (MCOs) will help ensure that a patient receives the appropriate therapy at the right time.

INTRODUCTION

In the past, most biotechnology products were used to treat conditions that affected relatively small patient populations. Now, however, specialty pharmaceuticals are being developed to target more common diseases. In 2005, expenditures for biologic agents, driven by a combination of product costs and increased utilization, in-

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creased 16 percent over the previous year (Ernst & Young 2006). Understandably concerned about ensuring that these costly agents are used appropriately, MCOs and their pharmacy and therapeutics (P&T) committees seek evidence on which to base utilization management decisions.

At the clinical level, MCOs and

pharmacy benefit managers employ numerous interventions to ensure the appropriate utilization of specific agents (Table 1). These strategies are intended to keep the benefit affordable while supporting appropriate use of pharmaceutical products. In one such intervention, third-party payers have designated traditional drug therapies within classes and, more recently, certain biologics, as preferred products. Another intervention related to this is *therapeutic interchange*, the practice of switching chemically distinct drugs that, on the basis of the available clinical evidence, are believed to be similar in terms of efficacy, safety, and tolerability while being less expensive.

Because the availability of several biologic agents for the treatment of RA, psoriasis, and psoriatic arthritis (PsA) provides a class-competitive market, we will use them as examples in discussing therapeutic interchange and other techniques for managing biologic therapies. We will review the use of these agents and

discuss the circumstances under which therapeutic interchange and other interventions are appropriate.

THERAPEUTIC INTERCHANGE

The goal of therapeutic interchange is to improve or achieve at least similar clinical outcomes with a drug that will reduce overall treatment costs (AMCP 2003). Therapeutic interchange programs are guided by evidence-based prescribing guidelines and by clinical trial data that suggest a class of drugs might be appropriate for interchange, having demonstrated similar patient outcomes while reducing pharmacy and/or medical expenditure.

Historically, therapeutic interchange has been applied within such drug classes as beta blockers, calcium channel blockers (CCBs), statins, and SSRIs, because clinical evidence suggested that agents in these respective classes were similar in terms of their risk/benefit profiles, even if they differed in many other respects. Despite

assessed equivalence, however, clinical response can vary widely, as seen with SSRIs (Hensley 2001, Kroenke 2001).

Disparities in clinical pharmacology among the biologic agents used to treat RA, psoriasis, or PsA (Table 2, page 54) are more pronounced than those among the aforementioned classes of traditional drug therapies, but the underlying principles of therapeutic interchange are essentially the same in either case. Because of differences in chemical structure, clinical pharmacology and pharmacokinetics, mode of administration, safety and long-term experience, black-box warnings, drug interactions, immunogenicity, and points of impact in the inflammatory cycle, therapeutic interchange of biologic agents for RA, PsA, and psoriasis should be thought through carefully; these differences may be significant for some patients. For example, Figure 1 (page 58) presents considerations for the use of biologics based on specific characteristics for patients with psoriasis.

TABLE 1
Clinical cost-containment strategies employed by MCOs

Techniques commonly employed by payer organizations

Prior authorization	Often used in conjunction with physician education <i>Examples:</i> bevacizumab, fertility agents, HGH, pegaptanib, psoriasis and RA agents, omalizumab
Step therapy	Patient must fail to respond adequately on preferred therapy <i>Examples:</i> multiple sclerosis, psoriasis, RA agents
Quantity limits	<i>Examples:</i> etanercept, fertility agents, HGH, adalimumab, epoetin alfa, efalizumab
Dosage limits	All dosages must be within U.S. Food and Drug Administration labeling <i>Examples:</i> hemophilia agents, infliximab, omalizumab
Length of therapy	<i>Examples:</i> hepatitis C agents
Dose optimization	<i>Examples:</i> erythropoietin, factor VIII, fertility agents
Generic substitution	Substitution of a generic product for a chemically identical branded drug <i>Examples:</i> simvastatin for Zocor
Therapeutic interchange	Interchange of assumed therapeutically equivalent yet chemically distinct drugs <i>Examples:</i> ACE inhibitors, nonsedating antihistamines, NSAIDs, PPIs, statins
Care management	<ul style="list-style-type: none"> • Patient education • Improved compliance and persistence • Coordination with clinicians and facilities <ul style="list-style-type: none"> • Assistance with drug administration • Side effect management • Identification of subsidies to offset copayments and co-insurance <i>Examples:</i> hemophilia, renal failure

ACE=angiotensin-converting enzyme, HGH=human growth hormone, NSAID=nonsteroidal anti-inflammatory drug, PPI=proton-pump inhibitor, RA=rheumatoid arthritis.

In some cases, therapeutic interchange might be requested by an MCO because new evidence has shown that patients are likely to fare better with a different drug. In others, new safety data may make a switch imperative for a specific group of patients. Certainly, financial considerations are a factor when therapeutic interchange is considered for any class of drugs (Wallack 2004).

When considering implementation of a therapeutic interchange program, payer organizations with sophisticated information technology systems can model the potential nondrug cost implications. Some of the resultant savings in drug expenditures, for instance, may be offset by new costs incurred in the course of effecting the switch. These expenditures include the direct-time costs of physicians, nurses, and other clinicians; time costs for discussing a switch with colleagues; and costs of additional laboratory tests or office visits to monitor therapy or to provide interventions to treat adverse reactions. These costs can be substantial and may be shifted to other parties, such as physicians and patients (Abourjaily 2005).

Unlike *therapeutic substitution*, therapeutic interchange does not involve chemically equivalent products; rather, it involves products that published data suggest are therapeutically equivalent in terms of outcomes and overall adverse-effect profiles. Considerations in instituting such a program for biologic therapies are the same as with nonbiologic drugs, though the agents involved may have different efficacy, tolerability, and safety profiles, among other characteristics, such as route of administration, immunogenicity, or dosing interval. At the population level, these differences may appear to be negligible when clinical evidence is weighed, thereby establishing their assumed therapeutic equivalence. But in the individual patient, these products may or may not result in substantial differences in treatment response. The

greater the potential response variation (both for efficacy and side effects) and the more severe the targeted condition, the greater the clinical implications of switching a stabilized patient from one agent to another. For these reasons, MCOs employing therapeutic interchange should have mechanisms in place to request exceptions on a case-by-case basis.

Thus far, most published studies examining therapeutic interchange have dealt with small molecules, such as statins, ACE inhibitors, or CCBs. A review of these studies found an equivalent or improved clinical effect from the switch as well as substantial savings (Carroll 2002). In several of these studies, however, design concerns have been raised. For example, several analyses eliminated patients who had had an inadequate response or who had experienced adverse effects. In other studies, substantial failure rates in switches involving PPIs, CCBs, and SSRIs offset savings or increased overall costs (Carroll 2002).

The relative newness of biologic therapies means evidence-based guidance on switching is limited. The available literature generally supports switching unstable patients from one biologic to another for clinical reasons such as lack of tolerability or effectiveness (van Vollenhoven 2004). However, with the exception of a few randomized controlled trials, much of the literature is based on small retrospective observational studies. At least 19 published reports address outcomes of switching unstable RA patients from one tumor necrosis factor-alpha (TNF- α) inhibitor to another, but most of these are not rigorous studies that would allow for sound generalization of results (Keystone 2006). The medical literature is devoid of studies specifically devoted to head-to-head comparisons of the efficacy and safety of biologics. These studies are needed to enable optimized patient care, but presently, no mechanism is in place to fund them.

Some conclusions can be drawn

from the data generated in the studies of switching TNF- α inhibitors. Failure of one TNF- α inhibitor does not preclude the use of another; patients who do not respond, lose their response, or cannot tolerate a TNF- α inhibitor can be switched safely to a second or third TNF- α inhibitor. The patient's response to a subsequent TNF- α inhibitor seems to be influenced significantly by the reason for discontinuing treatment with the previous agent (Villeneuve 2006).

If published data suggest that the drugs in question may be interchangeable, physicians and payer organizations must consider numerous questions pertaining to drug and patient variables. What is the dose equivalent of the new medication? How is the new agent to be administered? Is the patient capable of self-administration? How should the current medication be discontinued and the new one initiated? Is any monitoring required? What adverse effects should be anticipated, and, if they arise, how should they be treated? What are the drug and nondrug costs of substitution, and to whom?

These considerations are among the many practical issues raised by therapeutic interchange. At another level are the ethical questions: What is a patient seeking from a physician? What implicit promise is made when a physician accepts a patient? What is the physician's responsibility to that patient? Is a product prescribed for a patient because it is the best product for that patient or because it is beneficial for the physician's practice?

Although a physician's overriding responsibility is to the individual patient, the physician also has a responsibility to manage resources for the benefit of the community. Most physicians believe they resolve these potentially conflicting interests in the best interest of their patients, consistent with their professional responsibilities. Often, this is achieved through an MCO's exceptions process, a potentially valuable tool for

dispute resolution.¹

The American Medical Association

¹ The effectiveness of the MCO exceptions process may be hampered by differing perceptions of it. Payers view it as a vehicle for fostering communication with physicians and to learn why specific patients do not meet prescribing criteria. Patients or physicians, though, may view it as burdensome.

has accepted the concept of therapeutic interchange. The AMA undertook a thorough literature review on hospital-based therapeutic interchange and found, in most cases, that such programs reduced costs with no difference in patient outcomes, and in some cases, improved outcomes. The AMA did not, however, evaluate therapeutic

interchange programs used by third-party payers in ambulatory settings and, in a policy statement on therapeutic interchange, it reiterated previous AMA policy that “switching ... patients with chronic diseases who are stabilized on a drug therapy regimen should be discouraged” (AMA 2004). Often, the patient is unaware of

TABLE 2
Biologics available in the United States for treatment of psoriasis, psoriatic arthritis, and rheumatoid arthritis

	Description	Administration	FDA indications
TNF-α inhibitors			
Adalimumab (Humira)	Anti-TNF- α monoclonal antibody (humanized)	Subcutaneous injection	<ul style="list-style-type: none"> • Rheumatoid arthritis • Psoriatic arthritis • Ankylosing spondylitis
Etanercept (Enbrel)	Soluble human TNF- α receptor fusion protein	Subcutaneous injection	<ul style="list-style-type: none"> • Rheumatoid arthritis • Juvenile rheumatoid arthritis • Psoriasis • Psoriatic arthritis • Ankylosing spondylitis
Infliximab (Remicade)	Anti-TNF- α monoclonal antibody (chimeric)	Intravenous infusion	<ul style="list-style-type: none"> • Rheumatoid arthritis • Psoriatic arthritis • Psoriasis • Ankylosing spondylitis • Crohn's disease • Ulcerative colitis
T-cell inhibitors			
Abatacept (Orencia)	Selective T-cell costimulation modulator fusion protein	Intravenous infusion	<ul style="list-style-type: none"> • Rheumatoid arthritis
Alefacept (Amevive)	Dimeric fusion protein consisting of the extracellular CD2-binding portion of human leukocyte function antigen-3 (LFA-3) linked to Fc portion of human IgG1	Intravenous bolus or intramuscular injection	<ul style="list-style-type: none"> • Psoriasis
Efalizumab (Raptiva)	Monoclonal antibody against CD11 (humanized)	Subcutaneous injection	<ul style="list-style-type: none"> • Psoriasis
B-cell inhibitor			
Rituximab (Rituxan)	B-cell depleting monoclonal antibody against CD20 (chimeric)	Intravenous infusion	<ul style="list-style-type: none"> • Rheumatoid arthritis • Non-Hodgkin's lymphoma
Interleukin-1 inhibitor			
Anakinra (Kineret)	Recombinant, nonglycosylated form of human interleukin-1 receptor antagonist (IL-1Ra)	Subcutaneous infusion	<ul style="list-style-type: none"> • Rheumatoid arthritis

SOURCES: MANUFACTURERS' PRESCRIBING INFORMATION

the numerous factors that may affect prescribing decisions. These factors are beyond the scope of the medical considerations described in the following sections, which illustrate the complexities involved when special patient types are faced with the prospect of therapeutic interchange.

RHEUMATOID ARTHRITIS

Epidemiology/disease burden

In the United States, RA is prevalent in about 1 percent of the population (Lawrence 1998). Prevalence increases with age, such that about 7 percent of women over the age of 70 have RA. Left untreated, severe RA is a significant cause of premature mortality (Wolfe 1994), morbidity, diminished quality of life, and reduced productivity. Active RA is associated with depression and fatigue (Wolfe 1996). Uncontrolled RA is associated with increased incidence of cardiovascular events regardless of conventional risk factors (del Rincon 2001).

The lifetime costs of treating RA can exceed those for treating coronary artery disease and stroke (Allaire 1994). Annual direct medical expenditures for RA patients without comorbidities are about \$9,300, and indirect costs can total approximately 5 times that amount (Maetzel 2004), owing primarily to lost wages. As the disease advances, it may erode cartilage and bone, leading to anatomical variations (deformities) such as subluxation of the metacarpal-phalangeal joints, often leaving these patients unable to work. After 15 years with the disease, only 40 percent of patients are able to work (Blumberg 2001). Fortunately, RA is a highly treatable cause of disability (Emery 1994), and one of the most important goals of therapy is to keep people in the workforce.

Treatment of RA

Traditional agents used for treating RA are mostly orally administered small molecules, most of which are available as generics. Most of these agents have not been subjected to rig-

orous efficacy trials to assess whether they alter the progression of joint destruction. Older disease-modifying antirheumatic drugs (DMARDs) are associated, in varying degrees, with the potential for toxicities that require monitoring (Table 3, page 56). Rheumatologists are comfortable using methotrexate, which is common as an initial treatment for RA because of its low cost, established safety profile (methotrexate is administered in RA therapy at lower doses than during chemotherapy), and propensity to produce a long-term response (O'Dell 2004). Methotrexate is contraindicated in patients who use alcohol, who have underlying liver or renal disease, or who are or plan to become pregnant. It should not be given to patients unwilling to undergo periodic testing (complete blood count, albumin, and alanine aminotransferase).

Although the biologic agents are better than methotrexate alone in slowing disease progression,² some patients achieve a good outcome with methotrexate monotherapy. Methotrexate also is used in conjunction with hydroxychloroquine and sulfasalazine with good effect in the management of some people with RA. Gold compounds are seldom used today, and although cyclosporine is used by dermatologists in the treatment of psoriasis, it is rarely used by rheumatologists for RA.

Insights into the cytokine signaling pathways active in RA have identified numerous molecular targets for the biologic agents (Choy 2001). The intercellular messengers include interleukin-1, whose signaling is blocked by anakinra (Kineret), and TNF- α , a proinflammatory cytokine that is targeted by etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira). TNF- α plays a central role in RA, affecting the osteoclasts responsible for bone resorption; the

² Information about the use and efficacy of the biologic products listed herein is derived from the FDA-approved package inserts referenced at the end of this article.

synoviocytes that line the insides of joints, and the chondrocytes that produce cartilage. TNF- α also has other effects on the orchestrated inflammatory response. Influenced by TNF- α , osteoclasts are thought to become overly active, resulting in bone erosion; synoviocytes hyperproliferate, causing the joint swelling and pain that distresses patients; and the catabolic activity of chondrocytes is increased, leading to destruction of cartilage and joint space narrowing.

Signaling pathways also can be disrupted when cells involving the inflammatory cascade, such as B cells and T cells, are targeted. B cells, which promote the production of rheumatoid factor and other autoantibodies, can be depleted by rituximab (Rituxan). Abatacept (Orencia), alefacept (Amevive), and efalizumab (Raptiva) target cell-surface receptors on T cells.

Each of the biologics approved by the U.S. Food and Drug Administration for treating RA is effective, especially in combination with methotrexate. The combination is superior to methotrexate alone or to the biologic alone. The standard of measurement used by the FDA for approving a biologic is the ACR20 response — a 20 percent improvement from baseline in signs and symptoms and a laboratory indication of inflammation. About 60 to 70 percent of patients treated with a biologic and methotrexate achieve a 20 percent improvement in signs and symptoms, and as many as 40 percent may achieve an ACR70 response. These agents have a positive impact on quality of life (QOL) as measured by the Health Assessment Questionnaire, an indicator of QOL in patients with RA and other chronic diseases. With the exception of rituximab, all the biologics approved for treatment of RA can claim to halt the progression of structural damage. Some patients using biologics may achieve RA remission, defined as a 44-joint Disease Activity Score (DAS₄₄) <1.6 (van der Heijde 2006).

If treatment is discontinued, RA

TABLE 3
Traditional disease-modifying antirheumatic drugs (DMARDs)

Agent	Time to benefit	Potential for toxicity	Toxicities to monitor
Methotrexate	1–2 months	Moderate	Myelosuppression, hepatic fibrosis and cirrhosis, pulmonary infiltrates
Hydroxychloroquine	2–6 months	Low	Macular damage
Leflunomide	4–12 weeks	Low	Diarrhea, alopecia, rash, headache, risk of immunosuppression infection
Sulfasalazine	1–3 months	Low	Myelosuppression
Cyclosporine	4–8 weeks	High	Renal insufficiency, hypertension
Gold, oral	4–6 months	Low	Myelosuppression, proteinuria
Gold, parenteral	3–6 months	Moderate	Myelosuppression, proteinuria
Azathioprine	2–3 months	Moderate	Myelosuppression, hepatotoxicity, lymphoproliferative disorders
Minocycline*	1–3 months	Low	Hyperpigmentation, dizziness, vaginal yeast infections, lupus

* Not approved by the U.S. Food and Drug Administration for the treatment of rheumatoid arthritis.
 SOURCE: ACR 2002

will flare in 4 to 8 weeks in some patients. A recent study suggests that aggressive therapy with biologics or steroids, in combination with methotrexate, in patients with early, active RA may provide rapid improvement and enable sustained clinical response after the biologic is withdrawn and patients are continued on methotrexate monotherapy (Goekoop-Ruiterman 2005). A follow-up abstract presented at the American College of Rheumatology (ACR) 2006 Annual Scientific Meeting examined these data further and suggests there may be advantages to the biologic combination (van der Kooij 2006).

Further research is needed to provide clear interpretation of these results; at best, the study suggests that over the long term (3 years), aggressive therapy combining a TNF- α inhibitor and methotrexate may be superior to several other regimens that exclude biologics (van der Kooij 2006). Such findings, if validated by medical societies and others that promulgate evidence-based treatment guidelines, may have important implications for decision makers, be

they health plans or physicians. Flexibility in treatment and coverage options can help to incorporate these potential advances into therapy.

Only one biologic therapy, infliximab, was employed in these studies, so the question of whether other biologics would yield comparable or superior results remains unanswered. The question of which biologic or regimen is appropriate for a given patient remains complex, as the following case studies illustrate.

**Treatment considerations:
 case studies**

[Editor's note: The following case studies are patients from Dr. Flood's practice. These are not scientific studies, and the conclusions drawn from them are generalizations that do not account for patient-specific variables.]

Case 1. A 55-year-old man with a history of hepatitis C infection from intravenous (IV) drug use developed bilateral large and small joint inflammatory arthritis that prevented him from working. He tested positive for rheumatoid factor, which is common in patients with hepatitis C, even in

the absence of RA. Further testing suggested a diagnosis of RA. X-rays revealed that his RA was erosive, even though he had displayed signs and symptoms for only 6 months. He also was found to have active hepatitis C infection. Because of that infection, methotrexate was contraindicated. Trials of other nonbiologic agents were ineffective. In light of a recent study showing the safety of etanercept in hepatitis C infection (Zein 2005), he was started on etanercept 50 mg weekly. He achieved substantial improvement in signs and symptoms and QOL, sufficient enough to allow him to return to work. At that point, his MCO mandated a change to adalimumab, despite the physician's presentation of an argument justifying the use of etanercept. Within 4 weeks on the new therapy, the patient experienced recurrence of joint pain and disability, necessitating frequent office visits and joint injections. He became depressed, unable to work, and ultimately required surgery to prevent the tendon ruptures that can result from vigorous synovitis.

This case suggests that if a patient is controlled on a biologic, the ther-

apy should not be changed to another existing biologic therapy without patient consent. Consideration should be given to patient-specific variables (in this case, a history of hepatitis C) that suggest use of a specific drug. Mechanisms should be in place to enable redress of any adverse effect or lack of response to a switch.

Case 2. A 70-year-old woman had a diagnosis of RA that was active despite treatment with methotrexate and prednisone. Even at low doses, prednisone use is not desirable in an older woman. After a review of the available biologic therapies and their costs (prior to the advent of Medicare Part D), the patient selected infliximab because her health insurer did not cover etanercept (a self-injectable drug), but Medicare Part B did cover infliximab when administered via IV infusion at the physician's office. After 3 months of infliximab therapy she had some improvement but still had active disease. In addition, her husband experienced a disabling stroke that made it difficult for her to travel to the infusion center. Through the Medicare Replacement Drug Demonstration project, she was able to afford etanercept and experienced significant improvement. Later, she found a Part D plan that covered etanercept. Even though she fell into the "doughnut hole" because of the cost of the drug, she thought the etanercept was worthwhile because of the improvement.

This case illustrates some of the ways in which a patient's financial situation can prevent or delay provision of the most appropriate therapy. Such effects are well documented (Soumerai 1999, Huskamp 2003).

Case 3. A 48-year-old woman with a 6-year history of RA was initially treated with methotrexate, to which sulfasalazine and hydroxychloroquine were added, resulting in remission. After 3 years, her disease became more active and etanercept was started. After 4 months without improvement, her physician switched her to infliximab. Despite dosing and inter-

val changes, she still had active disease. Switching to adalimumab led to 3 years of improvement, followed by the return of disease activity. She now receives abatacept infusions and is in remission, with X-rays showing no progression of disease after 9 months.

This case suggests that if adequate control is not achieved with the biologic of choice after a reasonable trial, switching the patient to another biologic is warranted. A trial of anti-TNF- α agents from the different classes of anti-TNF- α agents (i.e., soluble receptor and monoclonal antibody classes) is a reasonable strategy before switching to a drug with a more distinct mechanism of action.

At present, there is no *a priori* means for choosing the most effective biologic for a given patient. The ACR recommends that if a patient with RA who is being treated with a DMARD has evidence of increased disease activity or progression of bony damage over a 6-month period, the DMARD therapy should be modified in one of the following ways: change the dose or route of administration, change to another DMARD, add a DMARD, start or increase the dose of a glucocorticoid, or provide local glucocorticoid injections (ACR 2006). Systematic individual comparisons and pooling postmarket data may eventually aid in the appropriate personalized selection of an agent, but this integration of research and practice is still years away.

No single biologic has been able to achieve a response in all patients with RA. If a patient fails on one agent, switching to another may be beneficial. Once a patient has been optimally stabilized on a specific therapy, the patient should not be switched to another without a sound clinical reason, though this should not preclude trying another agent if evidence suggests it might effect better clinical outcomes.

PSORIASIS

Epidemiology/disease burden

About 6 to 7 million Americans (2 to 2.6 percent of the population) have

some form of psoriasis (NIAMS 2003). However, only one third of this group — the patients with moderate to severe disease — are candidates for aggressive systemic therapy.

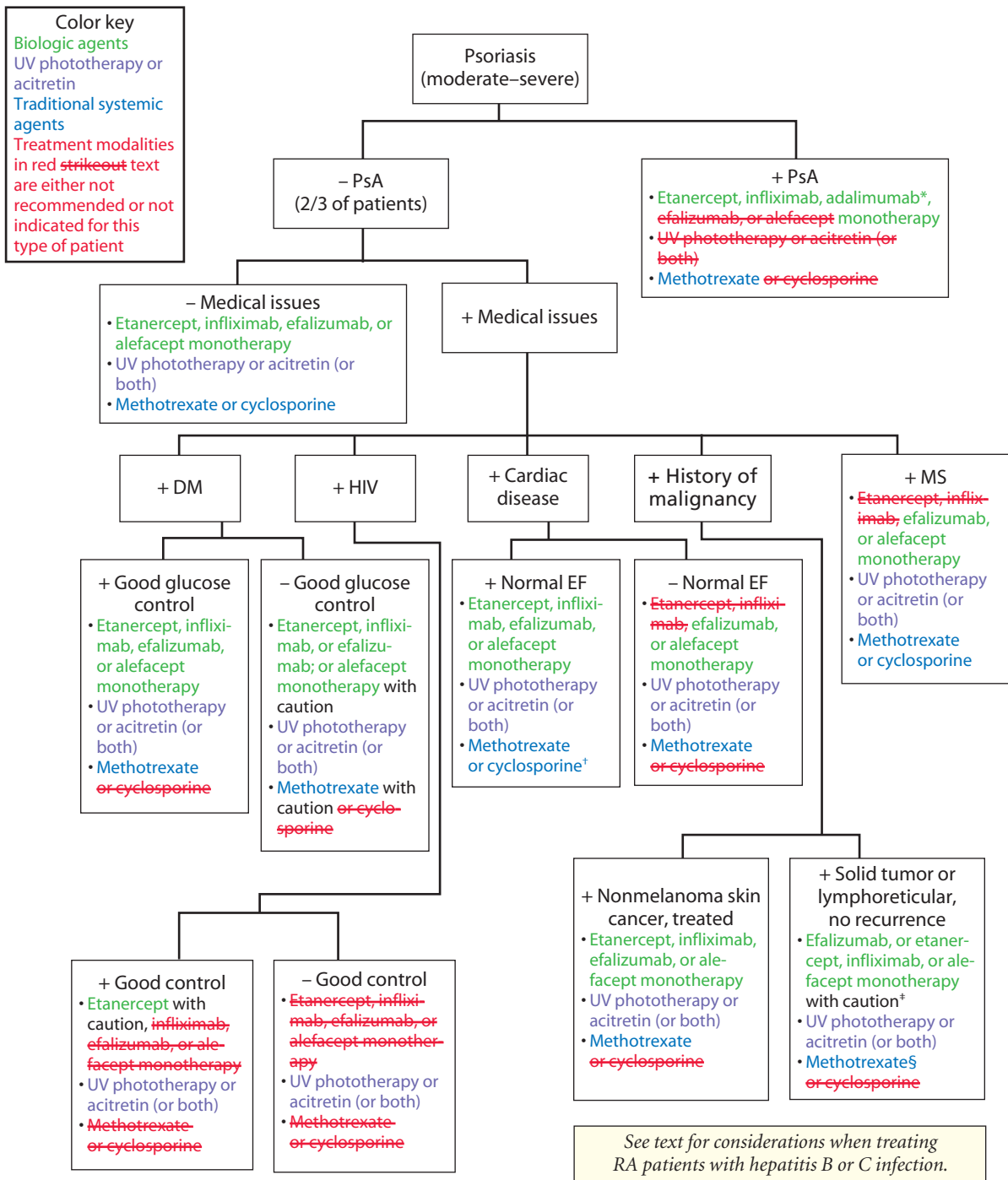
Psoriasis has many forms, but all the variants have similar pathophysiology. Eighty percent of psoriasis patients have chronic plaque psoriasis, which is very red and often scaly. It can occur anywhere on the body, although the elbows and knees, scalp, and lower back are common sites. If it occurs on the soles or palms, the condition is painful and debilitating. Most patients with plaque psoriasis complain of an intractable itch.

As with RA patients, people with psoriasis are more fatigued, experience greater incidence of clinical depression, miss more days of work, and have fewer social interactions than their healthy peers (Krueger 2001). Until recently, it could have been argued that psoriasis did not need to be treated as aggressively as RA because it lacks discernable long-term morbidity aside from psychosocial issues. Dermatologists had to justify treatment on the grounds of impaired QOL, i.e., inhibition of the patient's ability to function. However, evidence has come to light to suggest that inadequately treated psoriasis can carry serious sequelae. It is now understood that psoriasis is part of a spectrum of psoriatic diseases and may be a marker for psoriatic arthritis; as many as 4 in 10 people with psoriasis will go on to develop psoriatic arthritis (Gladman 1992). More recently, the association between moderate to severe psoriasis and increased cardiovascular risk has become better substantiated; new evidence suggests that patients with severe psoriasis have a greater risk of myocardial infarction (MI) — the relative risk of which is greatest in the younger patients (Gelfand 2006).

Treatment of psoriasis

In theory, psoriasis could be cleared by a topical product, provided an

FIGURE 1
Treatment options for patients with moderate to severe psoriasis



See text for considerations when treating RA patients with hepatitis B or C infection.

* Adalimumab is indicated for psoriatic arthritis but not psoriasis.

[†] Beware of hemodynamic effects of cyclosporine in patients with cardiac disease and normal ejection fraction.

[‡] Risks of immunosuppressant drugs were not studied in cancer patients.

§ Proceed with caution in patients with history of malignancy.

DM=diabetes mellitus, EF=ejection fraction, HIV=human immunodeficiency virus, MS=multiple sclerosis, PsA=psoriatic arthritis, UV=ultraviolet, +=with, -=without.

This algorithm is not endorsed by any medical society and should not be construed as prescribing advice. It is adapted from a presentation at the Scientific Expert Panel by Bruce E. Strober MD, PhD, and reflects the prescribing information for these products, the professional literature, and the clinical experience of the presenter.

ample supply of the agent is available. But if a large percentage of the body surface area is involved — 10 percent and upward — topical therapy becomes impractical, and systemic absorption may add to the adverse-event profile. When the disease is too extensive for topical treatment, other options must be explored. These include ultraviolet (UV) phototherapy, often used in conjunction with acitretin; traditional systemic agents, such as methotrexate and cyclosporine; and biologic therapies.

Although it is safe, light therapy has a major drawback: the need for a patient to make 2 to 3 office visits per week, indefinitely, which effectively makes this treatment inaccessible to patients who work during business hours. Acitretin is best suited for use in combination with UV therapy, not as monotherapy, and rarely works well at tolerable doses (Sterry 2004). Because it is a teratogen with a very long half-life, acitretin is contraindicated in women of childbearing potential, who constitute almost half the psoriatic population.

The biologic agents effective for treating psoriasis and PsA are similar to those available for RA. The biologic agents approved for the treatment of psoriasis include the TNF- α inhibitors etanercept and infliximab, which differ in their approved indications. In contrast, however, the T-cell inhibitors alefacept and efalizumab are useful for treating psoriasis, but not PsA or RA.

Being risk-averse, most dermatologists prefer not to treat their patients unnecessarily with a systemic agent, and thus frequently reserve biologics for patients with severe disease.

Treatment considerations

In a patient with moderate to severe psoriasis, selection of therapy can be very complex (Figure 1). As with the nonbiologic agents, comorbidities increase the risk for adverse events — risks that should be recognized and managed. This is true for any patient treated with a TNF- α in-

hibitor, regardless of whether the diagnosis is psoriasis, PsA, or RA.

The primary consideration is whether the patient has coexisting PsA. If the patient lacks discernable PsA and has no other medical issues, any of the nine treatment modalities may be considered. If the patient has PsA, the treatment options narrow to the TNF- α inhibitors and methotrexate, which works well in combination with TNF- α inhibitors. The ideal treatment for a patient with significant psoriasis and clinically significant PsA is methotrexate plus an anti-TNF- α agent, if there are no contraindications to these agents.

Diabetes. In psoriasis patients without PsA, treatment choices are affected by the presence of various comorbidities and the extent to which they are controlled. If a patient has diabetes that is well controlled, cyclosporine is the only therapy that should be excluded. Because patients with diabetes are at risk for nephropathy, cyclosporine therapy could compound the risk for kidney damage. If glucose levels are poorly controlled in a diabetic patient, and if the patient has frequent infections and diabetes-related complications, biologic agents should be used with caution because poorly managed diabetes can be regarded as an immunocompromised state. For such patients, UVA therapy or acitretin, or both, may be more appropriate. Methotrexate must be used with caution in a diabetic patient because of an increased risk of methotrexate-induced hepatotoxicity.

HIV infection. Immunodeficiency in the form of HIV infection tends to worsen psoriasis. If the patient is under good care with the use of highly active antiretroviral therapy and has a low viral load and a normal CD4 count, etanercept can be very effective. UV phototherapy and acitretin also may be considered for such a patient. Methotrexate and cyclosporine should not be used because of their immunosuppressive properties. If the HIV infection is poorly man-

aged and the patient has opportunistic infections, ultraviolet phototherapy and acitretin are the primary options. If these treatments fail, immunosuppressive biologics should be considered, but only used with extreme caution and with comanagement by a specialist in HIV disease who also cares for the patient.

Cardiac disease. In a patient with atrial fibrillation or a history of MI, any agent may be considered, provided the ejection fraction (EF) on echocardiogram is normal. Although it is capable of causing hemodynamic effects, even cyclosporine may be considered for such a patient. In a cardiac patient with a low EF, consider avoiding TNF- α blockers, with the caveat that the data supporting this contraindication are somewhat soft (Brooksbank 2005).

Multiple sclerosis. TNF- α blockade presents a greater issue in patients with multiple sclerosis (MS) or another demyelinating disease. They should not be treated with a TNF- α blocker (Kollias 1999), but instead should receive a T-cell agent, UV phototherapy and acitretin, or methotrexate and cyclosporine.

If a patient has a first-degree relative with MS or other demyelinating disease, TNF- α inhibitors should be avoided as initial treatment, owing to the possibility that there may be a familial predisposition to MS. However, if other treatment modalities fail, then a TNF- α blocker can be considered in a patient with a family history of MS.

History of malignancy. If a patient has been adequately treated for nonmelanoma skin cancer (e.g., basal or squamous cell carcinoma), any therapy but cyclosporine may be employed. In patients with squamous cell carcinoma, cyclosporine tends to promote creation of additional cutaneous nonmelanoma cancers in a short period (Behnam 2005).

If the malignancy was a solid tumor, immunosuppressants should be approached with caution because risks have not been evaluated for-

mally. Patients with lymphoma should not receive immunosuppressants or cyclosporine, but methotrexate can be considered. Acitretin is an option with or without phototherapy.

Hepatitis B or C infection. TNF- α blockade has been associated with the reactivation of hepatitis B virus in patients who are chronic carriers of the virus, with fatalities in some cases, and the labels for all products in this class have been modified to warn of this adverse effect. Rituximab³ also is contraindicated in hepatitis B infection. Methotrexate and cyclosporine are contraindicated in patients with hepatitis B. Acitretin is hepatotoxic in some patients. There is limited experience with the use of T-cell agents in the context of hepatitis B or C, but case reports have indicated some degree of safety (Thaci 2005). Phototherapy seems safe, but as noted, is not a realistic option for most patients.

For a patient with hepatitis C, etanercept may be the drug of choice, although some reports suggest that infliximab and adalimumab are safe in patients with hepatitis C (Oniankitan 2004, Roux 2006). Acitretin should be avoided because of the potential for liver toxicity, as should methotrexate and cyclosporine.

In summary, treatment of moderate to severe psoriasis is extremely complicated, owing to comorbidities or coexistent issues. Dermatologists do not want to unnecessarily prescribe systemic agents, and when they choose an agent, it may be the only product that is suitable for that patient from the perspective of practicality and safety. Psoriasis therapy should not be stepped, because the choice of therapy depends on individual patient characteristics.

PHARMACY INTERVENTION PROGRAMS FOR BIOLOGICS

Some other mechanisms traditionally used to manage the utilization of pharmaceutical products — prior authorization, designation of preferred

³ Indicated for RA, not psoriasis.

agents, step therapy, quantity limits, limits on dosage or length of therapy, retrospective utilization review, and copayments — can be useful for managing biologics, but not every tool in the kit is applicable to a given product.

Prior authorization. This technique is reasonable from a safety standpoint when there is concern that a product is being frequently used for off-label indications or at doses that exceed the evidence base. On a periodic basis, health plans evaluate the percentage of requests approved for an agent and the value of continuing prior authorization. In some instances, prior authorization requirements are removed once no longer needed. Similarly, the value of having selected biologics periodically reauthorized should be re-evaluated. Physicians' and patients' time required for these processes should be taken into account to reduce unnecessary burden.

Monitoring dosing irregularities. Case management, disease management, rigorous retrospective utilization review, and surveillance for dose escalation and administrative efficiencies can be effective ways to optimize utilization, reduce errors, and mitigate costs of care.

Preferred products. If a patient has been optimally stabilized on a covered agent, consideration should be given to "grandfathering" that patient on that product in the event that the patient's health plan later designates a different preferred product, or if a patient should be enrolled in a different health plan with a similar benefit design. In any such situation, an uncomplicated exceptions process can facilitate this process.

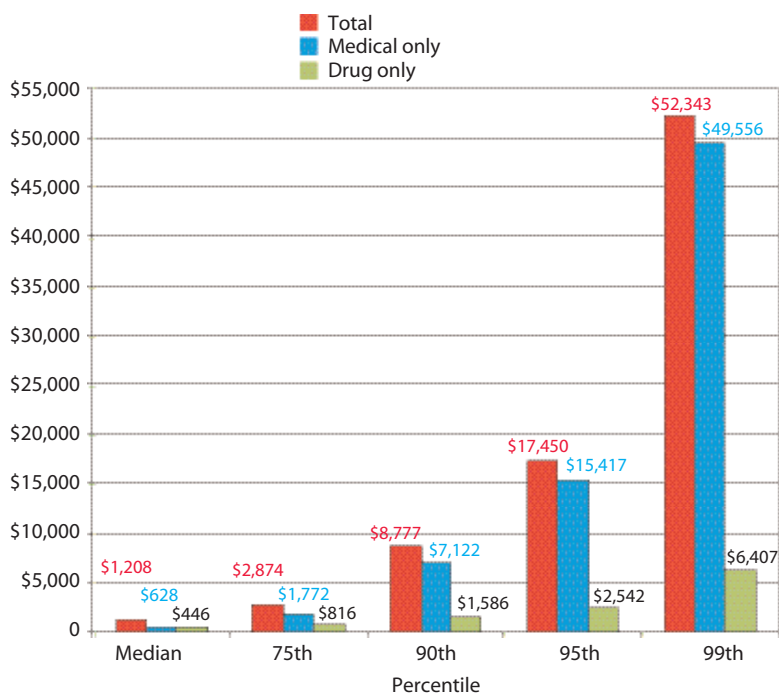
If an MCO has designated a preferred biologic, it is reasonable for a treatment-naïve patient to begin therapy with that agent if there is no evidence to suggest the patient should not receive it. Selection of a preferred first-line biologic by a P&T committee is a process that entails numerous considerations — primarily, FDA indications, safety and efficacy data, and

side-effect profiles, and secondarily, cost considerations. A careful utilization-review process will determine the potential for an MCO's exposure to financial liability beyond the initial cost of the agent, such as off-label uses or dose-escalation trends. Continued engagement with physicians about emerging evidence is critical for optimizing the use of various therapies as well as promoting change if more effective therapies become available.

Copayments. Based on a review of pharmacy and medical claims from 55 health plans offered by 15 employers and covering 1.5 million beneficiaries, Goldman (2006) constructed a model suggesting that while the doubling of copayments for traditional pharmaceuticals might reduce utilization by 30 to 50 percent, increases in cost-sharing have considerably less effect on spending for specialty drugs. Looking at four conditions often treated with specialty drugs, Goldman found that doubling the cost sharing would reduce spending on specialty drugs for cancer by 1 percent; MS, 7 percent; kidney disease, 11 percent; and RA, 21 percent.

In this population, beneficiaries' out-of-pocket spending for drugs was far outstripped by their out-of-pocket spending for medical services. Figure 2 illustrates how, at various percentiles of out-of-pocket spending by patients with RA, out-of-pocket spending for drugs is relatively small compared with out-of-pocket spending for medical services, and that the overall financial burden faced by some RA patients is substantial. Many argue that health care costs and behaviors do not follow traditional market forces. These findings could be interpreted to say that traditional cost-cutting mechanisms do not apply to these drugs because patients perceive a strong need for them. This is the most compelling explanation as to why, for instance, doubling the cost-sharing for a cancer specialty drug reduces utilization by only 1 percent (Goldman 2006).

FIGURE 2
Out-of-pocket spending* by RA patients in a managed care population



*Each spending category (drug-only, medical services-only, and total) was calculated separately at the percentiles shown, so the individual percentiles cannot be added together to produce the same total.
 SOURCE: GOLDMAN 2006

Regardless of the tools used to manage utilization, the key to ensuring that the right patient receives the right drug at the right time is respectful, two-way communication between physicians and MCO health care professionals. Plan professionals (pharmacists and medical directors) must work hand-in-hand with physicians and patients if any of these initiatives are to succeed.

Underlying the increased focus on therapeutic interchange of biologics is the broader issue of the cost of these medications. Although beyond the scope of this paper, balancing the prices of drugs with the provision of accessible and appropriate medical treatment is a critical practical and ethical issue to be addressed.

CONCLUSION

The biologic therapies discussed in this article have unique chemical structures and differing routes of ad-

ministration, dosing intervals, and safety profiles. No single agent has been shown capable of producing an optimal response in all patients. Because there is no *a priori* means to determine which biologic will be beneficial in a given patient, trials of several agents may be necessary before an effective agent is found. However, if a patient is naïve to biologic therapy and there are no patient-specific risk factors, the preferred agent may be selected. Once patients have been stabilized on a specific agent, they should not be switched to another agent without dialogue among the patient, the prescribing physician, and the health plan regarding the patient's condition. Payers need an appreciation of, and to be responsive to, patient-specific differences. Systems that help to analyze the various possible outcomes of a switch need to be developed and should consider all costs (drug and

nondrug) to providers, patients, and payers. Processes that result from this should be supported by evidence-based guidelines.

The issues surrounding therapeutic interchange for biologics are similar to those that have been raised in switching nonbiologic therapies. As treatments become available that can improve debilitating conditions, and as these interventions require increasingly large expenditures, it becomes important to address the inherent practical and ethical issues to resolve these issues to the satisfaction of all.

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