A Method for Classifying Biologics for Formulary Decision Making

Michael S. Broder, MD, MSHS,
Debi Reissman, PharmD

Pharmacy and Therapeutics Committees have been trying to determine the correct way to incorporate biologic agents into their formularies. As with any new drug, the first step is to determine the appropriate category or classification in which they will be evaluated. The biologics present some challenges to classification in significant ways. Even though two or more biologics may have a common indication, their differences in mechanism of action, method of delivery, dosing schedule, and other factors may be important considerations in choice of a useful classification. A method is suggested and illustrated, utilizing the group of biologic agents commonly used to treat psoriasis (including, for illustrative purposes, alefacept, efalizumab, etanercept, and infliximab).

In designing the formulary categories for biologics, it may be helpful to first list several possible levels of classes and hierarchy. These might include the disease treated/therapeutic class, therapeutic class/subclass, therapeutic class/mechanism of action (MOA), and combinations of the above.

Organizations also might find that benchmarking how other compendia and references classify biologics can be helpful. If one considers the biologic agents alefacept, efalizumab, etanercept, and infliximab, for example, the U.S. Pharmacopeia and the Centers for Medicare and Medicaid Services have classified these agents according to the therapeutic category/pharmacologic class/drug type, whereas *Drug Facts and Comparisons* classifies agents by therapeutic system/therapeutic category/pharmacologic class, and the American Society of Health-System Pharmacists, Bethesda, Maryland, uses therapeutic category/pharmacologic class. Several health plans have begun to place biologics within their drug formularies, under which alefacept and efalizumab may be listed as antipsoriatic agents (systemic), but etanercept and infliximab may be classified under anti-inflammatory agents (tumor necrosis factor [TNF] inhibitors). This information is summarized in Table I.

Within this group of agents, no standard classification system appears to be in use by the commonly used references and compendia. This is likely true with other categories of biologic agents that Pharmacy and Therapeutics (P&T) Committees evaluate as well.

FORMULARY CLASSIFICATION

Classification systems are used for numerous reasons: to ensure appropriate prescribing and avoid medication errors, to ensure availability and track usage, to assist in reimbursement decisions, and to allow for therapeutic substitution. It may be helpful to begin with clearly defined objectives for the classification system. The biologics, because of their diverse and targeted mechanisms of action, challenge existing methods of classification. Several, such as those in the illustrative example, may fall into one therapeutic category (i.e., psoriasis), and their fundamental differences may affect treatment outcomes. To determine the best classification to use for biologics, MCOs need to further investigate the approved uses and pharmacology of these agents and determine their exact mechanisms of action.

Etanercept, a soluble receptor originally approved

Dr. Broder is President and CEO, Partnership for Health Analytic Research, LLC, Los Angeles. Dr. Reissman is President, Rxperts Managed Care Consultants, Irvine, California.

TABLE I: CLASSIFICATION HIERARCHIES USED BY MAJOR COMPENDIA

	Therapeutic System	Therapeutic Class	Pharmacologic Class	Drug Type
USP/CMS				
Etanercept		Immunologic	Immunosuppressants	TNF inhibitor
Infliximab		Immunologic	Immunosuppressants	TNF inhibitor
Alefacept		Immunologic	Immunosuppressants	Non–TNF inhibitor
Efalizumab		Immunologic	Immunosuppressants	Non–TNF inhibitor
Drug Facts and Comparisons				
Etanercept	Biologic and immunologic agents	Immunologic	Immunomodulator	
Infliximab	Gastrointestinal agents			
Alefacept	Biologic and immunologic agents	Immunologic	Immunosuppressants	
Efalizumab	Biologic and immunologic agents	Immunologic	Immunosuppressants	
ASHP				
Etanercept	Unclassified	Miscellaneous antiarthritics		
Infliximab	Unclassified	Miscellaneous		
Alefacept	Skin and mucous membrane agents	Other dermatologics		
Efalizumab	Skin and mucous membrane agents	Other dermatologics		
Health Plan Sample				
Etanercept		Anti-inflammatory	TNF inhibitor	
Infliximab		Anti-inflammatory	TNF inhibitor	
Alefacept		Antipsoriatic	Systemic	
Efalizumab		Antipsoriatic	Systemic	

USP = U.S. Pharmacopeia; CMS = Centers for Medicare and Medicaid Services; TNF = tumor necrosis factor; ASHP = American Society of Health System Pharmacists

for treatment of rheumatoid arthritis, is a TNF-alpha and -beta antagonist. Infliximab, a chimeric monoclonal antibody, is a TNF-alpha antagonist. Alefacept is a dimeric fusion protein that interferes with activation and proliferation of T-cells by binding to CD2. Efalizumab is a humanized monoclonal antibody that blocks the activation, adhesion, and trafficking of T-cells by binding to CD11a (Table II).

TABLE II: SUMMARY OF FOUR BIOLOGIC AGENTS TO TREAT PSORIASIS

Variable	Alefacept	Efalizumab	Etanercept	Infliximab
Approved Uses	Psoriasis	Psoriasis	Rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis	Rheumatoid arthritis, Crohn's disease, psoriatic arthritis
Drug Type	Dimeric fusion protein	Humanized monoclonal antibody	Dimeric fusion protein	Chimeric monoclonal antibody
MOA	Binds CD2	Binds CD11a	TNF-alpha/beta receptor blocker	TNF-alpha receptor blocker

MOA = Mechanism of action; TNF = tumor necrosis factor

For the classification to be useful to both formulary decision makers and prescribers, it is important that all agents that could be used in the treatment of a specific disease be listed together. A health plan could categorize these agents in multiple ways:

Disease Treated/Therapeutic Class. For the agents used in this illustration, some would be classified in more than one category, as they have multiple disease indications. Although this system may be redundant, it allows users to compare agents based on the specific disease that is being treated rather than having to reference multiple sections of the formulary.

Therapeutic Class/Subclass. For the illustrative drug class, this nomenclature would allow an organization

to classify the agents as immunosuppressives/monoclonal antibodies and immunosuppressives/soluble receptors. However, this classification system does not consider the different sites of action/receptors of the agents that determine their action and does not remind prescribers of the approved uses of the agents.

Therapeutic Class/Mechanism of Action. The biologics used in the example would be placed under the major therapeutic classification of immunosuppressives, then further subcategorized into CD2 inhibitor, CD11a inhibitor, TNF-alpha blocker, and TNF-alpha/beta blocker. This system allows for the best description and differentiation of the agents, but does not help prescribers understand approved uses of the agents.

In this case, the best option may be to use a system that first identifies product indication (i.e., psoriasis), route of administration (i.e., systemic/injectable), pharmacologic class (i.e., immunosuppressives), and MOA. For example:

Psoriasis Therapies
Immunosuppressives:
- Systemic
  - Oral
  - Injectable
    - CD2 inhibitor
      - Alefacept
    - CD11a inhibitor
      - Efalizumab
    - TNF-alpha blocker
      - Infliximab
    - TNF-alpha/beta blocker
      - Etanercept
- Topical

APPLICATION OF THE FORMULARY CLASSIFICATION SYSTEM

The classification system chosen can be used by P&T Committees in evaluating agents for formulary coverage. Most organizations' P&T Committees include at least one agent within each formulary category listing, although they may include more than one unless head-to-head data exist comparing the agents within the category, on which to base a decision of product superiority.

In the case of the illustration class, a P&T Committee would likely decide to include all four available biologic agents, since each falls within a separate MOA category. This is similar to the decision on agents used to treat a disease like hypertension, when at least one agent from each drug class (i.e., beta blockers, alpha/beta blockers, angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, calcium-channel blockers [by subtype], peripherally and centrally acting vasodilators, thiazide and loop diuretics, aldosterone-receptor antagonists) will be included on formulary.

When and if they available, head-to-head studies across agents in different classes may prove useful in determining step algorithms or treatment protocols; without these data, P&T Committees should assure that equal availability status is provided to agents that have varied MOAs to maximize physician choice and patient outcomes.

This proposed classification system is the type of tool that could ease the decision-making burden on prescribers regarding when to prescribe certain drugs, and which prescriptions should take priority in the treatment of psoriasis. The system could be adapted quickly when new drug information becomes available that shows one drug's superiority over another. It would still provide a hierarchical basis for prescribing drugs for psoriasis, and lessen the time it takes prescribers to find all the drugs available in formulary for the treatment of the disease.

Classification of these biologics increases in importance as different indications are discovered and new data are published on long-term effects and cost effectiveness over longer periods. Having such a classification system in place would greatly simplify the sometimes complicated process of drug analysis by P&T Committees and ease the task of deciding which drugs to include based on MOA.

DISCLOSURE
Dr. Broder has disclosed that he has served as a consultant or on advisory boards for Genentech, Inc., and Amgen, Inc. Dr. Reissman has disclosed that she has served as a consultant for many pharmaceutical companies.

Address for correspondence: Michael S. Broder, MD, MSHS, Partnership for Health Analytic Research, LLC, 1950 Sawtelle Boulevard, Suite 280, Los Angeles, California 90025. E-mail: mbroder@pharllc.com.