

Off-Label Use of Approved Drugs: Therapeutic Opportunity and Challenges

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In this issue of the *JASN*, Booth *et al.* (1) report a well-designed study using TNF- α blockade with infliximab (Remicade) to treat ANCA-associated systemic vasculitis. The use of infliximab, already approved by the US Food and Drug Administration (FDA) for treatment of inflammatory bowel disease, raises the general question of off-label uses of approved drugs.

Clearly, off-label use of drugs by individual physicians is legal and leads to new therapeutic advances. A clever clinician putting together inferences from pathophysiology of disease and the known pharmacologic properties of approved agents may accumulate data on efficacy and toxicity in new settings. There are many examples in internal medicine of this type of use leading eventually to new approved indications and labeling. Beta-blockers for many years had approved indications in hypertension, angina, and cardiac arrhythmias. With research advances regarding the role of neurohumoral influences in congestive heart failure, beta-blockers have now become standard therapy in patients with congestive heart failure (2). Twenty years ago, the use of beta-blockers for these patients would have been contraindicated. Similarly angiotensin-converting enzyme (ACE) inhibitors are now known to improve survival in patients with myocardial infarctions and to benefit patients with congestive heart failure above and beyond anti-hypertensive actions. Aldosterone antagonists, thought to be of limited potency in patients with hypertension or edema, have had a resurgence in use due to recent evidence of the pathophysiologic role of aldosterone in cardiac failure (2). Patients with immune-mediated glomerulonephritis have been treated with off-label protocols using mycophenolate mofetil with apparent therapeutic benefit (3).

Although the FDA condones these off-label uses of approved drugs by physicians, they do present some risks for the therapist and potentially the patient.

Since these drugs have not been tested for safety and efficacy in the new populations studied, there is no large database of safety information. Clearly with the use of infliximab, serious infection is a risk. It is not known whether in the population with system vasculitis this risk is more, less, or the

same, but there is no a priori reason to presume that additional side effects might not be seen. This poses at least a theoretical risk of an adverse outcome that could result in legal action and, more importantly, devastating complications. Therefore, it is imperative that physicians explain the rationale for the therapy, the risk that patients are taking of unknown and unanticipated side effects, and the lack of proven data of efficacy for these off-label uses. In my view, this should be in the form of written informed consent to protect the physician from liability. The study by Booth *et al.* (1) properly obtained informed consent by participating centers' local ethics committees.

It is currently illegal for pharmaceutical manufacturers to promote their approved drugs for unapproved conditions. In a recent case, a whistle blower lawsuit was filed by a former employee of Parke Davis (now Pfizer) for giving kickbacks to doctors including tickets to the summer Olympics of 1996 to attend "educational activities" for promotion of gabapentin (Neurontin). This approved drug, which is a widely sold anti-convulsant, is being used for a variety of off-label uses including peripheral neuropathy and bipolar disease. The advertising of these products to physicians without FDA approval and without being in the context of a study is not allowed. In this case, the federal prosecutors argued that evidence presented suggested this was part of an "illegal off-label marketing scheme rife with false statements and fraudulent conduct all of which had one intended purpose and result: increasing sales and therefore the claims of off-label uses of Neurontin submitted to Medicaid." The prosecutors in that case said that Parke Davis misled doctors into believing that programs discussing Neurontin were independent educational programs when actually they were marketing efforts by Parke Davis. This type of adverse publicity certainly does nothing to enhance the image of physicians and ultimately undermines the confidence of the public.

Ideally, any off-label use of a drug should be in the context of a study in which informed consent is given and approval by an Institutional Review Board is obtained. The company should have filed an investigational new drug (IND) application with the FDA. This binds the company to collect data on both safety and efficacy upon which a decision to extend the labeling to a different indication would be based. With the soaring cost of prescription drugs to state and federal Medicaid programs, scrutiny is directed at companies who use illegal marketing techniques for unapproved indications. In the disclosures of professional education activities by the ASN, speakers are asked to disclose whether or not they will be discussing off-label uses of drugs. In the Parke Davis case, the

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government was seeking to reclaim expenditures that Medicaid incurred by these off-label uses. For example, Massachusetts spent \$25 million on Neurontin in 2002 compared with \$3 million in 1999. The US attorneys Michael Sullivan and Sarah Bloom wrote “For Medicaid programs to function in the best interest of public welfare. . .they must function free of the insidious effects of kickbacks and related financial conflicts on interest” (4).

The FDA encourages the off-label use of drugs with the implied commitment to the profession to do the necessary clinical research to gain approved labeling for the new indication. The fact that the drug is already approved bypasses the regulatory maze necessary for a physician to try these agents. While the manufacturer cannot advertise an off-label use of the drug they can disseminate studies. There is obviously a need for explicit disclosure that this is not an approved indication. If a manufacturer is collecting information about the off-label use of the drug, they have the responsibility to file an IND application with the FDA. Individual physicians interacting with their patients in the context of the practice of medicine should give careful thought to the benefits of off-label drug use based on pathophysiology and therapeutic logic and the side effects in that individual patient. One should inform the patient of your thought about these issues. This may not require an IND application or review by the Institutional Review Board; however, records should be maintained with the goal of accumu-

lating information that could form the basis for pilot studies that ultimately should lead to expanded indications for the already approved drug. Many of the off-label uses of the drug find their way into the literature as case reports, which alert other physicians to the possibilities of using these drugs in other patients. With appropriate transparency to the medical community and the patient, papers such as that of Booth *et al.* (1) will hopefully pave the way for more effective therapies of diseases that have been therapeutically problematic to date.

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References

1. Booth A, Harper L, Hammad T, Bacon P, Griffith M, Levy J, Savage C, Pusey C, Jayne D. Prospective study of TNF α blockade with infliximab in ANCA-associated systemic vasculitis. *J Am Soc Nephrol* 15: 717–721, 2004.
2. Jessup M, Brozena S: Heart failure. *N Eng J Med* 348: 2007–2018, 2003
3. Choi MJ, Eustace JA, Gimenez LF, Atta MG, Scheel PJ, Sothinathan R, Briggs WA: Mycophenolate mofetil treatment for primary glomerular diseases. *Kidney Int* 61: 1098–1114, 2002
4. Kowalczyk L: US filing backs suit against drug firm. Federal prosecutors: Epilepsy medication was illegally marketed. *Boston Globe*. May 28, 2003:D-1.

See related article, “Prospective Study of TNF α Blockade with Infliximab in ANCA-Associated Systemic Vasculitis,” on pages 717–721.